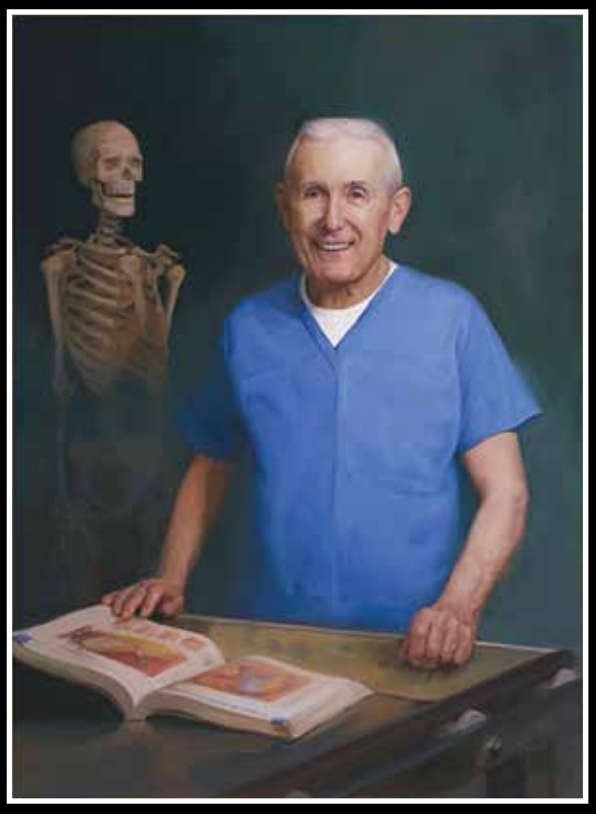
Temple University Journal of Orthopaedic Surgery & Sports Medicine



Carson Schneck, MD, PhD

Volume 10 Spring 2015

A John Lachman Society Publication

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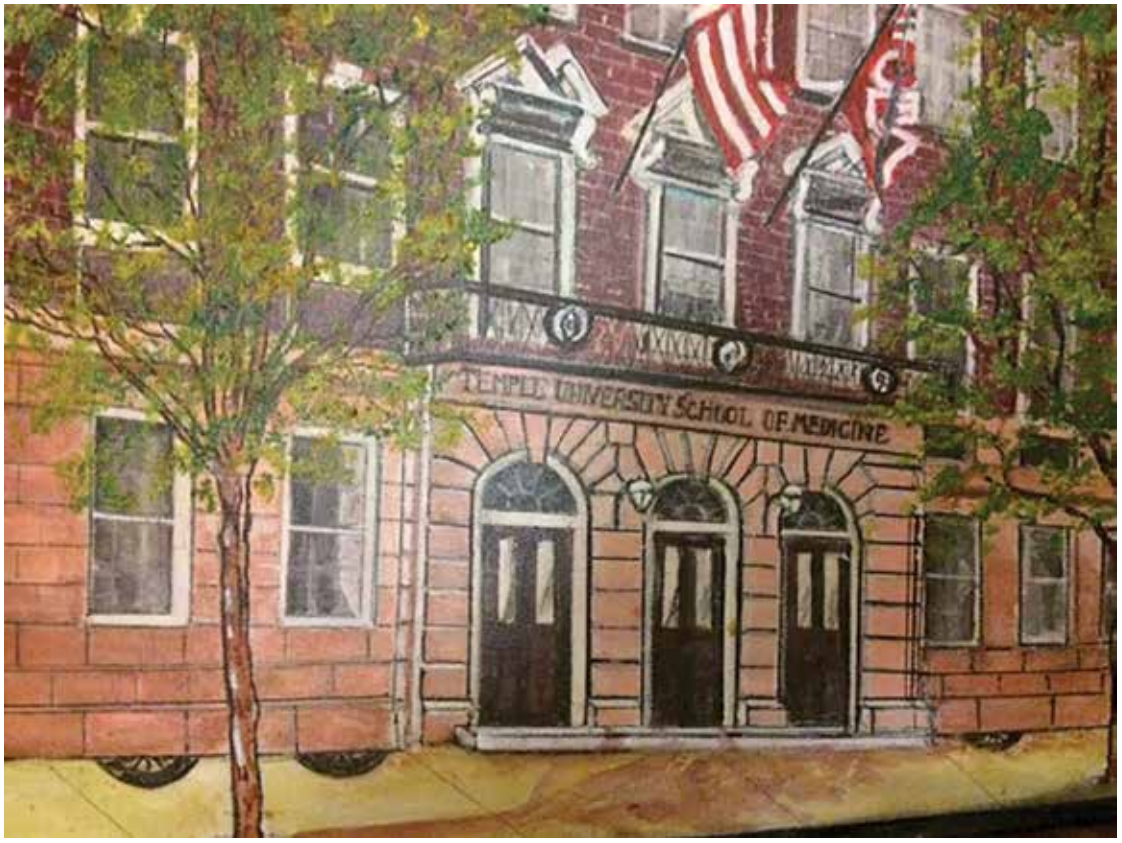


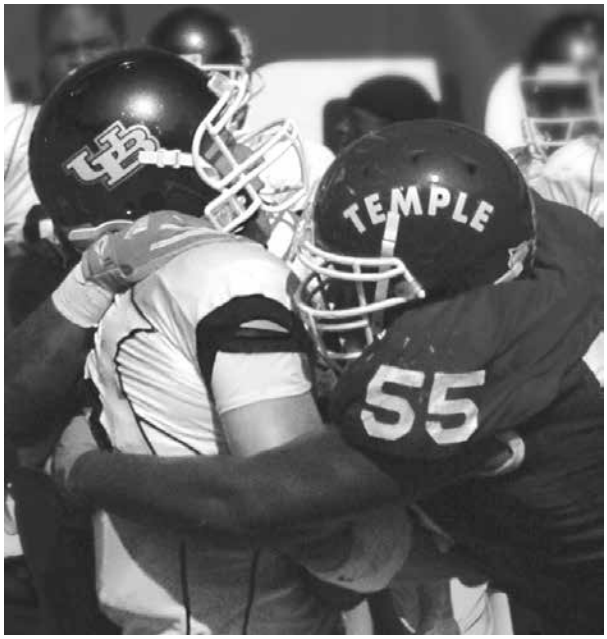
Temple University School of Medicine
1930–2014

The Temple University Concussion and Athletic Neurotrauma Program

Cerebral concussion, traumatic brain injury, transient spinal cord paralysis and brachial plexus injuries are potentially serious insults to the nervous system that are associated with contact athletic injuries. In accord with the principle that the management and return-to-play decisions should only be made by a qualified professional, Temple University has established its **Concussion and Athletic Neurotrauma Program.**

Temple's experienced, multidisciplinary faculty is well-suited to evaluate and manage athletic-induced neurotrauma, utilizing the latest imaging capabilities, neurocognitive **ImPACT™** testing and clinically established **return-to-play** protocols.

Utilizing the facilities of Temple University Hospital, Temple Orthopaedics & Sports Medicine satellite offices, Temple Medical School faculty and in concert with the Shriners Hospitals for Children in Philadelphia, this program is designed to provide the necessary experience to meet the needs of team and family physicians, athletic trainers, athletic administrators, coaches, parents and, most importantly — the athletes.



Proper tackling technique protects both head and cervical spine.

Research Goals

Current understanding of cerebral concussion and athletic-induced traumatic brain injury is limited to a variety of descriptive classifications and epidemiologic patterns. Lacking is an application of the known underlying pathophysiology to clinical management practice with particular regard to injury prevention. Clearly, much is not known and there are many questions to be answered regarding athletically-induced neurotrauma. The goal of this program is to bring this issue to the same meaningful conclusion that Temple physicians achieved with paralytic spinal cord injuries 35 years ago.

Temple University Hospital

Clinical Program

Athletes sustaining impact injuries and experiencing any of the following signs or symptoms should be evaluated and, if indicated, managed by a physician experienced with athletic injuries to the head, spine and brachial plexus:

Central Nervous System

- Loss of consciousness
- Confusion
- Dazed appearance
- Forgetfulness
- Unsteady movements
- Slow cognition
- Personality changes
- Retrograde/antegrade amnesia
- Headache
- Dizziness
- Nausea or vomiting
- Altered sense of well-being

Spinal Cord

- Four extremity paresthesias (numbness)
- Four extremity weakness
- Four extremity transient paralysis

Brachial Plexus

- "Stinger" lasting more than 20 minutes
- "Stinger" with persistent weakness
- Recurrent "stingers"

The neurotrauma team consists of orthopaedic sports medicine specialists, neurologists, neurosurgeons, neurophysiologists, physiatrists and biostatisticians.

ATHLETES REQUIRING EVALUATION AND/OR MANAGEMENT CAN BE SEEN AT FOUR OF TEMPLE'S CLINICAL SITES:

Cory J. Keller, DO, Sports Medicine
Michelle A. Noreski, DO, Sports Medicine

Temple University Hospital

3509 N. Broad Street
5th Floor Boyer Pavilion
Philadelphia, PA 19140
215-707-2111

Temple Orthopaedics & Sports Medicine Satellite Offices

515 Pennsylvania Avenue
Fort Washington, PA 19034
215-641-0700

11000 Roosevelt Blvd.
Philadelphia, PA 19116
215-698-5400

450 Corporate Ctr.
Oaks, PA 19456
610-650-5155

E-mail us at: concussion@tuhs.temple.edu
Website: www.templeconcussion.com

Temple Orthopaedics & Sports Medicine

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How to Reach Us

Temple University Hospital
Department of Orthopaedics, 6th Floor Outpatient Building
Philadelphia, PA 19140
Telephone: (215) 707-3411
Fax: (215) 707-7976

Letter from the Chairman

This past year has been one of growth and accomplishment for the Department of Orthopaedic Surgery and Sports Medicine. This year's Journal provides evidence of the record setting academic output of the faculty, residents, and students. This activity could not have taken place without the support of the alumni contributions to the John Lachman Society. We are all thankful for your continued support.

The clinical practice saw growth in all of its divisions and practice locations. We welcomed the addition of doctors Cory Keller and Michelle Noreski to the Sports Medicine program. These sports medicine, fellowship trained, internal medicine specialists have partnered with doctors Eric Kropf and Milo Sewards to provide comprehensive care for our collegiate and high school athletes. Their addition has allowed us to expand our coverage to the Temple recreational student athletes as well.

We have seen our faculty assume leadership positions at the national level in several areas:

Dr. Todd Wetzel is in leadership positions with NASS as the second Vice President and Chair of the Conflict of Interest Committee. He serves on the AOA Leadership Development Committee and is also the NASS liaison to the ABIM Choosing Wisely Initiative.

Dr. Saqib Rehman serves as Chair of the OTA Humanitarian Committee and is the course Chairman for the Annual Delaware Valley Orthopaedic Trauma Program now in its seventh year.

Dr. Eric Kropf serves on the Communication Committee for AANA and is the newly-appointed Pennsylvania delegate to the AOSSM Council of Delegates.

Dr. J. Milo Sewards serves on the Leadership Development for the Council of Orthopaedic Residency Directors (CORD) AOA. He also serves on the Emerging Leaders Forum for the AOA and on the AAOS Central Evaluation Committee.

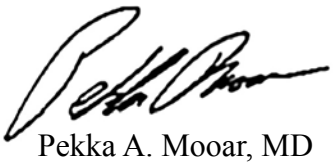
Dr. Joseph Eremus serves on the Post Graduate Medical Education Society for the American Orthopaedic Foot and Ankle Society.

The Orthopaedic faculty and residents have provided leadership for the Temple University Health System patient's satisfaction and Cost to Treat Programs. The Pain Management Program has been recognized as a national model with patients' satisfaction in the 95th percentile. Our departmental Cost to Treat initiative has saved the Temple University Healthcare System millions of dollars. As TUHS enters into the global health initiatives, the pioneering work being done by the orthopaedic faculty of balancing patient satisfaction with the expenditures on healthcare will clearly contribute to its success.

We have residents serving on many of the hospital committees as elected representatives, Operating Room Advisory, Medical Executive Committee, Peer Review, and Graduate Medical Education, and as departmental representatives to Cost to Treat, and Electronic Medical Records Committee.

Our program continues to grow with the opening of our new office location at Chestnut Hill Hospital and the development of two new faculty positions in Spine and Shoulder Replacement Surgery next year.

I would like to thank the entire faculty, residents, staff, students and alumni who have contributed to the success of our department this year. I know next year will prove to be another year of growth and accomplishment for Temple Orthopaedics.



Pekka A. Mooar, MD
Interim Chairman
Department of Orthopaedics and Sports Medicine
Temple University School of Medicine

Letter from the Editor-in-Chief

Welcome! It is with great enthusiasm that I introduce this year's edition of the *Temple University Journal of Orthopaedic Surgery & Sports Medicine,* Volume 10. The goal of the Editorial Staff was to compile a representative collection of our department's academic prowess; we believe the commentaries, technique guides, case report, and original research will provide you with a diverse and contemporary window of academic Orthopaedic Surgery at Temple University.

Temple University had the privilege of the podium and the poster board at several major national meetings including the American Academy of Orthopaedic Surgeons and American Association for Hand Surgery.

In addition, we have been featured in several peer-reviewed publications such as the *Journal of Bone and Joint Surgery,* the *Journal of Hand Surgery, Orthopedic Clinics of North America, American Journal of Orthopedics, Orthopaedics, Injury,* the *Journal of Pediatric Orthopaedics, Spine Deformity,* and *Surgical Technology International.*

I am excited to dedicate this issue to the face of Temple's Anatomy Department, Carson Schneck, who instilled the foundations of human body architecture in hundreds of our orthopaedic surgery trainees and thousands of our medical students. I would also like to extend a heartfelt thank you to the John Lachman Society, who have funded many (if not all) of the endeavors herein. I thank my associate editors, Arianna Trionfo, Colin Mansfield, and Will Smith, my faculty advisors, Joe Torg and Saqib Rehman, and the keystone of our research office, Joanne Donnelly, for all of their hard work in bringing the publication of this journal to fruition.

Rick Tosti, MD
Editor-in-Chief
Class of 2015

Letter from the Residency Director

Over the last several years, I have been honored to write an introductory statement for this journal as the Program Director of the residency. This journal represents the evolution of the program's and department's commitment to the research component of orthopaedic education. In reviewing past issues, it is difficult for me to describe my pride and admiration in the progress that has been made in that regard. I would like to recognize and thank this year's editor-in-chief, Rick Tosti, as well as our resident editors, Colin Mansfield, Arianna Trionfo, and Will Smith, and our faculty editors, Joe Torg and Saqib Rehman. Pekka Mooar, Dr. Torg, and Joanne Donnelly also deserve recognition for their work with the summer research program, which continues to produce substantial manuscripts for this journal.

Our residency program remains strong and well regarded. This year, we received 744 applications for our four PGY-1 positions. We had an excellent match last year and I would like to welcome Peter Eyvazzedeh, Justin Kistler, Courtney Quinn, and Megan Reilly to the program. We also will bid farewell to our graduating chiefs, Justin Iorio, Steve Refsland, Craig Steiner, and Rick Tosti. Justin and Craig will be continuing their training in Spine Surgery at the Hospital for Special Surgery in New York. Steve and Rick will be emulating Dr. Thoder in their training in Hand Surgery, with Steve going to New York for his fellowship at St. Lukes-Roosevelt Hospital, and Rick going to Boston, to the Massachusetts General Hospital.

Thanks to all of our colleagues on the faculty at Temple as well as our affiliate institutions, and the supporting members of the John Lachman society, I continue to have the privilege of leading a strong residency program that improves each year. It remains a distinctive honor for all of us to have graduated from or to have been affiliated in some way with the Temple Orthopaedic Surgery residency program.

J. Milo Sewards, MD
Assistant Professor
Residency Director

Message from the John Lachman Society

The John Lachman Society was founded in 2004 to honor Dr. Lachman and propagate his principles of integrity, teaching, and excellent patient care. The Society also provides discretionary funds for the Chairman to promote and support the academic mission of the Department including student and resident research. The mechanism to accomplish these goals is through the Society's support of the John Lachman Orthopedic Research Fund (JLORF), incorporated in Pennsylvania as a non-profit corporation. The Internal Revenue Service has determined that the John Lachman Orthopedic Research Fund is exempt from federal income tax under 501 (C) (3) of the Internal Revenue Code and that contributions to the fund are tax deductible.

Those interested in membership in the John Lachman Society should contact the Chairman of the Membership Committee, Philip Alburger, MD or Milo Sewards, MD, c/o The John Lachman Society, P.O. Box 7283, Wayne, PA 19087.

JOHN LACHMAN SOCIETY MEMBERSHIP — JANUARY 1, 2015

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Mohammed-Tarek Al-Fahl, MD
Henry Backe, Jr., MD
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Easwaran Balasubramanian, MD
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John Richmond, MD
Jack Rocco, MD
James Rogers, ATC
Michael Romash, MD
Jeff Ryan, ATC
Anthony Saker, MD
Anthony Salem, MD
Richard Sandrow, MD
Samuel Santengelo, MD*
Richard Savino, MD
H. William Schaff, MD
Joseph Scornavacchi, MD

*Deceased

(Continued on next page)

J. Milo Sewards, MD
Patrick Sewards, MD
James Shacklett
Gene Shaffer, MD
K. Donald Shelburne, MD
Abraham Shurland, MD
Michael Sitler, PhD
Gary Smith, MD
Gbolabo Sokunbi, MD
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Robert Sutherland, MD
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Albert Weiss, MD
F. Todd Wetzel, MD
Gerald Williams, MD
John Wolf, MD
Steven Wolf, MD
Thomas Yucha, MD

At the annual meeting of the board of directors of the John Lachman Orthopedic Research Fund, the following officers were re-elected for a one-year term:

President: J. Milo Sewards, MD
First Vice President: Eric Lebby, MD
Second Vice President: Dave Junkin, MD
Treasurer: Albie Weiss, MD
Secretary: Joe Torg, MD

The summer medical school intern program continues to be a most successful program. This past summer, 11 sophomore medical students participated in the program. In addition to a number of the students producing manuscripts suitable for publication in the *Journal,* it has been evident that a major value of this program is that in view of the curriculum changes no longer requiring students to rotate through orthopedics, those students interested have an opportunity to interface with our department. Clearly, this has become a major avenue of acquainting students to the residency program.

In view of the success of the Temple Orthopedic Summer Program, a course will be added to the first year medical student curriculum to teach the students how to conduct a clinical research project based on the model we have developed in our department. The course will be mandatory and will cover all aspects of clinical research. Topics that will be covered include: how to develop the research question, literature review including primer on the use of PubMed or OVID or other search engines, use and disclosure of public health information, role of the IRB and responsibilities to protect the data, IRB submission guidelines, and mandatory ethics certification. Clearly, Temple Orthopedics functions as a trendsetter in medical student education!

Once again, the John Lachman Society published and distributed the *Temple University Journal of Orthopaedic Surgery & Sports Medicine,* Volume 9. Eighteen hundred copies of the *Journal* have been distributed as follows: a) active faculty of the Temple University School of Medicine, b) orthopedic surgeons who are alumni of Temple University School of Medicine, c) members of the John Lachman Society, d) department chairman and residency directors of all orthopedic programs throughout the United States, and e) fellowship directors to all orthopedic programs throughout the United States.

Academic support for resident travel to meetings by the John Lachman Orthopedic Research Fund during the period January 1, 2014 through December 31, 2014, involved 12 residents who have attended either formal courses or national meetings.

The John Lachman Society web page can be entered at www.johnlachmansociety.org.

The John Lachman Orthopedic Research Fund is committed to a $2,500 year expenditure for texts and other educational materials for resident teaching.

The John Lachman Society, through the John Lachman Orthopedic Research Fund and working in close cooperation with the Temple-Shriners' Alumni group, continues its mission to support and enhance both the academic program of the department and the orthopedic residency program.

Joe Torg, Secretary

Letter from the Office of Clinical Trials

The Office of Clinical Trials and Research Support has been going strong since 2004 when it was established under the direction of Pekka A. Mooar, MD and supported by the School of Medicine's Office of Clinical Research Administration, with Ms. Joanne Donnelly as the full-time research and program coordinator.

The program is now in its eleventh year and continues to fulfill the vision of providing the Department of Orthopaedics and Sports Medicine with industry-sponsored clinical trials, resident-initiated research and the eight-week summer research program geared toward those Temple medical students with an interest in orthopaedics. Funding for the program is provided through the federal work-study program and supplemented by the department. The summer research program will host 17 Temple medical students in 2015. The eight-week program involves teaching the students the fundamentals of clinical research via a research topic selected by our orthopaedic surgeons and culminates in generating a finished manuscript. There is an orientation by Dr. Susan Fisher, Department of Clinical Sciences Professor and Chair on the "Nuts and Bolts of Statistics for Clinical Research." Lauri Fennell, Temple Reference and Emerging Technologies Librarian, provides the students with basic and advanced research searching options through PubMed and Ovid and other search engines, as well as RefWorks for managing citations. Chad Pettengill from the Temple Institutional Review Board will speak to the students regarding the guidelines pertaining to clinical research. I am looking forward to another exciting and fruitful year with the students.

Current Industry-Sponsored Clinical Trials Drug or Device

Stryker
(INSITE) Intramedullary Nail Versus Sliding Hip Screw Intertrochanteric Evaluation: A Multi-Center Randomized Controlled Trial of Intramedullary Nail Versus Sliding Hip Screw in the Management of Intertrochanteric Fractures of the Hip
Saqib Rehman, MD, Principal Investigator; Bruce Vanett, MD, Sub-Investigator;
Christopher Haydel, MD, Sub-Investigator, Phase IV Device. Ongoing enrollment — 19 subjects.

EMSI
The Electrostim Medical Services, Inc. (EMSI) Bone Growth Stimulator (BGS) Clinical Study for the Treatment of Long Bone Fractures Secondary to Trauma Where Serial Radiographs Taken at Least 90 Days Apart Have Shown No Visible Progressive Signs of Healing
Pekka Mooar, MD, Principal Investigator, Phase IV Device. Enrollment — active.

Department of Defense
Assessment of Severe Extremity Wound Bioburden at the Time of Definitive Wound Closure or Coverage: Correlation with Subsequent Post-Closure Wound Infection (Bioburden Study)
Saqib Rehman, MD, Principal Investigator; Christopher Haydel, MD, Sub-Investigator.
Prospective cohort observational study. Ongoing enrollment — 4 subjects.

AESCULAP
A Phase 3, Prospective, Randomized, Partially Blinded Multi-Center Study to Measure the Safety and Efficacy of Novocart® 3D, Compared to Microfracture in the Treatment of Articular Cartilage Defects
J. Milo Sewards, MD, Principal Investigator; Pekka A. Mooar, Sub-Investigator;
Eric Kropf, MD, Sub-Investigator. Enrollment — active.

Pending Industry Clinical Trials Drug or Device 2015

VANCO Study
Department of Defense Local Antibiotic Therapy to Reduce Infection After Operative Treatment of Fractures at High Risk of Infection: A Multi-Center, Randomized, Controlled Trial
Saqib Rehman, MD, Principal Investigator; Christopher Haydel, MD, Sub-Investigator.

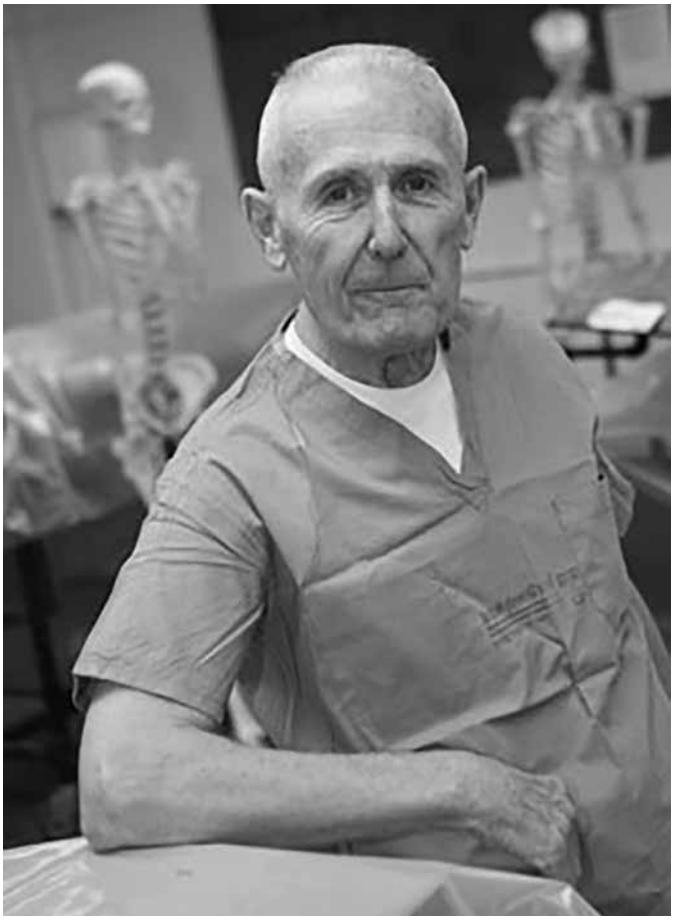
American Orthopaedic Foot and Ankle Society (AOFAS)
Venous Thromboembolic (VTED) Prophylaxis Following Orthopaedic Foot and Ankle Surgery: A Randomized, Controlled, Comparison Trial
Pending site selection. Joseph Eremus, MD, Principal Investigator.

Joanne Donnelly

Dedication

Carson Schneck, MD, PhD — A Teacher Personified and Role Model for the Ages

Megan Chiplock



In a class of 180 freshmen medical students, it's easy to be anonymous. However, Carson Schneck, MD, PhD, doesn't let that happen at the Temple University's School of Medicine. Before the students walk into his "Human Gross Anatomy" classroom, he knows each and every one of them. "In a lecture hall environment, they are just faceless people sitting there," says Schneck. "I think it's important in teaching to get to know the students as people." For Schneck, teaching begins with getting to know his students before the school year even starts. He spends a weekend in August memorizing student ID pictures until he can place a name with every face. It's just one part of what has made him one of the most unforgettable professors at Temple, having carved out a provincial career path on campus, teaching anatomy and more since 1960.

For nearly 50 years, Schneck has introduced first-year med school students like Alley to their first patient: a cadaver. When he began teaching, cadavers were often homeless people or drifters. Now, it's a much different story, as people donate their bodies for medical education and scientific research. Perhaps that is why Schneck respects the cadaver so much. He understands that all he knows about the study of the human body begins, not in life, but in death. It's that respect he passes along to his students in a Socratic teaching. Don't expect to see the Good Doctor lecture; instead, he poses problems and challenges students to solve them to prove they understand the anatomy they are learning. "He picks up an anatomy probe and plunges it into the cadaver's chest," reminisces Dr. Fred Hartman, MD '69, who says Schneck then asked the students to name all the structures his probe went through. "Invariably, we would miss one, and Carson would smile, his point made."

His point is that life is about learning and it never stops, not even for a 76-year-old professor of anatomy, who knows the human body, well, like the back of his manus, or hand. His accomplishments are many, having earned his MD at Temple in 1959 and the very first PhD in anatomy and cell biology at Temple. Schneck has chosen to teach class instead of becoming a clinician, but that hasn't lessened his impact on the many thousands of physicians who have graduated from Temple. For nearly 30 years, all kinds of physicians, from radiologists to psychiatrists, have been required to get re-certification in their specialty every 10 years. Who do they turn to for their post-graduate and continuing medical education training, of course, Carson Schneck.

The school launched a million dollar campaign for the Carson D. Schneck Gross Anatomy Laboratory in the new medical school that opened in fall of 2009. The laboratory boasts the latest technology — computers above every dissecting table — allowing students to get instruction while watching streaming video right at their workstation. And when the ultramodern lab opened, Schneck was right there helping to apply the newest technologies. But you can bet with his using the same teaching style that he has stuck with since 1960, today's students will still surround him. "You don't leave anything behind in this life except the imprints you put on other people," said Schneck. "I adopted other people's traits and hopefully I can communicate some of these other good traits to other people."

Adapted from the Carson D. Schneck Gross Anatomy Laboratory Campaign Letter

Distinguished Alumni Paper

The Pathomechanics and Pathophysiology of Cervical Spinal Cord Injury

Joseph S. Torg, MD;[1] Lawrence Thibault, ScD;[2] Brian Sennett, MD;[1] Helene Pavlov, MD[1, 3]

[1]*Department of Orthopaedic Surgery, University of Pennsylvania, Philadelphia, PA;* [1]*Department of Bioengineering, University of Pennsylvania, Philadelphia, PA;* [3]*Cornell Medical College, New York, NY*

Abstract

Cervical cord injuries caused during American football games have resulted in reversible, incompletely reversible, and irreversible neurologic deficits. An explanation for this variable response to injury has been obtained from the study of the histochemical responses of a squid axon injury model to mechanical deformation. Data obtained indicate that recovery or lack thereof is directly proportional to the intracellular calcium concentration which in turn is directly proportional to the amount and rate of tension applied to the axon. It is concluded that in most instances of acute spinal injury, disruption of cord function is a result of the effects of local cord anoxia and the increased concentration of intracellular calcium. It is proposed that implementation of therapeutic measures that restore blood flow and reduce cytosolic calcium will increase neurologic recovery.

Richard Schneider, MD, former professor and chairman of the Department of Neurosurgery, University of Michigan[3] has observed that "The football fields of our nation have been a vast proving ground or laboratory for the study of tragic neurologic sequelae of head and neck trauma in man."

In this article, the authors correlate clinical observations dealing with the pathomechanics and pathophysiology of cervical spine injuries that have occurred during American football games, with the response of an *in vitro* model of isolated neural and vascular elements subjected to controlled mechanical deformation. On the basis of analysis of the clinical material, it is apparent that cervical spinal cord injury can result in reversible, incompletely reversible, and irreversible neurologic deficit. Insight into the reasons for this variable response to injury has been obtained from the study of the histochemical responses of the axonal injury model to mechanical deformation. The clinical relevance of these observations are three-fold. First, an understanding of the pathophysiologic response of neural elements to mechanical stimulation will aid the clinician in developing an understanding of the mechanics of cord trauma and direct strategies for therapeutic intervention. Second, delineation of injury parameters responsible for the variable response of the cervical spinal cord to injury emphasizes the importance of prompt reduction of spinal malalignment in the face of acute injury. Third, clinical and laboratory data delineate the rationale for therapeutic approaches to manage the deleterious effects of the histochemical abnormalities that occur at the cellular level in acute spinal cord injury.

The authors believe that in many if not most instances of acute spinal cord injury, interruption of neural function is not attributable to an instantaneous disruption of axons or blood vessels, but rather a functional response that without therapeutic intervention will ultimately become a structural disruption (axotomy) secondary to aberrations in histochemical function. This presentation makes the case for cord resuscitation. It is proposed that measures initiated to obviate the effects of local anoxia and increased concentrations of axonal cytosolic calcium will result in improved neural recovery.

Clinical Observations

In accordance with Schneider's observation quoted above, the senior author and his colleagues have, during the past 20 years, studied reversible, incompletely reversible, and irreversible spinal cord trauma resulting from athletic injuries.[4, 6, 7, 11, 12, 15–18] Initial investigations involved epidemiologic and biomechanical analysis of clinical material with primary emphasis on preventing cervical spine injuries resulting from American football games. Documentation and analysis of >1200 cervical spine injuries that occurred between 1971 and 1990 have resulted in the description of the axial load mechanism. Axial loading has been implicated as the primary mechanism producing severe cervical spine injuries in tackle football through review of epidemiologic, biomechanic, and cinematographic data compiled by the National Football Head and Neck Injury Registry.[16–18] In the course of a contact activity, such as tackle football, the cervical spine is exposed repeatedly to potentially injurious energy inputs. Fortunately, most forces are dissipated effec-

Recipient of the 1995 Nicolas Andry Award.

Reprinted with permission from *Clinical Orthopaedics and Related Research,* No. 321, pp. 259–269.

tively by the energy-absorbing capabilities of the cervical paravertebral musculature and the intervertebral discs through controlled spinal motion. However, the vertebra, intervertebral discs, and supporting ligamentous structures can be injured when contact occurs on the top or crown of the helmet with the head, neck, and trunk positioned in such a way that forces are transmitted along the vertical axis of the cervical spine. With the neck in the neutral position, the normal alignment of the cervical spine is one of extension because of the normal lordotic curve. It is with 30° neck flexion that the cervical spine is straightened. With impact exerted along the longitudinal axis of a straight spine, loading of a segmented column occurs (Fig. 1). In this situation, in which the cervical spine assumes the physical characteristics of a segmented column, motion is precluded in response to axially directed impacts, and the forces are transmitted directly to the spinal structures.

At first, energy inputs are absorbed by the intervertebral discs and compressive deformation occurs. When maximum compressive deformation is reached, continued energy input results in angular deformation and buckling with failure of the intervertebral discs, ligamentous structures or bony elements. This results in subluxation, facet dislocation, or fracture-dislocation at one spinal level.[7] As a result of this observation, rule changes made in 1976 in scholastic and collegiate football that prohibited spearing and head impact have resulted subsequently in a marked decrease in permanent cervical quadriplegia (Fig. 2).[4, 9, 11, 15, 16, 18]

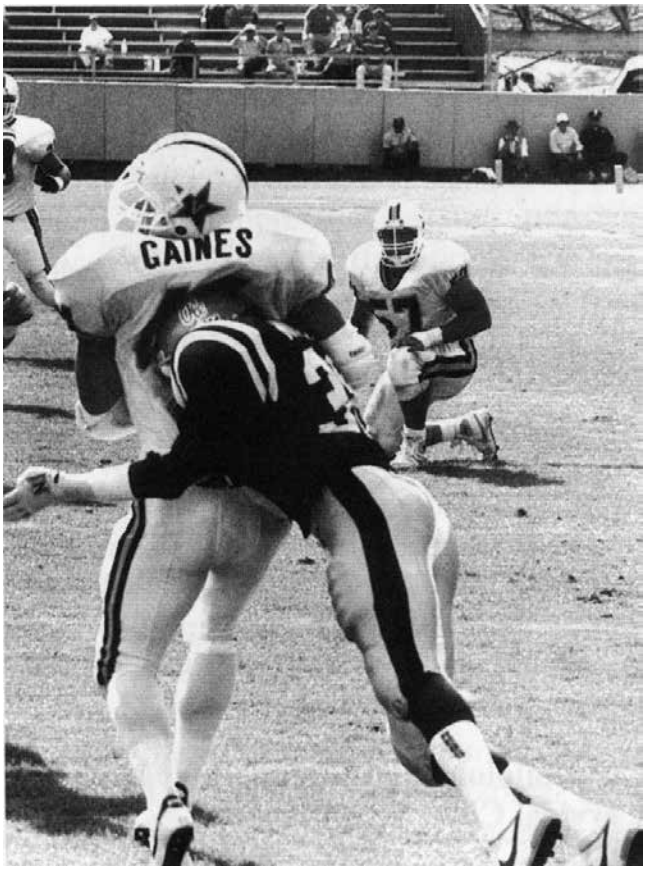


Figure 1. Classic at-risk playing technique in which injured player (dark jersey) strikes the opponent with the top or crown of his helmet, initiating an axial load on his cervical spine. The patient sustained multiple fractures involving C3, C4, and C5 with associated permanent quadriplegia.

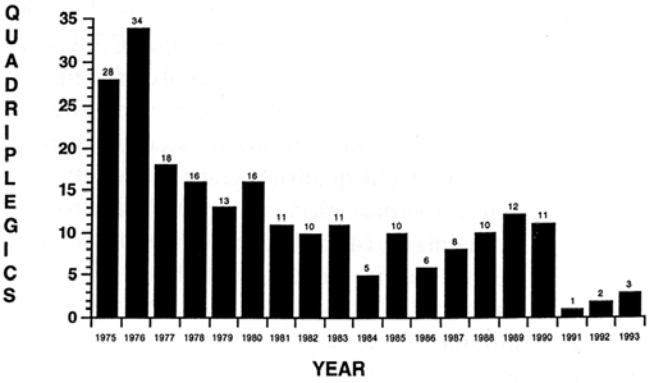


Figure 2. Implementation of football rule changes in 1976 prohibiting the use of the head as the initial point of contact resulted in a steady decline in quadriplegia at the high school and college levels.

Definition of the middle cervical segment (C3-C4) has clarified the relationship between degree of instability and severity of neurologic sequelae and the potential for neurologic salvage with prompt reduction of cervical spine subluxation and dislocation.[13, 14] Analysis of 25 cases suggests that traumatic lesions of the cervical spine in general can be classified as involving the upper (Cl-C2), middle (C3-C4), or lower (C4-C7) segments.[13, 14] This is based on the observations from this series that C3-C4 lesions (1) generally do not involve fracture of the bony elements; (2) acute intervertebral disc herniations are associated frequently with transient quadriplegia; (3) reduction of anterior subluxation of C3 on C4 is difficult to maintain; (4) reduction of unilateral facet dislocation is difficult to obtain by skeletal traction and is best managed by closed manipulation and reduction under general anesthesia; and (5) reduction of bilateral facet dislocation is difficult to obtain by skeletal traction and is managed best by open methods. The more favorable results observed in this series with immediate reduction of unilateral and bilateral facet dislocations deserve emphasis. In two cases of unilateral facet dislocation reduced within three hours of injury and subsequently fused anteriorly, significant neurologic recovery occurred. Four patients, two who had delayed open reduction and laminectomy and two treated with skeletal traction, remained quadriplegic. In four instances of bilateral facet dislocation in which reduction was achieved by either closed or open methods, although there was no neurologic recovery, all four patients survived their injuries. However, the three patients who were not reduced successfully died.

Description of the axial load teardrop fracture of the cervical spine has established the relationship of the degree of instability to neurologic sequelae.[10] There are two fracture

patterns associated with the anteroinferior corner fracture (teardrop) fragment: (1) the isolated fracture, usually not associated with permanent neurologic sequelae; and (2) the three-part, two-plane fracture, in which there are sagittal vertebral body fracture and fractures of the posterior neural arch and usually is associated with permanent neurologic sequelae, specifically quadriplegia (Fig. 3). Axial load is the mechanism of injury for both fracture patterns. The isolated anteroinferior corner fracture pattern and the three-part, two-plane fracture pattern have vastly different neurologic sequelae. Of the 31 patients in this series with a documented three-part, two-plane injury, 27 (87%) were quadriplegic. In the remaining four cases, all had initial neurologic symptoms of paresthesia or paresis, including one case of central cord syndrome, all of which eventually resolved. Of the six patients with an isolated anteroinferior corner fracture fragment without an associated sagittal fracture, five (83%) had no serious neurologic sequelae. The one remaining patient had fractures to the posterior elements of the subadjacent vertebra and was quadriplegic.

In the present series, an anteroinferior corner fracture without a sagittal fracture was a less detrimental pattern. This finding has been substantiated by other studies in which the sagittal fracture accompanying an anteroinferior corner fracture fragment has been reported associated with severe cord injury or quadriplegia or both.[10]

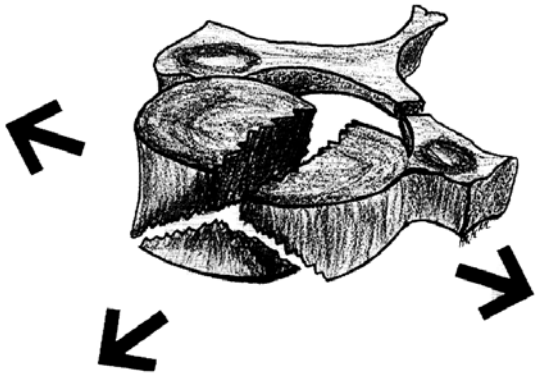


Figure 3. Diagrammatic representation of the axial load teardrop fracture. In addition to the teardrop, this fracture pattern includes a sagittal fracture of the vertebral body and a fracture involving the posterior elements.

Epidemiology and Histopathology of Cervical Cord Neurapraxia

Previously, the authors described, as a distinct clinical entity, the syndrome of neurapraxia of the cervical spinal cord with transient quadriplegia.[5, 8, 9] Sensory changes included burning pain, numbness, tingling, and loss of sensation. Motor impairment ranged from weakness to complete paralysis in upper and lower extremities. The episodes are transient with complete sensory and motor recovery usually occurring in 10 to 15 minutes, although in some patients gradual resolution may occur during a period of 24 to 36 hours. Except for burning paresthesias, pain in the cervical area is not present at the time of injury and there is complete return of motor function and full, pain-free motion of the cervical spine. In the authors' initial series of 32 patients, routine radiographs of the cervical spine were negative for fracture or dislocation in all patients. However, a significant finding in all patients was that of developmental narrowing (stenosis) of the cervical spine at one or more levels.

The phenomena of neurapraxia of the cervical spinal cord occurred in individuals with developmental narrowing of the cervical spine either as an isolated entity or associated with congenital fusion, cervical instability, or intervertebral disc protrusion. In athletes with diminution of the anterior posterior diameter of the spinal canal, the cord can, on forced hyperextension and hyperflexion, be compressed causing transient motor and sensory manifestations. The mechanics of cervical cord compression have been described by Penning[2] as the "pincer mechanisms": specifically, with hyperextension, the posterior inferior aspect of the superior vertebral body and the anterior superior aspect of the spinal laminar line of the subjacent vertebra approximate; conversely in flexion, the spinal laminar line of the superior vertebra and the posterior superior aspect of the body of the subjacent vertebra approximate. In each situation, a rapid decrease occurs in the anteroposterior diameter of the canal with compression of the spinal cord, resulting in a transient disturbance of sensory or motor function or both.

The laboratory application of microdeformation of the squid axon model has resulted in the histochemical explanation of this phenomena as it occurs at the cellular level. Correlation of data obtained from the axon injury model with the aforementioned clinical observations has resulted in a schematic that may explain one of the major components of reversible, incompletely reversible, and irreversible spinal cord injury.

Laboratory Study

As indicated, neurapraxia of the cervical cord occurs as a result of hyperflexion or hyperextension in an individual with a developmentally narrow (stenotic) canal. The pincer mechanism, a sudden, brief compressive deformation of the cord, is thought to produce sudden aberration of nervous function below the involved level, ranging from paresthesias to transient quadriplegia. From the engineering perspective, the spinal cord is considered an element of a low modulus of rigidity. In an element with this particular characteristic, the macroscopic loads applied to the cord result in localized tension within the tissue. Various macroscopic deformations result in local elongation (tension) of the element. The first and simplest case is pure axial elongation of the cord where all elements experience stretch. With extension or flexion (bending), the tension in the cord will vary across the diameter. Highly localized loading, such as shearing from sublux-

ation of the vertebral elements, or focal compression, such as a weight-drop experiment, result in elongation of the elements in the direction of the long axis of the cord (Fig. 4).

An experimental model was devised to determine the effects of high strain, uniaxial tension to various degrees of stretch in concert with the changes of neurophysiology of the single axon. The stretch ratio is defined as the ratio of the deformed length of the element to the undeformed length. Injury at the cell level then can be related to the spectrum of clinically relevant forms: reversible and irreversible spinal cord trauma. These relationships can be based on the electrophysiologic and biochemical events that occur in response to controlled levels of cell membrane deformation. In this manner, the data can be related to macroscopic loading conditions observed clinically.

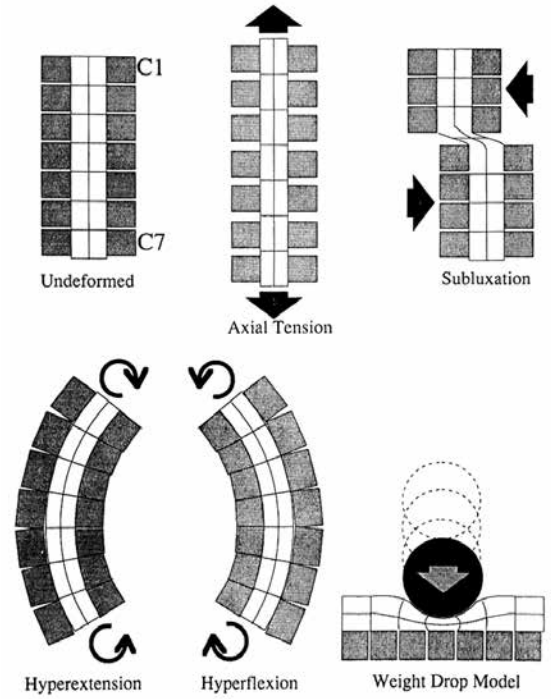


Figure 4. Diagrammatic representation of various macroscopic deformations resulting in local elongation or tension in an element, such as the spinal cord, with a low modulus of rigidity.

Materials and Methods

The giant axon of the squid, Loligo Pealei, was selected as the isolated tissue model, and a system was designed to apply uniaxial extension at high strain rates to the preparation. The system consists of an electromagnetic actuator, displacement transducer, isometric force transducer, membrane potential electrodes, all of which are mounted on the stage of a microscope (Fig. 5).

The actuator was programmed to deform the axons to various stretch ratios at specific strain rates. Recording of the membrane potential and the cytosolic free calcium ion concentrations as a function of the strain and the tensile forces

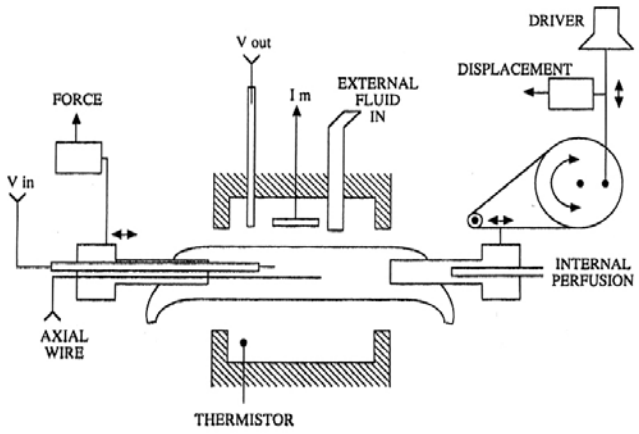


Figure 5. Diagrammatic representation of actuator designed to apply uniaxial tension to deform the axon to various stretch ratios at high strain rates.

developed within the axon enables one to study the response of the isolated tissue to mechanical stimulation. The purpose of these experiments was to elucidate the thresholds for the tissue response to a well-controlled mechanical insult. The ultimate aim was to be able to relate the field variables from the physical and analytical model studies to this isolated tissue response.

The typical experiment determined (1) the membrane potential; (2) axon deformation; (3) developed tension; and (4) cytosolic-free calcium ion concentration as a function of time (Fig. 6). The data for the dynamic stretch were recorded over the interval of 100 ms; the calcium response was presented over a time course of 30 seconds.

Results

The resting membrane potential for this experiment is modified by the rapid stretch in such a way that it is first hyperpolarized and subsequently depolarized to an extent that it is no longer excitable. The stretch of the axon is approximately 0.32 mm, and the resulting stretch ratio is 1.2. The developed tension under these conditions is in excess of 2 gms, and the result of this insult is a dramatic rise in the intracellular calcium concentration. Note that this rise in calcium is followed by an even greater rise that is indicative of a complete failure of the cell to restore ion homeostasis (Fig. 6). This particular experiment was selected to show the severe end of the pathophysiologic spectrum. It has been shown previously that the effects of elevated cytosolic free calcium above 50 micromolar will result in calcium-activated neutral protease that can damage the protein structures of the cell.

The isolated tissue studies afford the opportunity to investigate the issue of whether there is a direct correlation between the mechanical stimulation and the resulting pathophysiologic manifestations at the level of the axon. If such a correlation exists, then an injury tolerance criterion may be assigned on the basis of this correlation provided that one has the ability to relate the field variables of stress or strain

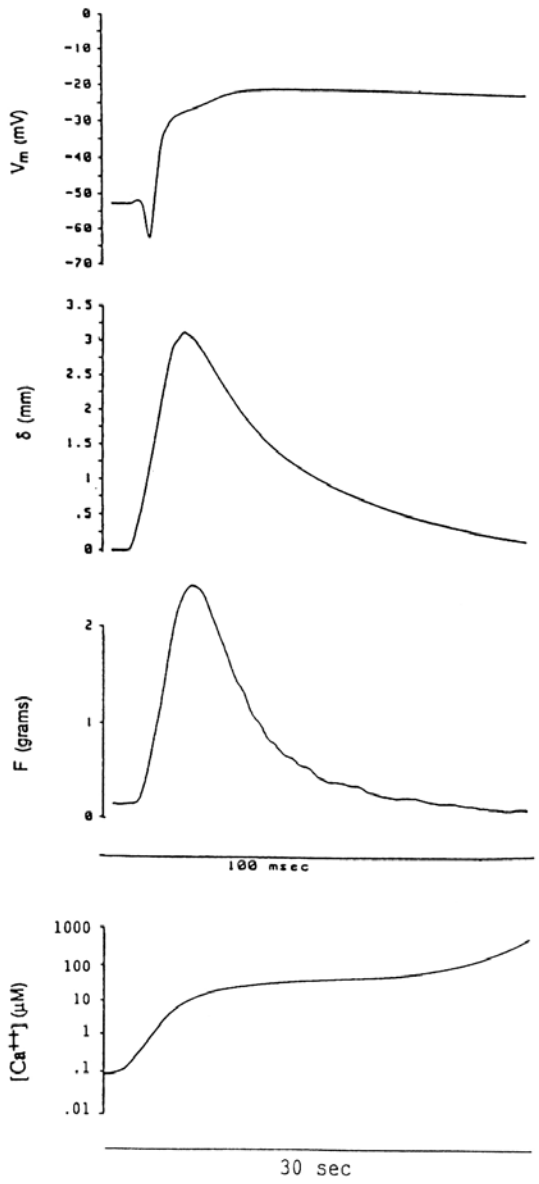


Figure 6. Results of a typical experiment shows that a stretch of an axon of 0.32 mm with tension in excess of 2 g results in initial cell membrane hyperpolarization and subsequent depolarization with marked increases in the cytosolic-free calcium.

within the spinal cord to the loads that are applied to the cervical spine.

Alterations in the membrane potential of the axon is a sensitive measure of the injury to this structure. Expressed as a percentage of change from the resting state, to normalize the data, it is a function of the mechanical stimulus, which is expressed as the stretch ratio. There is an exponential dependence of the depolarization on the magnitude of the mechanical stimulus. It should be noted that the membrane fails in a structural sense when the stretch ratio exceeds 1.25 at these levels of strain rate (Fig. 7). These experiments were conducted under a variety of chemical conditions that present the membrane as normal or modified with sodium and potas-

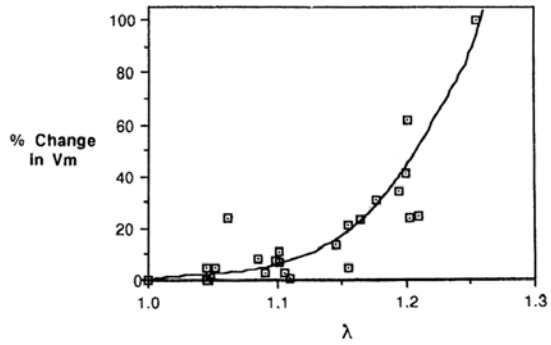


Figure 7. Graph of the results of determinations demonstrating the exponential dependence of cell membrane depolarization on the magnitude of the mechanical stimulus.

sium channel blockers present. There is no difference in the outcome with respect to the depolarization.

The degree to which the membrane depolarizes is a reasonable measure of the severity of the injury. However, the recovery of the resting membrane potential to a point where it is once again excitable is an important consideration from a functional point of view. Three different experiments were done where the level of the insult spans the range of stretch ratios from 1.07 to 1.20 (Fig. 8). In these studies, the intracellular-free calcium concentration was recorded for a period of 10 minutes and the recovery of the cytosol was examined during this interval. Shown on the ordinate is the calcium concentration immediately after injury. The three levels of mechanical stimulation that were selected show a spontaneous recovery at a stretch ratio of 1.07, a residual deficit at a stretch ratio of 1.12, and an irreversible injury at a stretch ratio of 1.20.

It must be emphasized that these studies are conducted *in vitro;* therefore, the interpretation of the data should reflect the relative aspects of the results, as opposed to the absolute numerical values. However, this study shows that the degree of mechanical injury to the axon influences the magnitude of the calcium insult and the time course of the recovery phase. This observation is not unlike the clinical aspects of cord neurapraxia regarding the duration of the neurologic changes that accompany the event.

The effects of mechanical deformation of the axon membrane lead to an alteration in membrane permeability as a

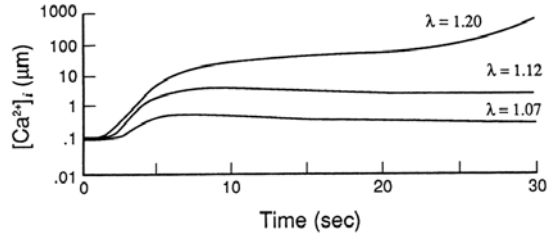


Figure 8. With excessive axonal stretch (λ = stretch ratio), there is failure of the membrane to recover resulting in an irreversible injury when >1.20.

result of the development of nonspecific defects in the membrane. This phenomenon is dependent on the strain on the membrane and the strain rate with which the loads are applied. This mechanism of injury can produce a broad spectrum of cellular responses. Figure 9 shows the functional relationship between the magnitude of the mechanical strain, expressed as the stretch ratio, and the peak values of the intracellular calcium changes after the injury. This curve is divided into five regions that are believed to represent the approximate ranges of stretch ratio that delineate the physiologic changes associated with the ultimate outcome of the experiment. These ranges labeled A through E are defined as follows: (A) The axon will spontaneously recover quickly with no residual deficit. (B) The axon will recover, but the time course of recovery is prolonged, and there will be no residual deficit. (C) The axon will attempt to recover, but there will be a residual deficit, and the ultimate outcome of the recovery will depend strongly on the ability of the cell to pump calcium. (Metabolic factors will influence this outcome strongly.) (D) The axon is injured irreversibly by the initial calcium insult, and eventually will die (Fig. 10). (E) The axon will fail structurally as a result of the mechanical deformation.

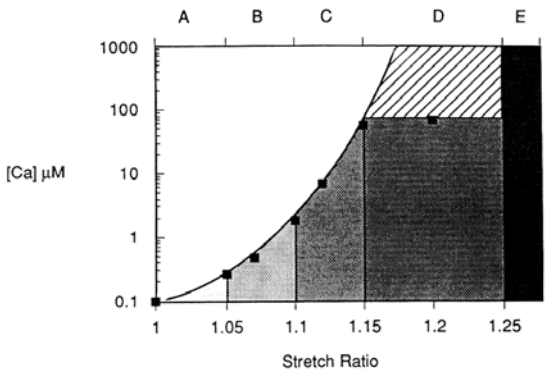


Figure 9. The functional relationship between the magnitude of mechanical strain expressed as the stretch ratio and the peak values of the intracellular calcium concentrations.

In addition to the immediate and direct effect of mechanical deformation on the cytosolic calcium concentration within the axon, the authors have shown that high strain rate elongation of isolated venous specimens elicits a spontaneous constriction: the decrease in vessel diameter as a function of the maximum strain (Fig. 11). This mechanically induced vasospasm has the effect of altering blood flow in various regions as a function of the level of vessel stretch.

The authors believe that the ultimate outcome for the neural tissue will depend synergistically on the level of calcium introduced into the cytosol and the degree to which the metabolic machinery of the cell may be compromised by regional reduction in blood flow. As the energy requirement of the

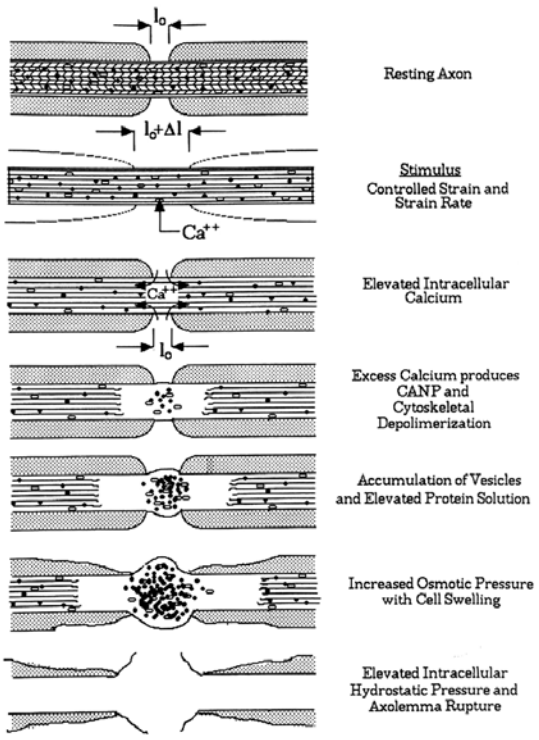


Figure 10. Schematic representation of the effects of elevated intracellular calcium concentration on cell viability. Specifically, elevated cytosolic-free calcium in excess of 50 micromolar will result in calcium activated neutral protease (CANP) that can damage protein structures of the cell.

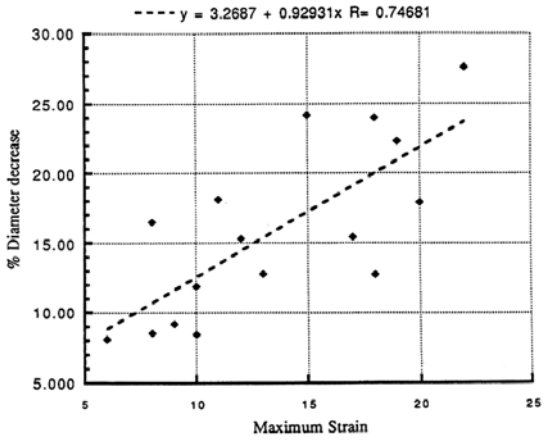


Figure 11. Determinations showing that a high strain rate elongation of isolated venous specimens results in spontaneous venal contraction.

calcium pumps is depleted, the result is an accumulation of cytosolic calcium, which one may think of as a shift of the curve presented in Figure 9 to the left.

Intact squid axons have been subjected to variable strain rate uniaxial elongation in an *in vitro* system that permits detailed electro-physiologic analysis. These experiments showed a mechanically induced and spontaneously revers-

ible depolarization that is dependent on the rate and magnitude of the applied stimulus. The studies indicated that a low rate of deformation produces only a small reversible depolarization. However, as the rate of loading is increased, the magnitude of the depolarization and the recovery time to the original resting potential increase in a nonlinear fashion. To be noted, the rate of loading of the squid axon, being in the order of 8 to 10 ms, correlates with kinematic analysis of cervical spine injuries resulting in quadriplegia. Also, current laboratory studies indicate that the unconstrained axon model is comparable with the constrained cervical cord as far as elongation or stretch and the threshold for tissue response is concerned.

Discussion

Athletic trauma to the cervical spine can result in complete disruption of cord function that may be reversible, incompletely reversible, or irreversible. On the basis of the epidemiology of cord neurapraxia, histopathologic analysis of stretch deformation of the isolated axon, and analysis of the epidemiology and pathomechanics of cervical spine injuries resulting from tackle football, insight into several parameters contributing to the final outcome of cord injury have been identified.

The mechanical effect of energy input on neural elements resulting in reversible and irreversible injury have been presented using the squid axon model. An understanding of the engineering principle, that a substance, such as the spinal cord, which has a low modulus of rigidity responds to bending, shear, and compression with resulting tensile strain, is essential: Apply a load to the spinal cord (compress), and at the site of energy input, the individual structural elements will be lengthened and placed under tension.

Data obtained from the squid axon model indicate that recovery or lack thereof to mechanical deformation in tension is directly proportional to concentration of intracellular calcium which in turn is directly proportional to the amount and rate of tension (stretch) applied.

Correlation of clinical data with the laboratory studies suggests that there are three histopathologic states that result from mechanical deformation of neural structures: (1) submaximal elastic deformation resulting in transient aberration of membrane permeability resulting in increased intracellular calcium without anatomic disruption and complete resumption of normal physiologic function; (2) maximal mechanical elastic deformation with excessive concentrations of intracellular calcium resulting in irreversible cellular injury with residual deficit or actual cell death (Fig. 10); (3) mechanical stretch resulting in functional plastic deformation, structural injury, and irreversible neurologic deficit.

On the basis of the data presented, parameters characteristically associated with cord neurapraxia and transient quadriplegia, a completely reversible lesion, are developmental narrowing of the cervical spine at one or more levels. Cord deformation must occur rapidly and is attributable to a hyperflexion mechanism. Disruption of cell membrane permeability results in an increase in intracellular calcium <50 micromolars. Spinal stability is not disturbed, the cell anatomy is preserved, and the deleterious affects of local anoxia secondary to venous spasm do not impede recovery of axonal function.

One characteristic of a cervical cord lesion with incomplete reversibility is relative instability, such as seen with subluxation or unilateral facet dislocation where the cord undergoes maximal elastic deformation. It is proposed that lack of full recovery is attributable to prolonged duration of deformity with local anoxia inhibiting cell membrane function and a reduction of intracellular calcium concentrations. Limited clinical experience indicates that when unilateral facet dislocation is reduced within three hours of injury, significant neurologic recovery can occur.[13, 14]

Irreversible cord injury with permanent quadriplegia results from an axial load mechanism which causes a fracture or dislocation that renders the spine markedly unstable. The cord undergoes functional plastic deformation with anatomic disruption of axonal integrity. Specifically, the studies presented here indicate an axonal stretch ratio of 1.25 or greater with concentrations of intracellular calcium in excess of 50 micromolars. In instances where axonal elements have not undergone plastic deformation with anatomic disruption, recovery is dependent on the deleterious effects of local anoxia on the cells' ability to remove calcium. This, as indicated, also is dependent on the duration of deformation or time from injury to reduction.

Correlating the permanency of neurologic impairment with type and extent of deformation, elastic or plastic, and the degree of spinal instability reveals an interrelationship between these three factors. Specifically, submaximal elastic deformation resulting from the pincer mechanism in a stable spine with developmental narrowing will result in a transient neurologic episode with immediate complete recovery. Spinal injury resulting in subluxation or unilateral facet dislocation that was reduced promptly explains the significant neurologic recovery observed in several patients previously reported in this series.[12, 13] Complete permanent quadriplegia results from spinal injury with marked instability and functional plastic deformation of the cord and irreversible anatomic disruption of the neural elements.

Current and Potential Clinical Management Implications

These observations support the concept that acute spinal cord injury with concomitant subluxation and dislocation should be reduced promptly. The recent report of Bracken et al.[1] clearly documents the efficiency of methylprednisolone in management of acute spinal cord injuries. These observations suggest the possible efficiency of other pharmacologic agents. Specifically, agents with properties that would increase vasodilatation and local blood flow and counteract the effects of local cord anoxia, and agents that could con-

ceivably enhance the removal of intracellular calcium, would be of potential benefit.

Conclusions

The observations described here indicate that in the otherwise normal cervical spine of the athlete, the occurrence of a permanent neurologic deficit occurs characteristically in the presence of instability. Thus, it is a function of at-risk playing techniques, such as spear tackling, and is independent of spinal canal diameter. Most important, it is emphasized that in many, if not most, instances of acute spinal injury, disruption of cord function is a result of the effects of local cord anoxia and the increased concentrations of intracellular calcium. The authors propose that the implementation of therapeutic measures that restore blood flow and reduce the pool of intracellular cytosolic calcium will increase neurologic recovery.

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Temple Pearls

Surgical Technique for Robotic-Assisted Total Hip Arthoplasty

Kate Harper, MD; Easwaran Balasubramanian, MD

Department of Orthopaedic Surgery, Temple University School of Medicine, Philadelphia, PA

Introduction

Total hip arthroplasty (THA) remains one of the staples of orthopedic surgery, with excellent reported outcomes. There are multiple factors that have the potential to influence the short and long term outcomes of THA including patient characteristics, surgical approach and implant features and positioning. One of the most vital aspects to a successful total hip arthroplasty is optimal placement of the acetabular component. Ideally, the acetabular cup should be placed between 35–45° inclination and 25° anteversion to closely resemble the natural anatomy and minimize dislocation risk, particularly with a posterior approach. The Robotic Arm Interactive Orthopedic System total hip arthroplasty employs the use of stereotactic surgery in order to ensure accurate placement of the acetabular component. This in turn reduces potential for implant wear, dislocation and impingement, and ensures limb lengths remain equal in patients.

Pre-Operative Planning

CT scanning of the patient is an imperative part of the pre-operative planning process for robotic assisted THA. When positioning for the CT scanner, attempts should be make to minimize pelvic obliquity through the following measures: align both ankles and both knees, ensure patient is in true supine position by palpating the anterior superior iliac spines and comparing relative height above the CT scanner bed, and align the longitudinal axis of the body with longitudinal axis of CT scanning bed. When scanning the pelvis and proximal femur, there should be 0.5–1.0 mm of spacing without overlap or gapping. Axial slices at a 1:1 pitch are performed using a helical scanning system. The scan includes the entire bilateral pelvis and at least 180 mm below the lesser trochanter on the femur.

Instrumentation and Special Equipment

Following acquisition of the CT pelvis and hip, a schematic preoperative plan is designed for optimal limb length, acetabular cup orientation and size. This plan is uploaded into the robotic system and used on the day of surgery. The unit used at Temple is the MAKO® robotic hip system (MAKOplasty total hip application; MAKO Surgical Corporation, Fort Lauderdale, FL, USA), which uses a Restoris® total hip implant in conjunction with their robot. This system uses a robotic-assisted computer navigation system that uses RIO (Robotic Arm Interactive Orthopedic System) for reaming the acetabulum and acetabular component placement.

In order to achieve optimal alignment, the system requires the placement of an array in the iliac crest that is used as a reference point to maintain orientation despite changes in patient position (Figures 1 and 2). Additional hand-held probes are provided for referencing along the acetabulum and femur as well as referencing the robotic reamer (Figure 3). Finally, an EKG lead is used at the level of the superior patellar pole for measuring of leg length (Figure 4). Acetabular and femoral checkpoints are placed intraoperatively to allow for leg length as well as cup orientation measurements.

Positioning

The patient is placed in a lateral position with Stulberg hip clamps on the anterior pubic symphysis and sacrum. A single Stulberg must be used on the anterior pelvis during a MAKO total hip (compared to a double Stulberg in traditional THA) so as to not interfere with the position of the pelvic array. An

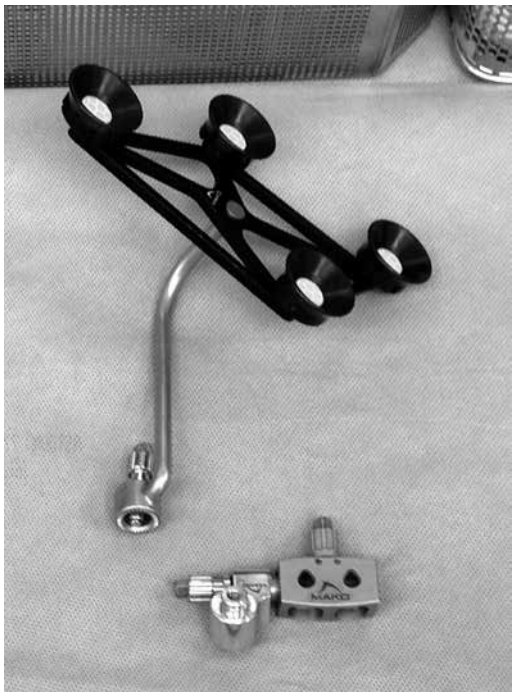


Figure 1. Clamp and tracker placed onto pelvic threaded pins.

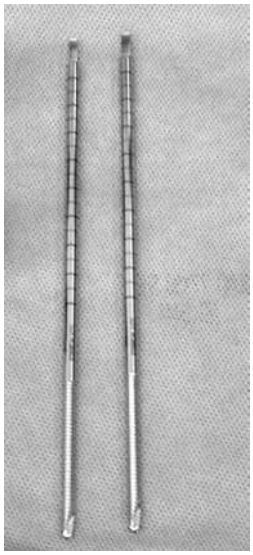


Figure 2. Threaded pins placed into iliac crest for stabilization of the pelvic array.

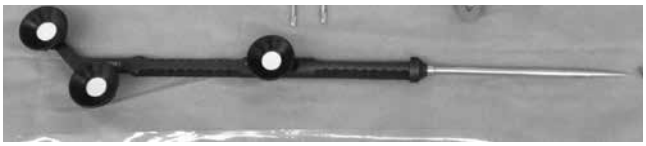


Figure 3. Handheld probe used for GPS navigation.

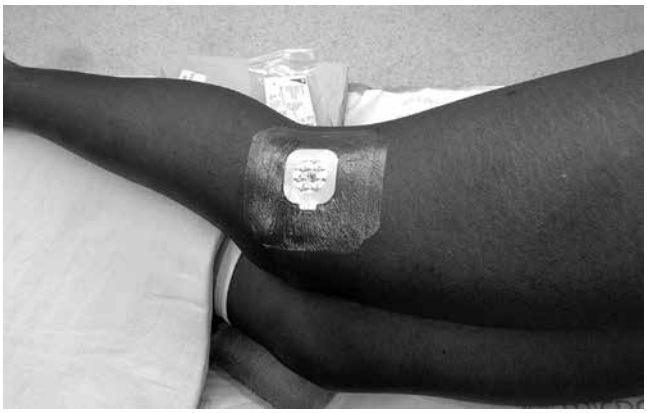


Figure 4. EKG lead placed onto the lateral femoral condyle for leg length referencing.

EKG lead is placed in line with the superior pole of the patella along the lateral femoral condyle as a reference point for leg length measurements (Figure 4). The well leg is placed in a gel trough and a sequential compression device is placed on the well leg for DVT prophylaxis. An axillary bump is used to prevent brachial plexus palsy, and the up arm is placed across the table on a well-padded arm board. The leg is the prepped and draped in the usual sterile fashion (Figure 5).

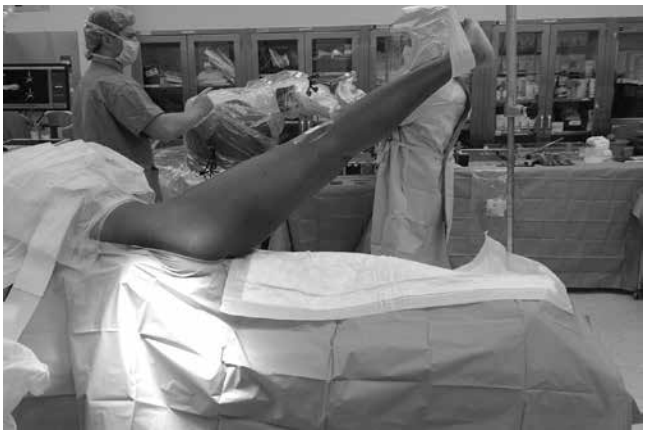


Figure 5. Operative leg being prepared for prepping and draping in usual fashion.

Approach and Surgical Technique

A 2–3 cm incision is made at the level of the iliac crest on the operative side. Blunt dissection with a hemostat is performed to expose down to bone. Two threaded pins (Figure 2) are placed parallel to one another into the thickest portion of the iliac crest. Then, a specially designed clamp is placed on both pins (Figure 1). The pelvic array is then attached to this clamp and all attachments are locked into place (Figure 6). This pelvic array remains in place throughout the entirety of the case and extreme care must be taken to not disturb the position. If the array moves during the case, the GPS landmarking will have to be restarted.

A standard posterior hip approach is utilized. As soon as the bony landmarks are exposed, robotic markers are placed on both the femur (just distal to the greater trochanter) and the acetabulum (superior to the acetabular rim at approximately the 12 o'clock position on the cup). These markers remain in place throughout the case and are used as additional reference points for making bony cuts.

Retractors are placed to isolate the femoral neck for the first bone cut. The lesser trochanter (LT) must be visualized through appropriate dissection of the soft tissue. Once the LT is visualized, measurements are made for the femoral neck cut. These are then navigated and confirmed with the preoperative plan created by the MAKO robotic system. This measurement is then confirmed on the actual patient and corresponded to the imaging. Once an agreement is reached regarding the neck length cut, the femoral cut is marked and performed.

Following the femoral cut, attention is turned to the acetabulum. Once all soft tissue is removed and adequate visualization of the acetabular cup is achieved, the GPS marking system is begun. It is important to note that osteophytes are not removed as part of the debridement process as this will negatively affect the navigation mapping system at a later step. The pelvic checkpoint is first registered using a handheld probe (Figures 7 and 8). Thirty-two points on the ace-

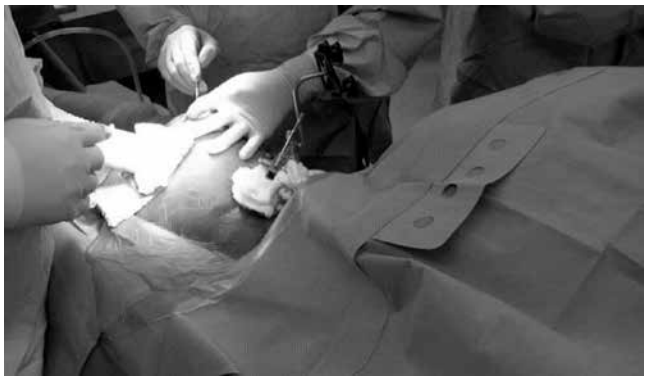
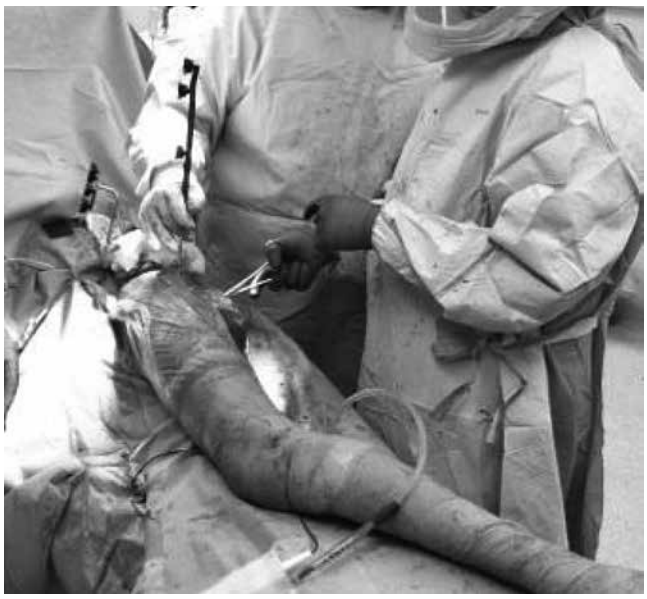
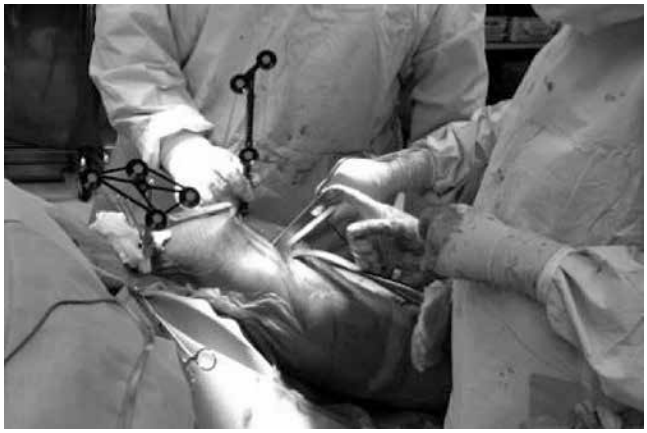


Figure 6. Pelvic array in position with threaded pins in the iliac crest and the tracker attached via specialized clamp.



Figures 7 and 8. Handheld probe being used to register the acetabular checkpoint in preparation to begin GPS mapping of the acetabulum (above and below).



tabulum are identified by the software for the registration process and are touched using the probe to the bone surface (Figure 9). Verification is then done by touching the probe to 8–10 points defined on the surface of the acetabulum in order to ensure correlation between digital marker with anatomical location (Figure 10). These points are then referenced to the CT, and the robot calculates a level of error in marker distance. If error is <0.5 mm, then the program may proceed to the next step.

Acetabular reaming follows GPS mapping. Using the MAKO system, there is no need to use multiple reamers to achieve final socket size, as appropriate cup size is predetermined with the CT program. Therefore, this system allows the surgeon to ream only once with the final planned size. In preparation for reaming, an array is attached to the robot, which is then registered to the computer system. The reaming arm is then attached, and a handheld probe is used to register the independent reaming arm to the computer. The reamer is engaged into the cup and depth, inclination angle and version angle are measured by the computer. Once the reamer is in an ideal position, it is locked into the cup and reaming can begin (Figure 11). The computer tracks depth and reaming concludes when the appropriate depth in all planes has been achieved. While reaming, the computer provides real-time feedback regarding inclination/version angle and depth, so minor adjustments can be made. This is illustrated using a 3D model of the bone that is projected onto the computer screen (Figure 12). The acetabular cup is then attached to the robotic arm which ensures that the inclination and anteversion is within 3° of the plan. Once in the desired position, the robotic arm is locked in place, and the cup is implanted. Depth is measured during insertion of the cup to ensure good bony contact following reaming. A screw may be placed based on surgeon discretion for more secure cup fixation. Finally, a standard acetabular liner is secured into the cup.

Attention is then turned back to the femoral component. Retractors are placed to isolate the canal, and the leg is flexed, abducted and internally rotated for a head-on view of the canal. First a box-cutter is used to lateralize the femoral canal reaming. Next a canal finder is used to broach into the canal. Finally, reaming is commenced in a sequential fashion until the appropriate size and anteversion is achieved. Following that, increasing sized broaches are used to further lateralize the stem and achieve the appropriate femoral version. With the final broach in place, a trial neck and head is attached and the hip is reduced and put through a full range of motion to assess stability. The femoral checkpoints are then registered to allow the software to determine ideal leg length and offset.

Once the appropriate sized neck, offset and head has been decided upon, the trial components are removed and the canal is irrigated. Then the permanent, press-fit femoral step is placed and the femoral head is applied. The hip is reduced and again brought through a full range of motion. Final measurements are taken with the array and computer screen displays the final leg length and offset change compared to the preoperative plan (Figure 13).

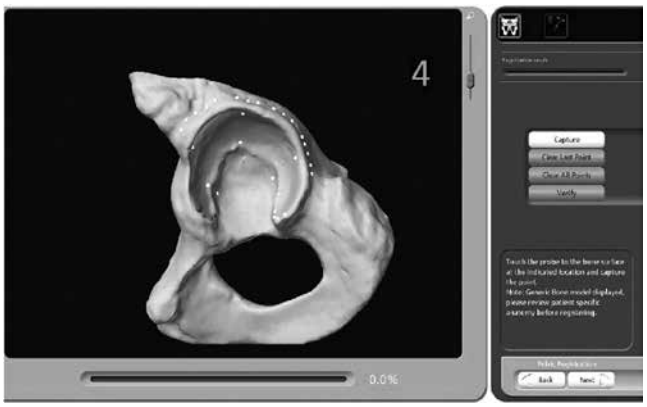


Figure 9. Schematic of the 32 verification points required by the MAKO robot for proper acetabular GPS mapping.

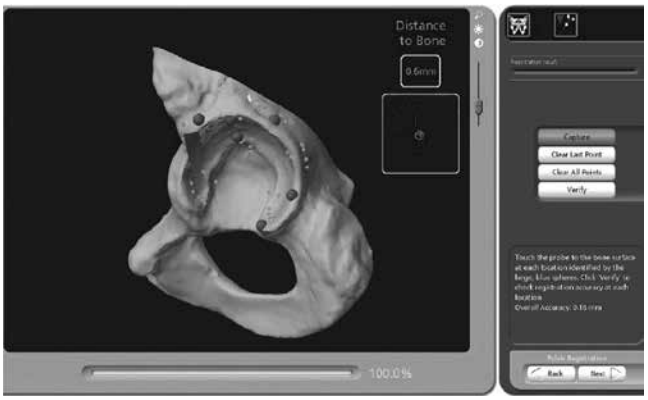


Figure 10. Verification process ensuring that previous mapped points line up anatomically with the patient.

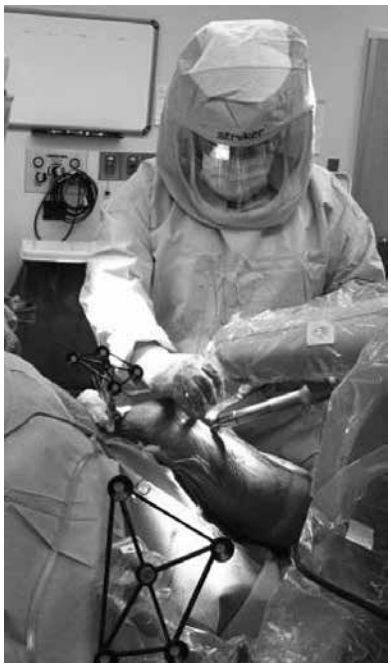


Figure 11. Reaming is begun with the MAKO robot with both the pelvic and robotic arrays visualized. Reaming will be tracked to ensure proper medialization, inclination and version angles.

Following the implantation of all hardware, the femoral and acetabular checkpoints are removed. A subsequent layer-by-layer closure is performed with careful repair of the short external rotators to their anatomic locations. The pelvic array in the iliac wing may be removed at any point in the closure once final measurements are performed.

Figure 12. A 3D model of the bone that provides real-time feedback regarding inclination/version angle and depth.

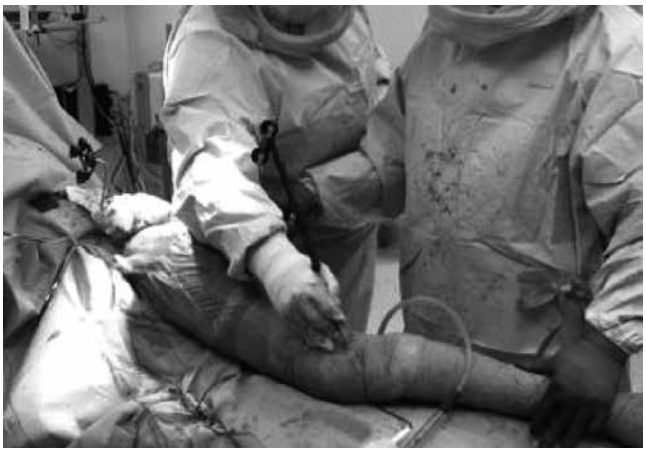


Figure 13. Handheld probe being used to confirm leg length intraoperatively by referencing EKG lead on femoral condyle at the end of the case.

Temple Pearls

Clinical Applications of Negative Pressure Wound Therapy in Orthopaedics

CHRISTOPHER HAYDEL, MD

Department of Orthopaedic Surgery, Temple University School of Medicine, Philadelphia, PA

Introduction

The use of a negative pressure wound therapy (NPWT) is a popular and widely accepted method for maintaining sterility while promoting healing. These benefits are possible via several mechanisms: Increased local perfusion, formation of granulation tissue, decreased bacteria load of the wound with regard to gram negative organisms, decreased venous congestion, decreased local edema, and increasing the mitotic rate of keratinocytes. The indications of NPWT have been expanded to treat "at risk" wounds that have been primarily closed. The benefits include decreased tension on sutures/staples, decreased wound drainage, more uniform skin edge opposition to prevent hematomas and seromas, and increased force necessary to separate the wound edges.

Special Equipment

The materials need to apply a NPWT dressing are usually prepackaged sterilely (Fig. 1). Included are the suction disk, a black or silver impregnated sponge, and the clear adherent dressing. The white sponge is packaged separately in sterile water. The porosity of the white sponge is significantly less than that of the black sponge. The white sponge is usefully for covering wounds in which vital structures are present (vessels or nerves) or areas where granulation tissue growth is not desired (tendons, bone or joints).

Other useful items include non-adherent petroleum impregnated or oil emulsion dressings to protect the underlying healthy skin from the black sponge. Benzoin is very helpful in maintaining an airtight perimeter seal. Vessels loops can be used to help stretch the skin to decrease the size of the wound.

Application Technique

First, the wound is thoroughly debrided and irrigated (Fig. 2). In this particular patient, a partial wound closure was performed with nylon suture. Because there are no vital structures within the wound bed, the black sponge can be used. The sponge is cut to fit the shape of the wound using scissors or a scalpel. Two vessel loops are tied together at one end. The vessel loops are then secured to the skin edges and the black sponge in a crossing pattern using staples (Fig. 3).

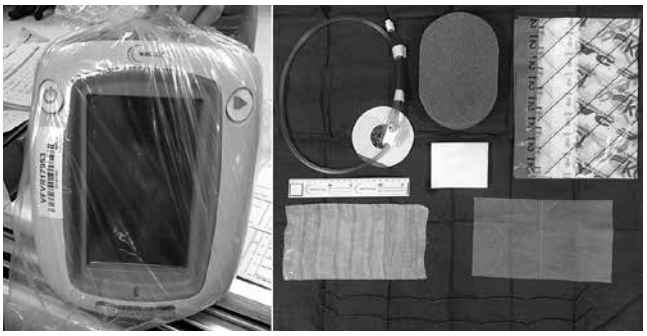


Figure 1. Equipment needed: on the left is the wound VAC machine; on the right, starting at the left upper corner is the VAC suction disc, black/silver and white foam sponges, adherent dressing, ruler, petroleum impregnated and oil emulsion non-adherent dressings, and vessel loops.

Figure 2. Lateral leg fasciotomy wound. This patient has a proximal tibia fracture which was complicated by vascular injury necessitating repair and fasciotomy. The wound bed is clean and the muscle is healthy. The wound vac provides a closed sterile dressing while promoting wound healing.

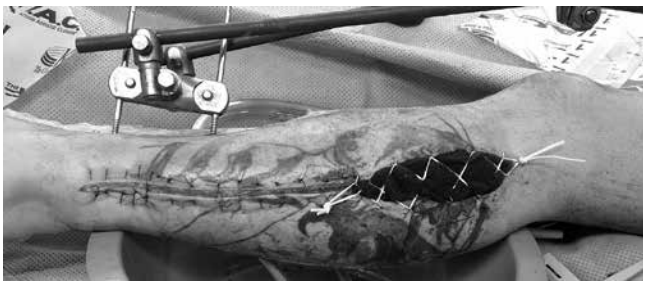


Figure 3. After surface debridement and irrigation, the wound is partially closed. The black vac sponge is cut to fit the wound. Vessel loops aid in bringing the skin edges closer together.

Once the black sponge is secured, the adherent dressing that is packaged with the sponge is cut into strips to ease its application. Non-adherent dressing (oil emulsion) is placed over the closed portion of the wound to protect the underlying healthy skin (Fig. 4). If the area of the black sponge in the wound is smaller in diameter than the suction disk, a second black sponge must be used to protect the skin. To decrease the width of this sponge, a scalpel can be used to cut it in half (Fig. 5).

After all of the components of the dressing are prepared, the wound edges are dried with a lap sponge and Benzoin is applied to the surrounding skin to help achieve an airtight seal. A thin strip of black sponge is placed over the closed portion of the incision making sure to keep the non-adherent dressing in between the sponge and the skin. The adherent dressing supplied with the vac sponge is placed over the entire area of the wound. A dime to quarter-sized hole is cut in the center of the wound. The black sponge that is to protect the skin from the suction disk is placed over this hole and sealed with more adherent dressing. A hole is cut over the protective black sponge and the suction disk is applied over that hole and connected to the NPWT machine and suction is initiated (Fig. 6). The dressing is then checked for leaks.

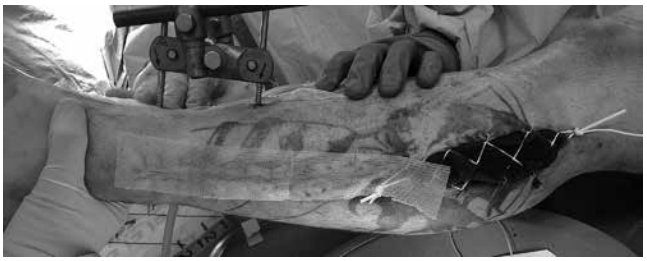


Figure 4. To protect the adjacent skin edges of the wound, a non-adherent dressing is applied to act as a barrier between the skin and the vac sponge.

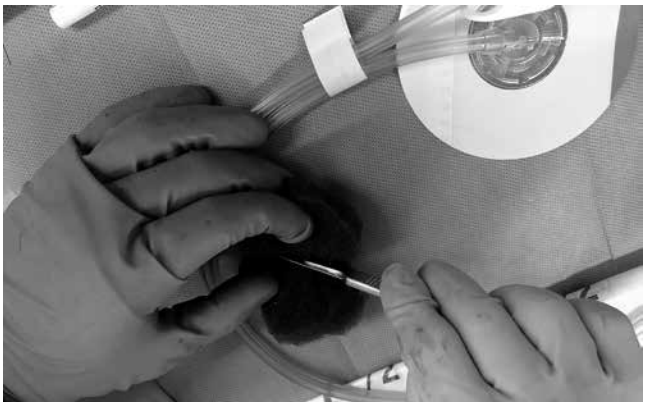


Figure 5. If the width of the vac sponge in the wound is smaller than that of the suction disc, a protective sponge must be used. Often the sponge may be too thick so a scalpel can be used to cut the sponge in half.

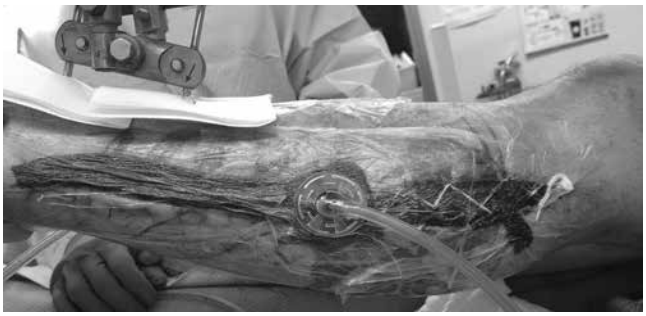


Figure 6. Complete dressing. A thin strip of black sponge is placed over the non-adherent dressing in the area of the closed incision (left). Benzoin is applied to the area surrounding the wound and the dressing is sealed. The suction disc is placed directly over the circular protective sponge in the middle of the wound.

If there is tendon, bone, cartilage, nerve or blood vessels in the wound bed, the white sponge should be used. Ideally, neurovascular bundle should be protected with overlying muscle (Fig. 7). Partial closure is performed and non-adherent (petroleum impregnated) dressing is applied. The white sponge is cut to fit the shape of the wound (Fig. 8) and secured into place with vessel loops (Fig. 9). Sterile gauze is then placed over the closed portion of the wound ensuring that the non-adherent dressing remain in between the skin and gauze. Benzoin is applied to the surrounding skin and the wound is then sealed with the adherent dressing packaged with the black sponge (Fig. 10). A circular protective black sponge is fashioned with a scalpel or scissors. A hole is cut over the adherent dressing in the middle of the wound and the protective black sponge is secured into place over the is hole with more adherent dressing. Another hole is cut over the protective black sponge and the suction disk is secured into place. Suction is then initiated (Fig. 11).

Summary of Tips

1) Use white sponge when tendon, bone, cartilage or neurovascular bundles are present within the wound bed. Neurovascular structure should be protected with overlying muscle.

2) The use of oil emulsion or petroleum impregnated non-adherent dressing is encouraged when applying NPWT to incisions.

3) Benzoin can be used to achieve an airtight seal.

4) The adherent dressing that is packaged with the black sponge can be cut into strips to ease its application, especially around the pins of an external fixator.

5) Vessel loops can be used to apply gentle tension on the skin if primary closure is the goal.

6) If the sponge in the wound is smaller in diameter than the suction disk, a second black sponge should be used to protect the surrounding skin from the suction disk.

7) If the black sponge is too thick, it can be cut in half using a scalpel.

Figure 7. Medial leg fasciotomy wound. This is the medial leg wound of the same patient. A vascular repair was done at the time of external fixation. The musculature of the deep and superficial posterior compartments was used to cover the repair.

Figure 8. Non-adherent dressings are applied to the closed portion of the wound. The white, less porous sponge is used to protect the vascular repair.

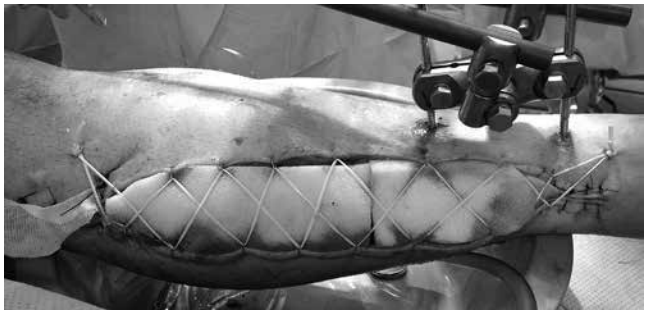


Figure 9. Vessel loops are used to promote skin advancement.

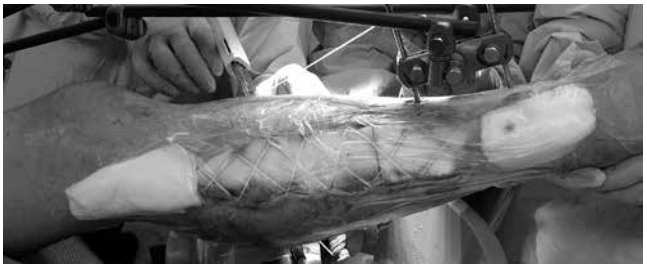


Figure 10. Sterile gauze is placed on closed portions of the incision on top of the non-adherent dressing. Benzoin is placed on the skin surrounding the wound and then the dressing is sealed.

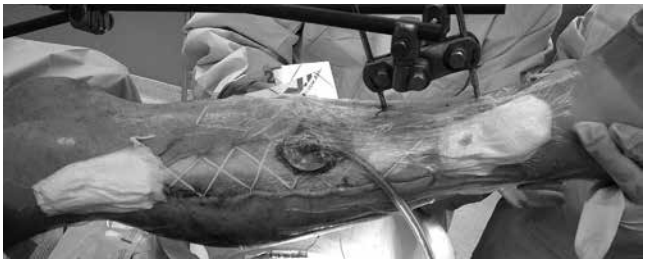


Figure 11. A protective circular black sponge is placed underneath the suction disc to protect the healthy skin.

Original Research

Emerging Multi-Drug Resistance of Methicillin Resistant *Staphylococcus Aureus* in Hand Infections

Rick Tosti, MD;[1] Brian T. Samuelsen, MD;[1] Samantha Bender, BS;[1]
John R. Fowler, MD;[1] John Gaughan, PhD;[1] Alyssa A. Schaffer, MD;[1] Asif M. Ilyas, MD[2]

[1]*Department of Orthopaedic Surgery and Sports Medicine, Temple University School of Medicine;*
[2]*Rothman Institute, Thomas Jefferson University, Philadelphia, PA*

Abstract

Background: Methicillin-resistant *Staphylococcus Aureus* (MRSA) has been the most commonly identified pathogen in hand infections at urban centers, but the evolving antibiotic sensitivity profiles of MRSA are not known. The purposes of this study are to determine if multi-drug resistance in MRSA is emerging and to provide current recommendations for empiric antibiotic selection for hand infections in endemic regions.

Methods: An eight-year longitudinal, retrospective chart review was performed on all culture-positive, hand infections encountered by an urban hospital from 2005–2012. The proportions of all major organisms were calculated for each year. MRSA infections were additionally analyzed for antibiotic sensitivity.

Results: A total of 683 culture-positive hand infections were identified. Overall, MRSA was cultured in 49% of cases; the annual incidence peaked at 65% in 2007. Over the study period, MRSA was universally resistant to penicillin, oxacillin, and ampicillin. Clindamycin resistance significantly increased approaching 20% by 2012 ($p = 0.02$). Levofloxacin resistance linearly increased from 12% to 50% ($p < 0.01$). Resistance to trimethoprim-sulfamethoxazole, tetracycline, gentamycin, and moxifloxacin were only sporadically observed. Resistance to vancomycin, daptomycin, linezolid, and rifampin were not observed.

Conclusion: Significant increases in resistance to clindamycin and levofloxacin were observed in recent years, and empiric therapy with these drugs may have limited efficacy especially in urban centers.

Level of Evidence: Prognostic Level II

Introduction

Staphylococcus aureus is the most commonly cultured organism in hand infections.[1–6] Traditional management of acute hand abscesses has been incision and drainage followed by a regimen of beta-lactam antibiotics such as methicillin, nafcillin, or cephalosporins.[1, 2] However, shortly following the introduction of methicillin in the 1960s, emerging strains of methicillin-resistant *Staphylococcus aureus* (MRSA) were reported in the literature as first occurring in the nosocomial setting and more recently in the community setting.[3–10] As MRSA has been more closely monitored, studies have noted associations with increased treatment failures, inpatient lengths of stay, and healthcare costs.[4, 7, 8, 11, 12] However, a few recent reports have suggested that treatment failures, costs, and lengths of stay may be equivalent to non-MRSA infections if an appropriate empiric antibiotic is selected.[4, 6]

As a result of multiple reports showing a greater prevalence of MRSA in urban settings, the Centers for Disease Control have recommended against selecting a given empiric antibiotic if the local resistance is greater than 10 to 15%, and many institutions have now subsequently excluded beta-lactams from empiric treatment.[4, 14, 15] However, the efficacy of contemporary empiric drug selections is not known and the possibility of growing multi-drug resistance exists, as alternative antibiotics are becoming more commonly selected to cover MRSA. The purposes of this study are to determine if multi-drug resistance in MRSA is emerging and to provide current evidence that clinicians can reference for empiric inpatient or outpatient treatment of hand infections.

Materials and Methods

A retrospective study was performed at an urban academic medical center over an eight-year period from January 1, 2005 through December 31, 2012. After approval was obtained from the institutional review board, all hand infection cases encountered by the emergency room, outpatient office, or inpatient wards were reviewed. We identified subjects by searching International Classification of Disease Ninth Revision codes relevant to hand infections, including codes 681.00, 681.01, 681.02, 682.4, 727.05, 727.9, 883.00, 883.1, 882.01, and 882.00 (cellulitis, abscess, tenosynovitis, and open wounds of the fingers and hands) but only analyzed those between the ages of 18 and 89 with a culture-positive hand abscess. Demographic and laboratory data was collected from medical records. Patients with multiple culture results in the same admission were also identified so that the same organism was not counted twice. Infections were con-

sidered nosocomial if records indicated a history of a surgical procedure, dialysis treatments, catheterizations, hospitalization, or nursing home stays within a year prior to admission.

We calculated the annual frequencies of culture positive infections for the three most common isolates (MRSA, methicillin-sensitive *Staphylococcus aureus* (MSSA), and *Streptococcus Pyogenes*) and polymicrobial infections. A polymicrobial infection was defined as an infection in which more than one organism was identified; these were not considered mutually exclusive with the frequencies of other organisms. MRSA infections were then further analyzed for their antibiotic sensitivity profiles. Isolates were assessed for yearly resistance rates to ampicillin, oxacillin, penicillin, clindamycin, erythromycin, levofloxacin, moxifloxacin, trimethoprim-sulfamethoxazole, tetracycline, gentamycin, rifampin, daptomycin, vancomycin, and linezolid. We also performed a post-hoc calculation for MSSA resistance to clindamycin and levofloxacin.

Statistical Analysis

Continuous variables were assessed with a linear regression model. Percentages of categorical variables and drug resistances were assessed for a significant increasing or decreasing trend with the Cochrane-Armitage trend test. Statistical significance was defined as a probability value (p-value) less than 0.05.

Source of Funding

No external source of funding was used for this study.

Results

Overall Demographics

A total of 683 culture positive hand infections were identified over the 96-month collection period. The average patient age was 41.4 years, and 56% were male; the average white blood cell count was 10.8 x 103/μL. Trauma and intravenous drug use (IVDU) were the most common etiologies representing 75% and 21% of cases respectively; bite wounds were causative in 3% of cases. The annual frequency of comorbidities was consistent over the study period for diabetics and human immuno-deficiency virus positive individuals, which comprised 14.6% (range 12.6–28.6% per year) and 3.3% (range 0–5.7% per year) of the population, respectively. However, IV drug users represented a larger percentage of people with culture positive hand infections over the time span of the study (13.8% in 2005 and 37.2% in 2012 ($p < 0.01$). Patients with a history of cancer or nursing home residence were each noted in approximately 2% of all hand infections. MRSA infections were considered community acquired in 76% of cases and nosocomial acquired in 24% of cases.

Cultured Organisms Per Annum

Overall, MRSA was the most commonly cultured organism followed by methicillin-sensitive *Staphylococcus aureus* (MSSA) and then Group A *Streptococcus* (CME). A variety of organisms were found in lesser frequencies (Table 1). MRSA was also the most common pathogen identified during every year of the study, and it was cultured in the following proportions: 53% in 2005, 63% in 2006, 65% in 2007, 43% in 2008, 47% in 2009, 45% in 2010, 37% in 2011, and 42% in 2012 (Figure 1). The number of MSSA infections fluctuated inversely with MRSA reaching a nadir in 2006 and 2007 but increasing to a peak of 27.5% in 2012. A significant increase ($p < 0.01$) was observed in the percentage of polymicrobial infections, as they comprised 7% in 2005, 16% in 2006, 13% in 2007, 30% in 2008, 31% in 2009, 36% in 2010, 37% in 2011, and 25% in 2012. *Streptococcus Pyogenes* infections was cultured in 6–17% of cases per year.

For intravenous drug users and diabetics with hand infections, MRSA remained the most common organism each year reaching a peak incidence in 2007 as well. IV drug users had the highest annual percentages of MRSA of all subgroups. Diabetic patients with hand infections commonly had polymicrobial infections (range 22–50% per year) but this percentage did not seem to be increasing over time. IV drug abusers and people without co-morbidities who had hand infections showed increases in polymicrobial infections over time ($p < 0.01$). IV drugs users had polymicrobial cultures in 8% of cases in 2005, increased to 35% in 2010, and declined to 20% in 2012.

Table 1. Cultured Organisms from Acute Hand Infections 2005–2012

Most Common Organisms			
MRSA	(49%)	Polymicrobial	(20%)
MSSA	(21%)	Streptococcus pyogenes	(8%)
Less Common Organisms			
Acinetobacter calco-baumannii		Mycobacterium avium complex	
Aspergillus species		Pastuerella multocida	
Bacillus species		Porphyromonas gingivalis	
Candida albicans		Proteus mirabilis	
Candida parapsilosis		Pseudomonas aeruginosa	
Citrobacter freundii,		Serratia marcescens	
Diptheroid species		Staphylococcus (coagulase-negative)	
Eikenella corrodens		Staphylococcus epidermidis	
Enterobacter cloacae		Streptococcus (alpha-hemolytic)	
Enterococcus faecalis		Streptococcus anginosus	
Escherichia coli		Streptococcus contellatus	
Haemophilus parainfluenzae		Streptococcus (groups B,C,F, and G)	
Klebsiella pneumoniae		Streptococcus intermedius	
Lactobacillus		Streptococcus mitis	
Leclercia adecarboxylata		Viellonella Species	

Staphylococcus Aureus Antibiotic Sensitivity Profiles Per Annum

MRSA resistance to clindamycin significantly increased over the eight-year period ($p = 0.02$); the three highest per-

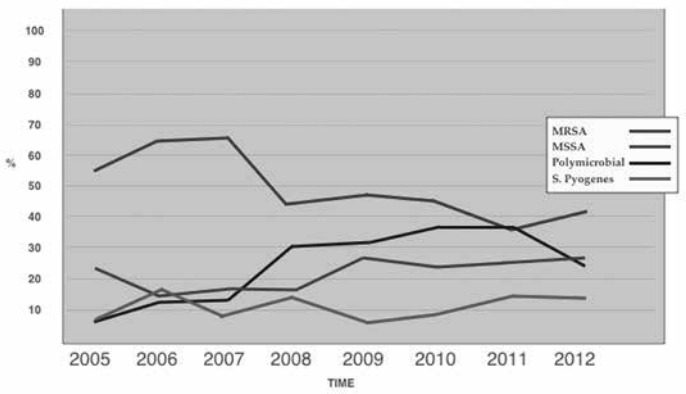


Figure 1. The annual percentages of MRSA, MSSA, polymicrobial organisms, and *S. Pyogenes* cultured in acute hand infections.

centages were found between 2010 and 2012 as resistance approached 20% (Table 2) (CME). MSSA resistance to clindamycin did not increase significantly over the study period but was present in 11% of cultures overall (range 8–12% per year). MRSA resistance to levofloxacin linearly increased over eight years from 12% to 50% ($p < 0.01$). MSSA resistance to levofloxacin did not significantly increase over the study period but was present in 12% of cultures overall (range 9–17% per year). Over the eight years studied, MRSA was uniformly resistant to ampicillin, oxacillin, and penicillin G; erythromycin resistance was also common and ranged from 85–100% per year. MRSA was only sporadically resistant to tetracycline, moxifloxacin, trimethoprim-sulfamethoxazole, and gentamycin. No resistance was observed for rifampin, vancomycin, linezolid, or daptomycin (CME).

Discussion

MRSA has gained attention in the literature and in popular media as a growing concern especially in urban environments, as several reports have estimated a high proportion in hand abscesses ranging from 34% to 73%.[4, 12, 14–19] Our results agree with prior studies and indicate that MRSA may be found in approximately half of all urban hand infections in recent years. Moreover, increased costs, failures in treatment, and increased mortality have also been associated with MRSA in endemic regions;[4, 6–9, 11, 12] however, multiple studies from our institution have shown that equivalent lengths of stay to non-MRSA infections can be achieved if appropriate empiric antibiotic coverage is selected.[4, 6] As MRSA continues to predominate in urban communities, we sought to further characterize its antibiotic sensitivities in order to optimize the empiric treatment regimen, reduce treatment delays, and improve cost containment associated with hand infections.

We found that MRSA cultured from hand infections was increasingly resistant to clindamycin and levofloxacin over the eight-year period, while the sensitivity to other antibiotics did not appear to change. In recent years, MRSA resistance to clindamycin has approached 20% at our center. Although not directly answered by the present study, we suspect the increased use of clindamycin to treat MRSA may be contributory. In 2005, we adopted a hand infection algorithm to improve the coverage of MRSA, which largely excluded beta-lactams from empiric treatment of hand infections.[4, 8] Therapeutics such as vancomycin, clindamycin, and trimethoprim-sulfamethoxazole were used with a much greater frequency, and in particular, clindamycin was the most commonly prescribed initial antibiotic for hand infections representing 40–50% of the empiric selections from 2005–2007.

In addition, levofloxacin resistance linearly increased over the past eight years in our study. A report by MacDougall et al. noted a significant association between emerging MRSA infections and quinolone prescriptions in a cross-sectional study of 17 regional US hospitals; the authors suggested that quinolones may be driving a selection process for MRSA, but their conclusions were limited in that the MRSA resistance to quinolones was not known.[20] Although levofloxacin is not commonly prescribed for hand infections, some reputable sources suggest "fluoroquinolones" as an alternative to penicillin-based drugs in the presence of an allergy.[21] Our results suggest that levofloxacin would not be a wise choice in this class, but moxifloxacin, however, appeared to be an effective quinolone with only sporadic cases of resistance observed in this series.

Despite the narrowing of antibiotic choices, MRSA infections still remain consistently sensitive to a number of therapeutics. Tetracyclines, gentamycin, moxifloxacin, and trimethoprim-sulfamethoxazole were only found to be resistant in only a few cases in our study, and no resistance was observed for vanco-

Table 2. Annual Resistance of MRSA to Selected Antibiotics

Resistant	2005	2006	2007	2008	2009	2010	2011	2012	p
Ampicillin	100%	100%	100%	100%	100%	100%	100%	100%	1
Oxacillin	100%	100%	100%	100%	100%	100%	100%	100%	1
Penicillin G	100%	100%	100%	100%	100%	100%	100%	100%	1
Erythromycin	100%	90%	98%	94%	85%	96%	100%	92%	0.59
Levofloxacin	12%	22%	37%	39%	33%	41%	43%	50%	<0.01*
Clindamycin	7.0%	6%	9%	4%	6%	19%	13%	20%	0.02*
Tetracycline	2%	0%	2%	3%	6%	0%	3%	0%	0.97
Moxifloxacin	0%	3%	8%	0%	0%	0%	0%	3%	0.17
Trimeth/Sulfa	0%	0%	0%	0%	4%	5%	3%	0%	0.14
Gentamycin	0%	0%	0%	0%	5%	0%	0%	0%	0.50
Rifampin	0%	0%	0%	0%	0%	0%	0%	0%	1
Vancomycin	0%	0%	0%	0%	0%	0%	0%	0%	1
Linezolid	0%	0%	0%	0%	0%	0%	0%	0%	1
Daptomycin	0%	0%	0%	0%	0%	0%	0%	0%	1

*Significant

mycin, daptomycin, linezolid, and rifampin. Vancomycin intermediate resistance in *S. Aureus* has been sparsely reported in the literature, but to the best of our knowledge, no cases of vancomycin-resistant MRSA have occurred in hand infections.[8] Despite frequent use, vancomycin still remains an effective first line agent for empiric treatment for hand infections.

The present study has several limitations. The retrospective design limits the patients we were able to identify. Additionally, our local prevalence of MRSA may be dissimilar to non-urban medical centers, and our results may not be generalized to other regions. Further, the number of polymicrobial infections may have been overestimated, as some cultures were obtained in a non-sterile environment. We were not able to accurately retrieve the number of cultures obtained by bedside procedures; however, we routinely attempt to reduce contamination during bedside procedures with sterile draping and chlorhexidine-alcohol skin preparation prior to incision.

Infections caused by MRSA have a significant presence especially in urban areas.[22] In our region, MRSA was found in nearly half of all hand infections, and those isolates became increasingly resistant to clindamycin and levofloxacin over the study period. As a result, we would not recommend these drugs as empiric antibiotics to clinicians who practice in endemic areas with a significant prevalence of MRSA. Additionally, the Centers for Disease Control do not recommend antibiotics for empiric therapy that have a regional resistance that exceeds 10% (Figure 2).[13] However, other therapeutics such as vancomycin, tetracylines, moxifloxacin, and trimethoprim-sulfamethoxazole still appear to have potent activity against MRSA. Organisms found in polymicrobial cultures were often sensitive to most antibiotics, and we would not recommend empiric treatment for anaerobic or gram negative bacteria unless specific situations such as bite wounds, aquatic injuries, or severe infections warranted such coverage. In this series, infections caused by bite-wounds were generally susceptible to beta-lactam antibiotics and should be treated with a different protocol. Finally, we would encourage future studies evaluating the efficacy of common empiric antibiotics in other soft tissue and joint infections of the extremities with interval monitoring to ensure relevant and current management recommendations.

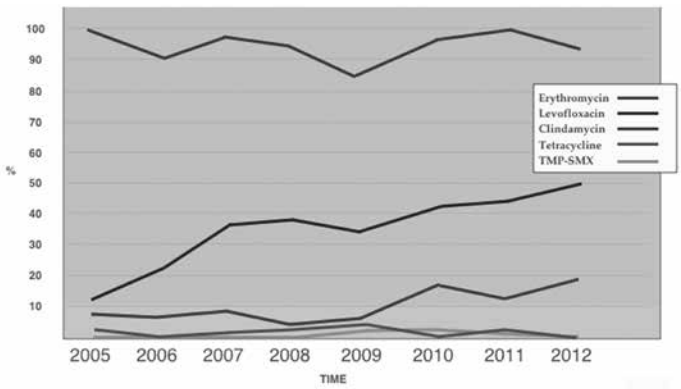


Figure 2. Multi-drug resistance in MRSA by year. The region shaded in red represents an unacceptable resistance level for use in empiric coverage as defined by the Centers for Disease Control. Antibiotics found to have 100% resistance or sensitivity are not displayed.

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Original Research

Risk Factors Associated with Clindamycin-Resistant Methicillin Resistant *Staphylococcus Aureus* in Hand Abscesses

Rick Tosti, MD;[1] Arianna Trionfo, MD;[1] John Gaughan, PhD;[1] Asif Ilyas, MD[2]

[1]*Department of Orthopaedic Surgery and Sports Medicine, Temple University School of Medicine, Philadelphia, PA;*
[2]*Department of Orthopaedic Surgery, Thomas Jefferson University School of Medicine, Philadelphia, PA*

Abstract

Purpose: Recent findings of clindamycin-resistance in hand infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) have been reported. The purpose of this study was to identify risk factors for clindamycin-resistance in acute hand abscesses caused by MRSA.

Methods: A retrospective review of 247 consecutive culture-positive hand abscesses from 2010–2012 was performed at an urban hospital. Historical and laboratory data from patients with abscesses that grew MRSA with and without clindamycin resistance were compared in a multivariate analysis.

Results: MRSA grew on culture from 103 abscesses, and 16% of those isolates were resistant to clindamycin. Multivariate analysis showed that younger age, intravenous drug use, and nosocomial acquired MRSA were significant risk factors for concurrent clindamycin resistance. Patients with a history of intravenous drug use and nosocomial acquired MRSA were respectively 11 and five times more likely to have concurrent clindamycin resistance. History of prior MRSA infection and human immunodeficiency virus were not identified as risk factors.

Conclusion: Patients with a history of intravenous drug use or recent contact with health-care facilities appear to be a potential reservoir for emerging multi-drug resistant MRSA. Selection of clindamycin as an empiric antibiotic should be especially avoided for these groups.

Level of Evidence: Prognostic III

Introduction

Acute abscesses of the hand are a common problem that can potentially lead to irrevocable consequences. Outcomes such as stiffness, fibrosis, sepsis, and amputation can be avoided with prompt recognition and treatment, which usually consists of antibiotics and surgical drainage.[1] Abscesses caused by antibiotic resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), have been correlated with increased costs and morbidity;[2–4] however, recent reports have indicated that proper selection of an empiric antibiotic can mitigate such complications.[5, 6] Several studies have identified a growing epidemic of hand infections caused by MRSA in urban and suburban centers across the United States.[7–13] As a result, empiric antibiotic selection at most urban centers routinely bypasses traditional beta-lactam antibiotics for alternatives such as vancomycin or clindamycin.[7–14]

Recently, an eight-year longitudinal study at our urban hospital suggested that concurrent resistance to clindamycin in MRSA has significantly risen in recent years.[14] However, the patients at risk for multi-drug resistant MRSA are not known. This study aims to compare patient historical and laboratory data in order to identify risk factors associated with clindamycin resistance in MRSA and guide optimal empiric antibiotic selection.

Methods

A retrospective study was performed at an urban academic medical center over a three-year period from January 1, 2010 through December 31, 2012; this time period was chosen because clindamycin-resistance in MRSA was significantly higher than previous years.[14] After approval was obtained from the institutional review board, all hand infection cases encountered by the emergency room, outpatient office, or inpatient wards were reviewed. We identified subjects by searching International Classification of Disease Ninth Revision codes relevant to hand infections, including codes 681.00, 681.01, 681.02, 682.4, 727.05, 727.9, 883.00, 883.1, 882.01, and 882.00 (cellulitis, abscess, tenosynovitis, and open wounds of the fingers and hands) but only distinguished those between the ages of 18 and 89 with a culture-positive hand abscess. We collected demographic and laboratory data from medical records. Presence of fever was recorded if body temperature was ≥100.4°C prior drainage. Infections were considered nosocomial if records indicated a history of a surgical procedure, dialysis treatments, catheterizations, hospitalization, or nursing home stays within a year prior to admission. Finally, we analyzed a cohort of patients that had abscesses that grew MRSA on culture. We compared those infections with and without clindamycin resistance with odds ratios and a univariate analysis to identify

each risk factor alone for an association with clindamycin resistance in MRSA. Significant predictors in the univariate analysis were additionally tested with a multivariate analysis to evaluate the risk factors adjusted for combinations with each other. A minimum sample size of 7–10 events per variable was achieved for adequate statistical testing.[15]

Results

A total of 247 abscesses were identified over the three-year period. MRSA grew on culture from 103 abscesses (42%) and was the most commonly identified pathogen overall. Clindamycin resistance was discovered in 16% of those isolates that grew MRSA on culture. Risk factors associated with clindamycin-resistance in MRSA by the univariate analysis were age, history of hepatitis C, intravenous drug abuse (IVDA), and nosocomial acquired infection (Table 1). However, when performing a risk-adjusted multivariate analysis, only age, IVDA, and nosocomial acquired infection were identified as significant risk factors (Table 2).

The odds ratio for age was 0.94 indicating that for each year of increasing age, the risk of a clindamycin-resistant MRSA decreases 6%. Patients with a history of IVDA or nosocomial acquired infection were respectively 11 and five times more likely to have a concurrent resistance to clindamycin. For patients infected with clindamycin-resistant MRSA, 81% had a history of IVDA and 50% had a history of nosocomial contact. For patients with clindamycin-sensitive MRSA, 26% admitted to a history of IVDA and 21% had nosocomial contact.

Table 1. Univariate Analysis of Risk Factors Associated with Clindamycin Resistance in MRSA

	Odds Ratio	P
Age	0.9	**0.04***
Hypertension	0.9	0.87
Diabetes Mellitus	1.2	0.77
Hepatitis C	4.6	**0.007***
HIV**	<0.001	0.98
Mental Illness	1.2	0.77
Cancer	<0.001	0.98
Intravenous Drug Abuse	11.2	**0.0003***
Prior MRSA Infection	3.0	0.12
Nosocomial Acquired	5.3	**0.003***
Fever	2.3	0.21
White Blood Cell Count	1.1	0.32
Erythrocyte Sedimentation Rate	1.0	0.83
C- Reactive Protein	1.0	0.94
Time: Presentation to Drainage	1.0	0.39

*Significant
**Human immunodeficiency virus

Table 2. Multivariate Analysis of Risk Factors Associated with Clindamycin Resistance in MRSA

	P
Age	**0.05***
Hepatitis C	0.45
Intravenous Drug Abuse	**0.002***
Nosocomial Acquired	**0.04***

*Significant

Discussion

MRSA is the most common pathogen isolated from abscesses in urban centers ranging from 34% to 73% of all culture positive hand infections.[7–13] The combination of drug resistance and increased virulence makes MRSA a potentially serious infection that has been associated with increased costs and morbidity.[2–4] Proper selection of an empiric antibiotic has been shown to be critical in reducing complications, and as MRSA continues to dominate the urban setting in the United States, routine surveillance of its drug sensitivities is warranted. Recently, a report from our urban academic center has shown that concurrent clindamycin resistant has significantly risen in the three years from 2010 to 2012.[14] The purpose of this study was to identify risk factors from this cohort so that clinicians can better predict which patients are infected with multidrug resistant MRSA and thus could tailor treatment with appropriate empiric antibiotics.

Patients with a history of intravenous drug abuse were 11 times more likely to have concurrent clindamycin resistance, which was a significant increase in risk. In an eight-year longitudinal study by Tosti et al., clindamycin resistance in MRSA significantly increased approaching 20% of all MRSA infections in 2012.[14] In that study, all other demographics remained stable over the eight-year period except the proportion of patients using intravenous drugs, which also significantly increased. Additionally, the results suggested that increased use of clindamycin from 2005–2007 might have been contributory in subsequent resistance by creating a selection process for resistant bacteria. However, in the present study, a prior history of MRSA was not associated with clindamycin resistance, which suggests that the growing population of intravenous drug users in our region may have created a reservoir for multidrug resistant MRSA. This distinction may be important for future guidelines, as our results suggest that clindamycin may still be acceptable in MRSA endemic regions where intravenous drug users represent a minor proportion of the population. Multidrug resistance in this population may additionally be of interest from a public health standpoint. Currently, most strategies for combatting growing multi-drug resistant organisms appear to focus on monitoring the use of antibiotics.[15] The data presented herein suggest that multidrug resistance could

also be potentially decreased through social programs aimed at reducing drug abuse.

Nosocomial acquired infections were also identified as a significant independent risk factor. Patients with any reported health-care facility contact within a year of presenting with the infection were found to have five times the risk of concurrent clindamycin resistance. This finding is not surprising as multidrug resistance in many species of microbes is often linked to contact with the hospital setting. Health-care facilities contribute to multi-drug resistance on a few levels: people with infections live in close quarters, require a variety of antibiotics, and have immune-comprising diseases.[16] Interestingly, in our study, the latter risk factors of immune-comprising conditions such as cancer, diabetes mellitus, and HIV were not predictive of multidrug resistance, but they were also not separated on the basis of good or poor control of the disease.

The present study has several limitations. The retrospective design limits the patients we were able to identify and classify. Although our proportion of IV drug users is quite high, the true number of patients may be higher because some patients may not want to disclose this information; we believe this may explain why younger age was a significant risk factor. Last, our location in an urban setting may have a disproportionately high prevalence of MRSA and larger population of intravenous drug users, and our results may not be generalizable to community or international institutions.

At present, we would not recommend clindamycin as an empiric antibiotic for a patient with a hand infection and history of IVDA or contact in a health care facility within a year prior to presentation. At our institution, vancomycin is the first line agent for inpatients, which has appropriate coverage for the most commonly encountered organisms.[13] For severe cases, delayed cases, or those at risk for gram negative involvement (e.g., aquatic contamination), we add piperacillin-tazobactam or ciprofloxacin for patients with a penicillin allergy. For outpatient management, we recommend double strength trimethoprim-sulfamethoxazole or doxycycline for patients who have a sulfa allergy.[14]

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Original Research

Does Nighttime Bracing Have a Role After Vertebral Body Stapling for Thoracolumbar/Lumbar Scoliosis?

Justin Iorio, MD;[1] Patrick J. Cahill, MD;[2] Amer F. Samdani, MD;[2] Joshua M. Pahys, MD;[2] Anuj Singla, MD;[3] John P. Gaughan, PhD;[4] Harsh Grewal, MD;[5] Randal R. Betz, MD[6]

[1]*Department of Orthopaedic Surgery, Temple University Hospital, Philadelphia, PA;* [2]*Shriners Hospitals for Children, Philadelphia, PA;* [3]*Department of Orthopedic Surgery, University of Virginia, Charlottesville, VA;* [4]*Biostatistics Consulting Center, Temple University School of Medicine, Philadelphia, PA;* [5]*Department of Pediatric Surgery, Cooper University Hospital, Camden, NJ;* [6]*Institute for Spine & Scoliosis, Lawrenceville, NJ*

Abstract

Background: Vertebral body stapling (VBS) for idiopathic scoliosis (IS) provides superior outcomes when curves correct to <20° on first-erect radiographs. However, the use of postoperative bracing for improved curve correction has not been studied. The purpose of this review is to describe the clinical and radiographic outcomes of patients with thoracolumbar/lumbar (TL/L) IS treated by VBS and adjuvant nighttime bracing.

Methods: We performed a retrospective chart reviewed of IS patients treated by VBS and postoperative, nighttime bracing. Inclusion criteria were: age 11–14 years, moderate curve size (Cobb, 25–45°), primary TL/L curve pattern, Risser ≤2, and Sanders ≤4 followed to skeletal maturity and for a minimum of two years. From a pool of 221 patients who underwent VBS, we identified 26 patients with primary TL/L curves, eight of whom met inclusion criteria specifically including the bracing management.

Results: There were eight patients with an average TL/L Cobb angle of 34° (range: 25–44°) who underwent VBS at a mean age of 13 years (range: 11–14). Average follow-up was 3.2 years (range: 2–5.5). Mean coronal curve at most recent follow-up improved to 21° (range: 14–32°; $p = 0.001$). Mean Cobb correction was 12° (range: 5–24°). Trunk shift improved from an average 1.8 cm (range: 0.5–3.1) preoperatively to 0.4 cm (range: 0–1; $p < 0.001$) at most recent follow-up. Inclinometer, Nash-Moe score, and lordosis were not significantly different from preoperative to most recent follow-up.

Conclusion: VBS and nighttime bracing can correct coronal Cobb and trunk shift in patients with moderate (25–45°) thoracolumbar/lumbar curves.

Introduction

The standard treatment of patients with juvenile and adolescent idiopathic scoliosis with moderate curve magnitude (20–45°) is either observation or bracing with a thoracolumbosacral orthosis (TLSO). Despite the widespread use of full-time bracing for controlling progression, results are variable[1–13] and are affected by compliance and poor self-image.[14–16] Curve progression in skeletally immature patients despite bracing is especially problematic for scoliosis with coronal deformity greater than 30°.[11, 17–19]

The concern of many patients is trunk asymmetry[20] which does not improve with bracing.[21] The cosmetic appearance is a result of thoracic hypokyphosis, rib deformity, waist asymmetry, vertebral rotation, and Cobb angle.[22, 23] Studies have shown that psychological disturbance in patients affected by scoliosis is associated with negative self-image and magnitude of deformity.[24–25] Scoliosis and trunk imbalance can have adverse consequences on pelvic obliquity and function[26–28] in addition to self-image and are important aspects of treatment.

Vertebral body stapling (VBS) is a motion-sparing, fusionless treatment option for idiopathic scoliosis (IS) that produces growth modulation and curve stabilization.[29] VBS has been shown to be feasible, safe, and effective at achieving curve stability in IS patients with thoracic curves ≤35° and lumbar curves ≤45°.[30–32] VBS studies have shown superior outcomes when curves correct to <20° on first-erect radiographs.[30, 33] As a result of these findings, the treatment algorithm for VBS is transitioning from stabilization of the preoperative curves to maintenance of intraoperative correction by the addition of postoperative nighttime bracing. The purpose of this retrospective review is to describe the clinical and radiographic outcomes of patients with thoracolumbar/lumbar (TL/L) idiopathic scoliosis treated by VBS and adjuvant nighttime bracing.

Materials and Methods

After obtaining IRB approval, we retrospectively reviewed medical records and radiographs of AIS patients who were treated by VBS and adjuvant nighttime bracing with a minimum two-year follow-up from a single institu-

tion. From a pool of 221 patients who underwent VBS, we identified 26 patients with primary TL/L curves, eight of whom met our inclusion criteria of: (1) idiopathic scoliosis; (2) primary TL/L curve pattern; (3) age ≤14 years at time of surgery; (4) moderate curve size (Cobb, 20°–45°); (5) postoperative nighttime Providence bracing started within three months after surgery; (6) Risser grade ≤2; and (7) Sanders score ≤4. These eight patients underwent VBS at the end of the series of 26 TL/L curves when the senior author (RRB) began observing the corrective ability of the procedure. RRB began recommending routine postoperative nighttime providence bracing as soon as the patients incisional pain was tolerable. The goal was to obtain permanent improvement of the deformity instead of curve stabilization. This is a retrospective objective review of these eight specific cases.

Surgical Technique

Under general anesthesia, the patient is placed in the lateral decubitus position with the convex side of the scoliosis curve in the 'up' position. An axillary roll is placed cephalad to the apex underneath the concave side, and the patient is positioned such that the curve apex is allowed to sag and correction is maximized. For instrumentation of levels T10–T12 above the diaphragm, single-lung ventilation and thoracoscopic access are utilized. In the lumbar spine, tubular retractors and a minimally invasive retroperitoneal lateral approach to the spine can be used as well as a small open standard retroperitoneal approach.

Vertebral bodies are identified using biplanar fluoroscopy, enabling identification of the precise location for intercostal portals. The thoracoscope is placed through portals in the anterior axillary line. In the thoracic spine, most incisions for staple insertion portals are made close to or within the area of the posterior axillary line. Both fluoroscopy and direct visualization with the thoracoscope are reliable methods for planning the incision. Incisions for the lumbar approach are also localized based on the image intensifier. We prefer to place staples by retracting the psoas posteriorly past the midline of the vertebral body rather than via a transpsoas technique.

Using fluoroscopy, the appropriate sized trial is selected to span the distance across the disc, apophyses, and physes. Once the correct size for the trial is determined, it is tapped into place where the staple will be located. The tines of the trial are thus used to create the pilot holes for the staple tines. Following creation of the pilot holes, the trial is removed and the appropriate sized staple is quickly inserted. Staples are positioned anterior to the rib heads in the thoracic spine. In the lumbar spine, the staples are placed as far posteriorly on the vertebral body as possible to maintain normal lordosis.

Chest tubes were routinely removed the day after surgery (mean: 1.1 days; range: 1–2). One patient had a chest tube maintained until POD #2 because of atelectasis.

Adjuvant Bracing

Patients began their nighttime bracing at an average of eight weeks post-surgery (range: 1–12 weeks), and were instructed to continue bracing until Risser grade 4. In-brace radiographs were taken to confirm proper curve correction by the orthosis and adjustments were made if the brace did not apply enough corrective force. Prior to radiography at scheduled appointments, all patients were instructed to have not worn their braces for at least 24 hours. Out-of-brace standing radiographs (posteroanterior [PA] and lateral) were obtained at first erect and at six-month intervals.

Surgical Data

Surgical data collection included age at time of VBS, gender, hospital length of stay, number of levels stapled, estimated blood loss (EBL), length of surgery, duration of chest tube, and complications. Clinical and radiographic measurements were made preoperatively, at first erect, one-year, two-year, and most recent follow-up. The clinical data collected were inclinometer readings from the Adam's forward bend test. PA and lateral radiographs were performed with the patient standing at each time point, and preoperative bending films were taken to confirm curve flexibility. All radiographs were taken using the same standards and techniques. Measurements obtained from PA radiographs were: (1) Risser grade; (2) Cobb angle; (3) level of curve apex; (4) trunk shift; and (5) Nash-Moe rotation. Lumbar lordosis as measured from the superior endplate of L1 to the superior endplate of S1 was determined from lateral radiographs.

Statistical analyses were performed using unpaired t-tests to analyze relationships between preoperative and each follow-up time point. A P value of <0.05 was used to denote statistical significance.

Results

Of the 26 patients with primary TL/L curves, eight patients (female: n = 8; average age at the time of surgery: 13 years [range: 11–14 years]) met inclusion criteria specifically including bracing management. The remaining 18 patients were excluded because they were not treated with postoperative bracing. Average follow-up was 3.2 years (range: 2–5.5 years) and all patients were Risser 4 at most recent follow-up. Average duration of postoperative nighttime bracing was 2.2 years (range: 1.1–2.9 years). OR time averaged 2.3 hours (range: 1.7–2.6) and EBL averaged 81 mL (range: 20–200). No patients required blood transfusion (Table 1). Seven patients were Risser grade 0 and one patient was Risser grade 2 at the time of surgery.

Preoperatively, the average TL/L curve measured 34° (range: 25–44°). The mean first erect Cobb angle was 15° (range: 8–24°, p = 0.0001). At most recent follow-up, the average Cobb angle measurement was 21° (range: 14–32°; p = 0.001). Overall mean coronal curve correction was 12° (range: 5–24°) (Table 2).

Table 1. Surgical Data and Postoperative Complications After Vertebral Body Stapling

Surgical Data	Average (Range)
Length of Surgery (hours)	2.3 (1.7–2.6)
EBL* (mL)	81 (20–200)
Blood Transfusion Volume (mL)	0
Neuromonitoring Changes	0
Number of Levels Stapled	4.4 (3–5)
Duration of Chest Tube (days)	1.1 (1–2)
Length of Hospital Stay (days)	4.7 (4–6)
Complications	**Number (%)**
Pneumothorax	0
Pleural Effusion	0
Atelectasis	1 (12.5)
Staple Complications	0
Curve Progression	0
Need for Surgical Fusion	0
Neurologic foot dystonia	1 (12.5)

*EBL, estimated blood loss

Table 2. Results of Thoracolumbar/Lumbar Vertebral Body Stapling

Time Point	Cobb Angle (°)	Lumbar Lordosis (°)	Nash-Moe	Trunk Shift (cm)	Inclinometer (°)
Preoperative	34 (25–44)	54 (34–72)	1.1 (0–2)	1.8 (0.5–3.1)	10 (6–15)
First Erect	15 (8–24)*	46 (23–62)	0.9 (0–2)	0.8 (0–2.3)*	7 (3–12)
≥2-Year Postoperative	21 (14–32)*	52 (36–72)	1.3 (1–2)	0.4 (0–1)*	7 (0–14)

[a]Radiographic and clinical (inclinometer) measurements prior to vertebral body stapling, at first-erect posteroanterior radiograph, and at most recent follow-up.
[b]Values are given as mean and range in parentheses.
*Indicates P value <0.05 compared to preoperative measurement.

All patients corrected ≥5° and 4 (50%) corrected ≥10° by most recent follow-up. The four lumbar curves that improved ≥10° were in Patients 4, 5, 6, and 7 (Table 3). The remaining patients (1, 2, 3, and 8) had between 5° and 8° of coronal correction.

Trunk shift improved from an average of 1.8 cm (range: 0.5–3.1) preoperatively to 0.4 cm (range: 0–1) at most recent follow-up ($p < 0.001$). Lordosis was not significantly different from preoperative to most recent follow-up (54° vs. 52°).

Clinical rotation was not statistically different from preoperative (average: 9°, range: 6–15°) to latest follow-up (average: 7°, range: 0–14°) ($p = 0.3$). When analyzed individually, four patients had improvements in inclinometer readings between 5° and 10° (Patients 3, 4, 6, and 7). Two patients (Patients 1 and 8) had an increase of rotation of 3° and 7°. Two patients (Patients 2 and 5) did not have inclinometer values recorded in their charts. Radiographic rotation, assessed using Nash-Moe score, was stable from presurgery to latest follow-up as a group ($p = 0.6$). None of the vertebrae progressed beyond a Nash-Moe score of 2.

No patients had persistent or major pulmonary complications requiring reinsertion of chest tube, secondary procedures, prolonged hospital stay, or antibiotics. There were no major complications resulting from staple placement (loosening, breakage, or malposition) and no patients had curve progression. No patient had neuromonitoring changes. One patient had transient development of a left lower extremity varus foot presenting at a few weeks postoperatively, which resolved by 12 months.

Discussion

Our study is an analysis of a group of idiopathic TL/L curves treated with VBS and postoperative nighttime bracing who are at high risk for curve progression. Our findings build on the treatment success reported in previous studies of VBS for idiopathic scoliosis.[30, 33] VBS has been studied for thoracic and lumbar curves without adjuvant postoperative bracing.[29–33] Success rates between 83% and 89% have been reported for lumbar curves, defined as curve maintenance to within 10° of preoperative or greater than 10° improvement of Cobb angle.[30, 33, 34] Subanalyses from these studies revealed better outcomes in lumbar curves that corrected to less than 20° on first erect film.[30, 33] In the largest series of VBS for lumbar curves,[30] 13% of lumbar curves, which did not receive postoperative bracing, progressed greater than 10° and is in contrast to our study in which no

Table 3. Curve Magnitude Before and After Treatment of Each Patient

Patient Number	Age at Surgery (Years)	Recent Age (Years)	Preop Risser	Preop Sanders	Preop Curve (°)	First Erect (°)	Recent (°)	Improvement (°)	Improvement (%)	Follow-up (Years)
1	11.6	16.7	0	N/A	31	13	24	7	22.6	5.1
2	13.4	18.9	0	4	39	24	32	7	17.9	5.5
3	13.8	15.9	2	4	30	16	22	8	26.7	2.1
4	11.0	14.6	0	1	35	11	16	19	54.3	3.7
5	13.4	15.5	0	4	25	12	15	10	40.0	2.1
6	12.7	15.4	0	3	38	21	14	24	63.2	2.8
7	11.0	13.5	0	2	44	8	26	18	40.9	2.6
8	13.3	15.3	0	4	27	13	22	5	18.5	2.0

[a]Individual patient data at preoperative, first-erect x-ray, and most recent follow-up.
[b]Improvement indicates difference between latest follow-up and preoperative measurement.

curves progressed. The earliest series of patients were not prescribed postoperative bracing because the benefit of correction to less than 20° had not yet been observed. Initially, the goal of VBS was curve stabilization without requiring postoperative bracing. Because greater success was achieved in lumbar curves that corrected to less than 20° on first erect radiographs, the treatment algorithm has changed to include adjuvant nighttime bracing to maintain curve improvement seen from surgery. Patients are still required to comply with nighttime bracing until Risser grade 4 is achieved; however, only full-time bracing, in contrast to nighttime bracing, has been correlated with negative self-image and psychological ramifications.[14, 15]

Although our study contains a small number of patients, we believe that our treatment success is a result of a better understanding of intraoperative correction techniques and postoperative bracing with a Providence orthosis. The advantage of Providence bracing in addition to VBS is explained by the corrective properties of the orthosis. The Providence brace applies a lateral corrective force to the curve apex with the goal of aligning the curve apex with the center line of the spine (measured from the center of C7 to the middle of the sacrum). In contrast to full-time bracing, nighttime bracing has the advantage of providing corrective forces to a recumbent patient in which the deforming forces of gravity are minimized. Lastly, the Providence brace is able to elevate the patient's shoulder for application of forces that correct spinal deformity, which is not tolerable with full-time bracing. Thus, stapling provides the initial deformity correction and postoperative Providence bracing improves the maintenance of the spinal alignment. In our study, all curves corrected ≥5° and half of the patients had ≥10° improvement by mean follow-up of 3.2 years. In comparison to a previous study of lumbar stapling,[30] 13.3% of AIS patients progressed and one patient developed a 50° curve by final follow-up. In another study of the utility of VBS,[31] curve progression ≥5° occurred in 40% of patients by mean follow-up of 1.8 years.

One limitation of this study is that there is no nighttime bracing control group. Nighttime bracing has not been shown to provide lasting curve correction when used alone. As a result, we did not include a nighttime bracing control group because patients at our center are not treated solely with Providence bracing. Based on our findings, we believe that nighttime bracing has utility when used in conjunction with VBS and may improve upon the results of VBS without postoperative bracing. Lee et al.[35] reviewed 95 patients with moderate (25–40°) AIS who were treated by Charleston nighttime bracing and followed for 3.8 years after discontinuation of bracing. Of the TL and lumbar curves, 83% (5/6) and 87% (7/8) respectively were stable at skeletal maturity. However, subanalyses of the 95 patients found that treatment success was only 76% for curves between 31° and 40° and only 68% for those who were Risser grade 0. Additionally, 29% of the patients with TL or lumbar curves eventually underwent surgery. In our study, seven patients (87.5%) were Risser grade 0 at time of VBS. In contrast to Lee et al.,[35] none of the patients in our study are planning or have undergone a spinal fusion. D'Amato et al.[7] reported a 79% success rate (defined as ≤5° progression) in curves treated by Providence bracing. However, due to the small number of curves greater than 35°, the authors were unable to recommend bracing for larger curves. In our study, 50% of patients had presurgical curves ≥35° and improved between 7° and 24°.

Historically, the results of bracing for IS have been variable for several reasons including poor compliance. Recently, however, the Bracing in Adolescent Idiopathic Scoliosis Trial (BRAIST) found that full-time bracing for an average of at least 12.9 hours per day is associated with a success rate of 90% to 93%.[13] We do not advocate supplanting VBS for full-time bracing. We present VBS and nighttime bracing only as a treatment alternative for high risk patients who are unwilling to comply with full-time bracing or are seeking alternative, surgical options.

We report a significant improvement in trunk shift after VBS and bracing. Although health-related quality of life outcomes have not correlated with trunk shift, trunk imbalance has been shown to negatively impact self-image.[26] In our study, trunk shift improved from an average of 1.8 cm preoperatively to 0.4 cm at latest follow-up ($p < 0.001$). Bassett and Bunnell[36] evaluated the effect of Wilmington bracing on lateral trunk displacement in 46 TL/L curves. Sixty-five percent of curves demonstrated an average improvement of 1 cm in lateral trunk shift at a mean follow-up of 22 months. In another study of TL/L curves, trunk shift improved an average of 1.5 cm in 69% of patients that had 2.5 cm of pretreatment trunk shift.[37] Compared to these studies in which less than 70% of patients improved, all patients in our study had improvement of lateral trunk displacement. Permanent improvement of trunk shift, however, has not been reported with bracing alone. Korovessis[21] observed that trunk shift returned to prebrace values after braces were removed. In our study, data was obtained with patients out of their braces for 24 hours prior to radiography because we believe this reduces any potential effect of bracing on curve correction. Our results show that VBS and adjuvant bracing can maintain the correction of trunk shift after brace removal unlike TLSO alone.

Clinical and radiographic vertebral rotation did not improve following this treatment strategy. These findings are not unexpected because derotation maneuvers are not used during stapling and inclinometer readings have not been shown to correlate closely with Cobb angle.[38] In 1954, John Royal Moore commented, "stapling has no place in the correction of scoliosis unless [staples are inserted] before rotation has taken place."[39] Our study included patients with minimal to moderate vertebral rotation and our data suggests that VBS is able to improve Cobb angle correction, but not rotation, in these patients.

Complications were uncommon. One patient developed atelectasis; however, pulmonary complications occur after exposures to the anterior spine[40, 41] and are not specific to vertebral stapling. One patient presented with postoperative left plantar foot dystonia (Table 1). Malposition of implants was not visualized on radiographs and computed tomography. Neurology consult confirmed that there were no focal motor or sensory deficits. The patient's symptoms resolved spontaneously.

The limitations of this study are small patient cohort, lack of control group, inability to monitor brace compliance, and retrospective design. Our small sample size is due to the recent initiation of adjuvant bracing after VBS by the senior author. These results are a preliminary study of VBS and postoperative bracing, which demonstrate promising results and support the consideration of bracing in the postoperative period. We plan on reviewing a larger cohort in the future. Brace compliance is variable and our measure of compliance is based on patient and family reporting. The correlation between brace compliance and curve progression has been studied;[13, 16, 42] we do not routinely equip braces with compliance monitors. Lastly, we are unable to perform a prospective study because the use of staples is considered physician directed (off-label), and prospective studies are not permitted without an investigation device exemption study. A prospective comparison between stapling-only or bracing-only versus VBS with postoperative bracing is not able to be performed.

In conclusion, VBS and adjuvant nighttime bracing may improve moderate curve deformity and trunk shift in AIS patients with primary TL/L curves.

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Original Research

Serial Casting for Infantile Idiopathic Scoliosis: Outcomes and Factors Associated with Response to Treatment

Justin Iorio, MD;[1] Giuseppe Orlando, MD;[2] Chris Diefenbach, MD;[3] John P. Gaughan, PhD;[4] Amer F. Samdani, MD;[5] Joshua M. Pahys, MD;[5] Randal R. Betz, MD;[6] Patrick J. Cahill, MD[5]

[1]*Temple University School of Medicine, Department of Orthopaedic Surgery and Sports Medicine, Philadelphia, PA;* [2]*School of Orthopedics, University of Messina, Messina, Italy;* [3]*University of Pittsburgh Medical Center–Hamot, Department of Orthopedic Surgery, Erie, PA;* [4]*Biostatistics Consulting Center, Temple University School of Medicine, Philadelphia, PA;* [5]*Shriners Hospitals for Children, Philadelphia, PA;* [6]*Institute for Spine & Scoliosis, Lawrenceville, NJ*

Abstract

Background: Serial casting for early onset scoliosis has been shown to improve curve deformity. Our goal was to define clinical and radiographic features that determine response to treatment.

Methods: We retrospectively reviewed patients with idiopathic infantile scoliosis (IIS) with a minimum two-year follow-up. Inclusion criteria were: progressive IIS and initial casting prior to six years of age. Two groups were analyzed and compared: Group 1 (≥10° degree improvement in Cobb angle from baseline) and Group 2 (no improvement).

Results: Twenty-one patients with an average Cobb angle of 48° (range, 24 to 72°) underwent initial casting at an average age of 2.1 years (range, 0.7 to 5.4). Average follow-up was 3.5 years (range, 2 to 6.9). Gender, age at initial casting, and magnitude of spinal deformity were not significantly different between groups. Group 1 (n = 15) had a significantly lower Cobb angle (21 vs. 56°) and RVAD (13 vs. 25°) compared to Group 2 at latest follow-up ($p < 0.05$). A significantly larger proportion of children who were casted at <1.8 years of age had a Cobb angle <20° at latest follow-up ($p = 0.03$). Group 2 maintained stable clinical and radiograph parameters from pretreatment to most recent follow-up.

Conclusion: Key aspects of treatment that may determine success include age <1.8 years at initiation of casting, derotation of the spine to correct RVAD <20°, and obtaining maximal Cobb angle correction during initial casting.

Level of Evidence (study type and numerical rating): Therapeutic, level 4.

Introduction

Early onset scoliosis (EOS) may resolve without treatment[1–3] and is potentially reversible,[4] but many patients develop rapidly progressive scoliosis causing severe deformity and thoracic insufficiency syndrome.[5–8] Negative prognostic factors include development of scoliosis after one year of age, rib vertebral angle difference (RVAD) >20°, phase II rib-vertebra relationship, curve progression >10°, and a Cobb angle >20°.[1, 4, 9]

The optimal management for children younger than 10 years old with progressive deformity is controversial. Bracing for infantile idiopathic scoliosis (IIS) provides temporary, modest curve correction followed by rapid loss of correction.[10] Techniques to improve spinal alignment such as distraction-based or guided-growth procedures are fraught with complications.[11–14] Growing rods, although effective for increasing spinal length, undergo a "law of diminishing returns" whereby each consecutive lengthening yields a smaller net gain.[15] This suggests that delaying initiation of treatment with growing rods may reduce the incidence of surgical complications and the number of unnecessary procedures. Serial casting for IIS as described by Mehta[4] has shown good results when implemented early in life. Casting emphasizes extension, derotation, and flexion (EDF) of the spine and relies on casting forces to correct spinal deformity during periods of rapid growth. The objective of this study is to retrospectively review our experience in treating patients with progressive IIS and elucidate factors associated with response to EDF casting.

Methods

We retrospectively reviewed patients from two institutions with progressive IIS who underwent EDF casting. Inclusion criteria were progressive IIS, Cobb angle >20°, and age <6 years at initial casting. Patients with EOS of other etiologies were excluded. All patients were followed regularly at 2–4 month intervals for a minimum of two years.

Demographic and clinical information included gender, age at initial casting, years of follow-up, duration of casting, number of cast applications, number of times anesthetized, position for radiographs (supine or standing), number of

radiographs per patient, and plan for spinal implant. Patients had anteroposterior radiographs of the spine while standing (or supine if unable to stand) out of the cast prior to initial or new cast application and/or after cast application on the same day. We utilized the casting technique described by D'Astous and Sanders.[16] Casts were removed 24 hours before pre-treatment radiographs to remove potential confounding of measuring residual in-cast correction. Major curve magnitude (Cobb angle), RVAD, rib phase (Fig. 1A and 1B), and Nash-Moe rotation of the apical vertebra were measured at pretreatment, first follow-up after initial casting, one year post initiation of casting, two years post initiation of casting, and most recent follow-up. Complications of treatment were recorded.

Success was defined as ≥10° improvement in Cobb angle, while failure of response to treatment was defined as <10° improvement from pre-treatment to most recent follow-up. Patients were divided into two groups based on outcome: Group 1 (≥10° improvement) and Group 2 (no improvement).

Statistical Analysis

A two-way mixed-model analysis of variance with repeated measures was used to analyze the differences between groups and treatment periods. The analysis of main effects was followed by multiple comparisons between and within groups and periods. There was no adjustment for multiple comparisons. Differences between groups and periods (rejection of the null hypothesis) were considered significant if the probability of chance occurrence was <0.05 using two-tailed tests.

Source of Funding

No funding was received for this investigation.

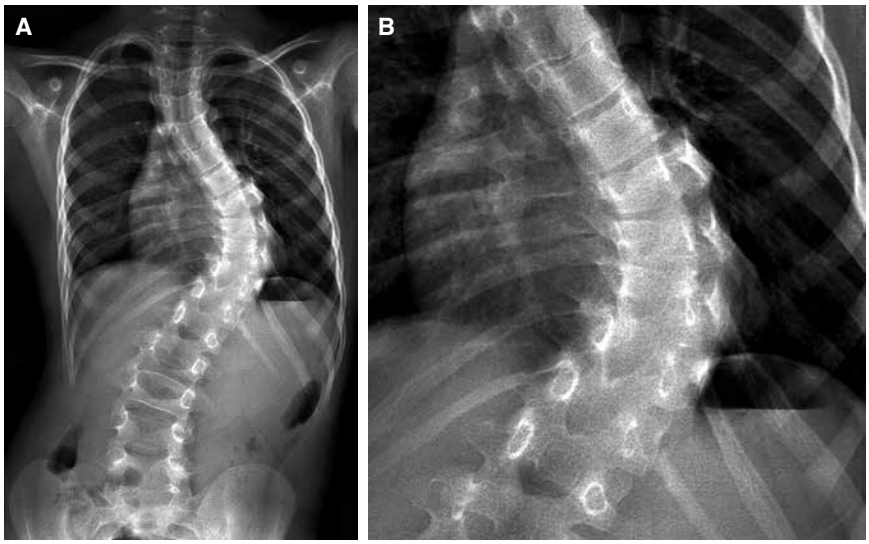
Results

Twenty-one children with an average follow-up of 3.5 years (range, 2–6.9 years) underwent serial casting (Table 1). Average age at time of initial casting was 2.1 years (range, 0.7–5.4 years) for an initial Cobb angle of 48° (range, 24–72°) and RVAD of 20° (range, 1–44°). Rib phase I was present in 68% of curves. Nash-Moe rotation ranged from one to three (1 = 47.5%, 2 = 47.5%, 3 = 5%) prior to casting. At latest follow-up, rotation was significantly improved ($p = 0.02$) (0 = 5%, 1 = 81%, 2 = 9%, 3 = 5%). Average age at follow-up was 5.5 years (range, 2.8–9.7).

Group 1 included 15 patients, representing a 71% success rate (Table 2). Mean pretreatment Cobb angle and RVAD

Table 1. Pretreatment Characteristics and Final Outcomes of All 21 Patients

	Average (Range)
Radiographic	
Cobb Angle (°)	48 (24–72)
RVAD (°)	20 (1–44)
Rib Phase II (%)	32
Nash-Moe Rotation ≥ 2 (%)	52.6
Demographic	
Female n (%)	14 (67)
Age at Initiation of Casting	2.1 (0.7–5.4)
Years Casted	1.8 (0.2–5.2)
Age at Most Recent Follow-up	5.5 (2.8–9.7)
Years of Follow-up	3.5 (2–6.9)
Final Outcomes	
Casts Per Patient	6.9 (2–16)
X-ray Per Patient	24 (13–43)
Anesthetizations Per Patient	6.9 (3–18)
Plan for Any Spinal Implant n (%)	5 (23.8)
Plan for Fusion n (%)	2 (9)
Plan for VEPTR or GR n (%)	4 (18.2)
Underwent Spinal Implant	0
Complications	0



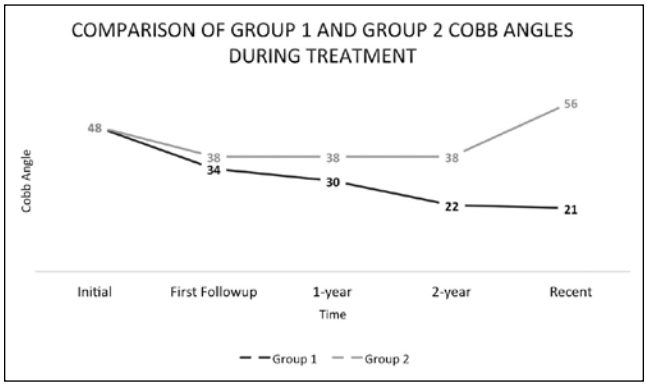
Figures 1A and 1B. Anteroposterior **(Fig. 1A) a**nd close-up **(Fig. 1B)** radiograph of a left, main thoracic deformity in rib phase II. Note the overlap of the rib and vertebra at the curve apex, which is the area of maximal downward obliquity of the ribs.

Table 2. Group 1 vs. Group 2 Radiographic Measurements

	Cobb (Avgerage, Range°)			RVAD (Avgerage, Range°)			N (%) Rib Phase 2		N (%) Nash ≥2	
Group	**1**	**2**	**P**	**1**	**2**	**P**	**1**	**2**	**1**	**2**
Pre-treatment	48 (24–72)	48 (26–67)	0.97	17 (1–31)	27 (2–44)	0.26	5 (33)	1 (25)▪	7 (47)	3 (75)▪
First	34 (17–67)*	39 (28–54)	0.44	21 (7–42)	22 (6–38)	0.93	6 (40)	1 (20)†	9 (60)	1 (20)†
1-Year	30 (3–68)*	38 (31–45)	0.12	18 (0–60)	24 (12–40)	0.24	4 (27)	2 (33)	5 (33)	1 (17)
2-Year	22 (0–43)*	38 (29–52)	**0.01**	14 (0–55)	23 (17–38)	0.06	4 (27)	3 (50)	3 (20)	2 (33)
Recent	21 (0–61)*	56 (33–82)	**<0.001**	13 (0–59)	25 (7–49)	**0.03**	4 (27)	4 (67)	1 (7)*	2 (33)

*Indicates $p < 0.05$ compared to pretreatment
▪Rib phase and Nash-Moe data are available for 4/6 patients
†Rib phase and Nash-Moe data are available for 5/6 patients

were 48° (range, 24–72°) and 17° (range, 1–31°), respectively. These measurements were in the supine position in five of 15 (33%) patients and in the upright position for the remainder. Group 1 only demonstrated a significant improvement in Cobb angle from pretreatment to the out-of-cast study after the first cast was removed ($p = 0.009$). As seen in Graph 1, the steepest portion of the curve, and only statistically significant difference in Cobb angle ($p < 0.01$), is seen between pretreatment and after the initial cast was removed. Afterward, gradual improvement is observed until an average Cobb angle of 21° at most recent follow-up. Four patients had curve resolution, and these children underwent casting at a younger age (average, one vs. 2.6 years; $p = 0.004$) and had a lesser Cobb angle (average, 43° vs. 60°; $p = 0.05$) than patients who progressed to a curvature >40° (Table 3). Eight patients had Cobb angles of ≤20° at recent follow-up and underwent casting at average age 1.76 years (average Cobb angle, 42°; average RVAD, 17°). A significantly larger proportion of children who were casted at <1.8 years of age had a Cobb angle <20° at latest follow-up compared to those casted at ≥1.8 years ($p = 0.03$). In contrast,



Graph 1. Degree of Cobb angle from pretreatment to most recent follow-up. The improvement in Group 1 Cobb angle from initial to first follow-up is significant (mean, 48° to 34°) ($p < 0.01$). Group 2 had transient improvement in Cobb angle at two-year follow-up and then progressed an average of 18° between two years and latest follow-up ($p > 0.05$).

Table 3. Pretreatment Characteristics Associated with Recent Cobb Angle

Recent Cobb Angle	Patients (n)	Average Age at Casting	Average Initial Cobb	Average Initial RVAD	Initial Phase 2 (n)
10 or less	4	1	43	21	0
11 to 20	4	2.6	40	12	0
21 to 40	7	2	46	15	2
40 or more	6	2.6	60	35	2
Cobb worsened	2	2	57	38	2
Total or average	21	2.1	48	20	6

those who progressed to >40° were casted at a mean age of 2.6 years and exhibited an average RVAD of 35°. Nash-Moe rotation at pretreatment improved at most recent follow-up ($p = 0.02$). Rib phase remained constant from pretreatment (67% phase I) to latest follow-up (73% phase I) ($p = 0.7$).

Group 2 (n = 6 or 29%) maintained a stable Cobb angle ($p = 0.38$), RVAD ($p = 0.81$), rib phase ($p = 0.19$), and Nash-Moe ($p = 0.19$) at latest follow-up (Table 2). Mean pretreatment Cobb angle was 48° (range, 26–67°) which measured 56° (range, 33–82°) at latest follow-up ($p = 0.38$). Pretreatment x-rays were in the supine position in one of six patients and in the upright position for the remainder. A mean Cobb angle of 38° was measured at first follow-up, one-year, and two-year follow-up, suggesting that a modest improvement (10°) was achieved from baseline and was maintained for two years. Curve progression approached, but did not reach, statistical significance (18°, $p = 0.06$) between two-years and most recent follow-up. Four (67%) patients had Cobb angles within 10° of pretreatment at latest follow-up, i.e., avoided rapid deformity progression. Mean RVAD measured 27° (range, 2–44°) at initiation of casting and 25° (range, 7–49°) at latest follow-up ($p = 0.81$).

Pretreatment gender, Cobb angle, Nash-Moe, RVAD, rib phase, and age at initial casting were not different between Groups 1 and 2 (Tables 2 and 4). Nash-Moe ($p = 0.08$) and rib phase ($p = 0.09$) trended towards, but did not reach, statistical significance.

Table 4. Group 1 vs. Group 2 Non-Radiographic Outcomes

	Group 1	Group 2	P Value
Female (%)	67	67	1.0
Age at 1st cast (years)	2.0 (0.7–5.4)	2.3 (1.5–3.4)	0.66
Casts per patient	6.5	7.8	0.4
Duration of casting (years)	1.5 (0.2–4.5)	2.7 (0.9–5.2)	0.07
Follow-up (years)	3.0 (1.8–4.9)	4.6 (2.8–6.9)	0.01
X-rays per patient	24	23	0.28
Anesthetizations per patient	8.2	9.2	0.58
Need surgery (%)	7	67	0.02

Main thoracic curves (n = 16) significantly improved during treatment from an average of 47° to 29° (p = 0.01). RVAD (average, 21°) and rib phase (21% phase II) were unchanged from pretreatment to most recent follow-up (p > 0.05). Mean pretreatment thoracic Cobb and RVAD of double major curves (n = 5) were 53° and 15°, respectively, and were similar to single thoracic curves (p > 0.05). Thoracic Cobb angle, RVAD, and rib phase (60% phase II) remained stable throughout treatment (p > 0.05). Lumbar curves improved from a mean of 32° to 21° (p = 0.002).

None of the patients who had Cobb angles ≤20° at recent follow-up were phase II at time of initial casting (Table 3). Curves in rib phase I had a lesser Cobb angle (average, 43° vs. 58°, p < 0.05) but similar age (average, two vs. 2.1 years) and RVAD (average, 17° vs. 23°) at initial casting. Cobb angles were significantly greater at latest follow-up if they were in phase II (53° vs. 17°, p < 0.001). All curves that are planned for spinal implantation are phase II.

No patients have undergone spinal surgery, but five (24%) patients (four from Group 2) are awaiting a procedure, with an average of 4.4 years (2.2–6.9) between the initiation of treatment and most recent follow-up. An analysis of the patients awaiting instrumentation versus those who do not have a need for instrumentation reveals greater Cobb angle (average, 60° [range, 46–72°) vs. 45° [range, 24–60°]; p = 0.008) and RVAD at initiation of casting (average, 33° [range, 23–45°] vs. avg. 17° [range, 1–33°]; p = 0.01). Average age at initiation of casting was not found to be significantly different between patients requiring surgery and those who do not require surgery (2.4 vs. two years; p = 0.5). Likewise, average number of casts per patient (6.2 vs. 7.3), frequency of anesthesia, and number of radiographs were similar (p > 0.05) (Table 4).

Discussion

We analyzed a homogenous group of patients with IIS whereas other studies included neuromuscular and syndromic scolioses.[4, 17–19] Another unique feature of our series is the young age of treatment initiation (within the first few years of life) whereas similar studies have analyzed an older population.[19–22] Age at first cast application,[4, 17, 23] in addition to etiology,[17, 18] has been shown to affect the responsiveness to casting. Mehta[4] found that curve resolution occurred in younger children (average age, 19 months) with smaller Cobb angles (average 32°). Sanders et al.[17] reported a resolution rate of 35% occurring in children who were casted at an average age of 1.1 years with an average Cobb angle of 37°. We report similar findings. The average age and Cobb angle at casting of curves that resolved were one year and 43°, respectively. Additionally, children who underwent casting at an average age of 21 months (1.76 years) were significantly more likely to achieve a Cobb angle <20° with serial casting. This is in contrast to older children who often improved but did not experience resolution. Recent studies have reported on serial casting in older age groups[18, 20, 24] as a means of delaying spinal instrumentation, but they were not able to demonstrate resolution of spinal deformity.

We report a 71% success rate of serial casting. This is possibly an underestimation of the success of treatment since 6/21 procedures with initial Cobb angles of 44° were performed in a supine position (thereby eliminating gravity and underestimating curve deformity) and only one of the most recent cases were in a supine position. The average Cobb angle of curves that improved was similar to curves that improved in other studies.[4, 17, 18, 25, 26] Baulesh et al.[18] reported an average improvement of 15° after casting idiopathic curves that averaged 46° at pre-treatment. Forty of 55 patients in the Sanders et al. study[17] improved to <40° at final follow-up. In their study, pretreatment Cobb >60° either progressed or measured > 40° at latest follow-up. We report similar findings: Cobb angles measuring 40° or more at most recent follow-up displayed an average pretreatment Cobb of 60°.

To our knowledge, no study has reported Cobb angles at consecutive time intervals. The assumption that correction occurs gradually during casting may be incorrect. We found that the majority of Cobb angle correction was achieved during the first casting. The Cobb angle corrected an average of 14° at initial casting and then improved gradually at each successive casting. This trend was not observed in Group 2. This suggests that the correction obtained during initial casting is an important prognostic indicator of successful treatment. This early observation may be helpful in determining a child's responsiveness to casting.

Our curve resolution rate (19%) is similar to that of Baulesh et al.[18] who reported resolution in 26% of patients with idiopathic scoliosis who were casted at an average age of 2.4 years. Studies with higher resolution rates[4, 17] included a larger proportion of children under the age of two years. Our results of curve resolution compare favorably to the rate of expected resolution in untreated, progressive IIS curves with similar characteristics.

Other studies have only reported pretreatment RVAD[17, 22] or failed to report RVAD[18, 20] during casting. In our study, an average initial RVAD ≥35° was associated with a Cobb

angle ≥40° at most recent follow-up. All of the Cobb angles in our study that were ≤20° at most recent follow-up had an associated RVAD <20° (average, 4°) and are thus at low risk of progression. Although not significantly different, the mean pretreatment RVAD in Group 1 was 17° versus 27° in Group 2. The findings suggest that pretreatment RVAD may be a determinant of response to casting. Our results of improvement in curves with an initial RVAD <20° parallel the findings of Mehta,[4] who reported a mean RVAD of 2° at latest follow-up in children with curve resolution. In contrast, Group 2 exhibited a mean RVAD >20° throughout the duration of casting. This highlights the importance of achieving correction of the rotation of the thorax and not merely the coronal Cobb angle.

Of the 21 patients in our study, 21% had double major curves which often have normal RVADs despite portending a poorer prognosis than main thoracic curves.[27, 28] The mean Cobb angle in the main thoracic curve group improved significantly, and all curves that resolved were main thoracic. Sanders et al.[17] similarly reported better results in thoracic curves compared to double major curves but did not describe these results in detail. Other casting studies also did not explore the relationship between curve type and improvement.[4, 18, 20, 25] The thoracic component of double major curves did not improve in our study, but the lumbar component did improve, suggesting greater responsiveness of this spinal segment. The difference in treatment response is likely multifactorial, and our results may be confounded in this subset: children with double curves underwent casting at an older age (mean, 2.9 vs. 1.8 years) and were more often in phase II at initiation of treatment (60% vs. 21%).

The majority of curves that improved were phase I at initial casting and remained in phase I throughout treatment. Phase II curves in Group 1 improved, but did not resolve. In Mehta's study,[4] 46 of 86 phase I curves resolved and, of those, 83% demonstrated an RVAD < 20°. In our study, five of 13 phase I curves resolved and all had an RVAD <20°. Cobb angle also appears to have an association with rib phase: rib phase I curves had a lesser initial Cobb angle (avg. 43° vs. 58°, $p < 0.05$), and phase II curves at latest follow-up exhibited much larger Cobb angles (17° vs. 53°, $p < 0.001$). Phase II curves were more likely to be refractory to serial casting regardless of age, paralleling previous findings that phase II is prognostic of curve progression.[27, 29] All children who are planned for spinal instrumentation are rib phase II; however, casting improved the Cobb angle in four phase II patients and, of these four, only one is planned for surgery. The remaining three Cobb angles are ≤33°, and the patients may be able to avoid surgery altogether. Radiographic rotation significantly improved from pre-casting to latest follow-up, which reflects the findings of Mehta.[4] This is an expected finding because derotation is a focus of the technique.

The average percent Cobb correction in Group 1 was 56%, which is nearly identical to the 59% percent correction reported by Smith et al.[25] RVAD was lower in Group 1 (mean, <20° throughout treatment) compared to Group 2 (mean, >20° throughout treatment) and may explain the differences in correction, emphasizing that achieving rotational correction is paramount.

The patients who are awaiting spinal implantation are differentiated from other patients by their large, average Cobb angle (60°) and RVAD (33°) at the onset of treatment. These patients met criteria for spinal implantation prior to casting but, due to their young age and high complication rates associated with guided-growth techniques,[14, 30–33] spinal implantation would have been suboptimal. Casting delayed spinal implantation an average of 4.4 years during a time of rapid skeletal growth and risk of progression. By delaying progression, casting clearly altered the natural history of the spinal deformity in these patients. In a study of 140 patients, Bess et al.[31] reported a 13% reduction in complication rates for each year of increased patient age at the initiation of growing rod instrumentation. Thus, we estimate that, to date, our patients who require implant surgery had a 57% decrease in complications associated with implants.

Weaknesses of our study include a retrospective design, small sample size, and lack of follow-up through the adolescent growth spurt, which would provide useful information regarding curve progression and additional procedures. Additionally, this study focuses on radiographic outcomes and does not include health related quality of life outcomes nor does it include a brace control group. Strengths of our study include our granular examination of the various time points in treatment, the exclusion of non-idiopathic diagnoses to better analyze a homogenous sample, and a standardized treatment protocol. Children who respond to casting will, for the most part, be able to delay growing spine surgeries without increasing x-ray exposure or anesthetizations, or avoid surgery altogether. Initiation of casting before 1.8 years of age is prognostic of achieving a Cobb angle ≤20°. Curve resolution can be expected in those who are casted at one year of age and have only a moderate Cobb angle. Achieving an RVAD <20° and imparting maximal Cobb angle correction by the initial cast are key aspects of treatment that predict success.

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Original Research

Gunshot Injuries of the Spine

Andre Jakoi, MD;[1] Justin Iorio, MD;[2] Richard Howell, MD;[1] Jay M. Zampini, MD[3]

[1]*Department of Orthopaedic Surgery, Drexel University College of Medicine, Philadelphia, PA;*
[2]*Department of Orthopaedic Surgery, Temple University, Philadelphia, PA;* [3]*Harvard Medical School, Spine Service, Department of Orthopaedic Surgery, Brigham and Women's Hospital, Boston, MA*

Abstract

Spinal gunshot injuries (spinal GSI) are a major cause of morbidity and mortality in both military and civilian populations. Spinal GSI now comprise the third most common cause of spinal injury. Firearms that produce spinal GSI can be divided into categories of high- and low-energy depending on the initial velocity of the projectile. Neural and mechanical spinal damage varies with these types and results from several factors including direct impact, concussion waves, tissue cavitation, and thermal energy. Management of spinal GSI also depends on several factors including neurologic function and change over time, spinal stability, missile tract through the body, and concomitant injury. Surgical treatment for spinal GSI is typically indicated for progressive neurologic changes, spinal instability, persistent cerebrospinal fluid (CSF) leak, and infection. Surgical treatment for GSI affecting T12 and caudal often has a better outcome than for those of cranial to T12. Surgical exploration and removal of missile fragments in the spinal canal are typically indicated for incomplete or worsening neurologic injury. Treatment of spinal GSI requires a multidisciplinary approach with a goal of maintaining or restoring spinal stability and neurologic function and minimizing complications. Concomitant injuries and complications following spinal GSI can present immediate and ongoing challenges to the medical, surgical and rehabilitative care of the patient.

Introduction

A spinal gunshot injury (spinal GSI) can be a devastating event leading to considerable morbidity and mortality of the injured. Once found primarily in military personnel, spinal GSI now also occur frequently in civilian populations because of the prevalence of firearm involvement in violent crime.[1] Although surgical and medical management of spinal GSI varies among healthcare providers, the overall goals of treatment include maintenance or restoration of mechanical spinal stability, neurologic function, and prevention of the complications of injury and treatment. Concomitant injuries add to the complexity of the pathology and often require a multidisciplinary team of providers for patient care. This purpose of this review is to summarize the ballistics, epidemiology, evaluation, treatment, and outcomes of spinal GSI among civilian and military populations.

Ballistics

Several of the factors that affect the severity of a spinal GSI are related to ballistics of the projectile. These factors include the velocity, path, and size of the projectile, and distance between firearm and target.[1] Firearms with a muzzle velocity less than 2,000 ft/sec are defined as "low-energy" and are typically responsible for spinal GSI in civilian populations. These firearms mainly cause direct injury to tissue as there is little to no blast or cavitation wave effect on the target. In contrast, high energy weapons, such as the AR-15 and M-16 military assault rifles (Colt's Manufacturing Co., West Hartford, CT), fire with a muzzle velocity of greater than 2,000 ft/sec. The damage produced by these firearms is a result of both direct impact of the missile to tissue and indirect injuries due to shock wave or cavitation wave effect.[2] Although high-velocity firearms were once isolated to military trauma, the use of these weapons has increased in civilian populations as has the observation of the characteristic injury patterns that they produce.[3]

The injury pattern and complication profile of spinal GSI can also be affected by the design of and material used in the manufacture of the bullet. Many bullets are manufactured with metallic plating or "jacket" designed to protect the lead bullet from deformation during firing and flight. Unjacketed bullets, which may remain undeformed after impact, are most often identified by the small amount of lead along the missile path.[4] Copper-jacketed missiles may be identified on radiographs by visualizing two distinct metal densities and observing a non-deformed object without traces of metal along its path.[4] Semi-jacketed missiles, in contrast, undergo a large amount of deformation and two different radiodensities, caused by separation of lead from copper, will be apparent in imaging studies. Hollow-point bullets flatten or "mushroom" on impact, which is in contrast to other missiles.[5] Rifle bullets are identified on radiographs by a "lead splatter" which occurs from shedding after entering soft tissues.[5]

Epidemiology

Spinal GSIs account for approximately 17–21% of all traumatic spinal injury.[6–8] These injuries are now the third most common cause of spinal injury in civilian populations, after fall from height and motor vehicle accidents.[9, 10] Over the past decade, the United States military has been experiencing an increase in spine trauma, with spinal GSI becoming the second most common cause of spinal injury among military populations after those caused by explosions.[8, 11] In all populations, victims are disproportionately male (78–91% of patients injured) with the highest incidence in the third decade of life.[8, 11–14] The thoracic spine is affected most commonly (45.6–63% of spinal GSI) followed by cervical (20–30%) and lumbar (10–24.5%).[10, 13, 15–17] Considering that, in the United States in 2011, the expected lifetime health care cost for a 25-year-old with tetraplegia, not including loss of economic opportunity, was more than $4.5 million per patient, the effect of both military and civilian spinal GSI on the healthcare system is staggering.[10, 18]

Initial Evaluation and Management

Physical Examination

A thorough, systematic evaluation is required for any patient with a suspected spinal GSI. The American College of Surgeons Advanced Trauma Life Support protocol should be initiated as soon as possible after injury.[19] The protocol begins with the "ABCDE" of the primary survey: evaluation for a patent airway, sufficient breathing and circulation, followed by a neurologic examination to characterize the deficits resulting from the spinal GSI ("D" standing for disability), and finally exposure of the entire patient to evaluate for gunshot entrance and exit wounds. Initial evaluation will often reveal concomitant injuries to other body systems, the treatment of which may take precedence over that of the spinal injury. This commonly includes damage to the airway, carotid or vertebral arteries, trachea and bronchi, and esophagus with cervical spinal GSI.[15, 20–23] Selective neck exploration should be undertaken by an otorhinolaryngologist or trauma surgeon emergently to address life threatening compromise to the airway, breathing, or circulation.[21, 24, 25] Additionally, lung, heart and great vessel damage will often be seen with thoracic or thoracolumbar spinal GSI[20, 26] and should be treated emergently if hemopneumothorax, cardiac tamponade, or persistent arterial bleeding threatens the patient's life.

With the evaluation of airway, breathing, and circulation complete, attention can be turned to characterization of the neurologic injury. Physical examination has been shown to have 100% sensitivity and 87.5% specificity for detecting spinal cord transection as well as injury significant enough to require surgery or immobilization.[27] Sensory, motor and reflex function of the cervical, thoracic, and lumbar regions should be tested as should the bulbocavernosus reflex. The clinical presentation of spinal GSI ranges from minimal clinically significant trauma to complete spinal cord injury and mechanical instability. Neurologic compromise has been reported to occur in 33–92.4% of patients with a majority of cervical and thoracic spinal GSI resulting in complete loss of neurologic function.[10, 12, 15, 25, 28, 29] This has been postulated to be a result of the small diameter of the spinal canal relative to the neural elements, and the variable and tenuous blood supply of the spinal cord. When injuries such as these occur as a result of blunt trauma, high dose corticosteroids can be prescribed to stabilize cell membranes, reduce local edema, and augment blood flow to neural tissue.[16, 30, 31] The use of steroids following penetrating spinal cord injury, however, is not recommended because of a higher risk of infection, gastrointestinal complications, and pancreatitis.[16, 17] Additionally, the use of high dose corticosteroids is not associated with an improved neurologic outcome.

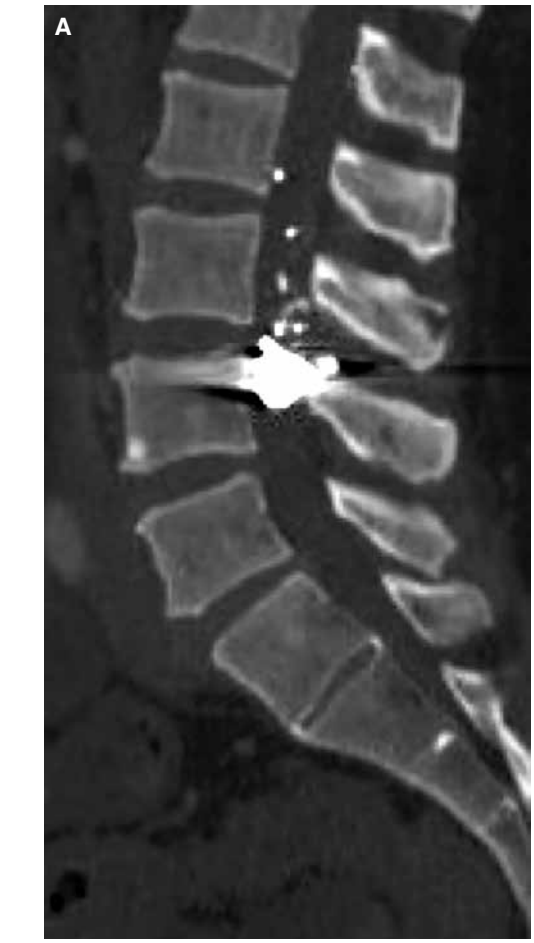
Initial evaluation and management of any potential spinal injury also includes immediate immobilization of the cervical spine and positional precautions with team "logroll" mobilization for the thoracolumbar spine until clinical and radiographic evidence can be obtained to assure mechanical spinal stability. While this is certainly the best practice, spinal GSI, particularly of the cervical spine, are associated with airway compromise in up to 84% of cases.[32] This information, coupled with reports that spinal instability following spinal GSI occurs less frequently in only 3.7–30% of cases,[10, 32] suggests that airway management should not be compromised because of the need to obtain proper imaging to evaluate spinal stability.[21, 25, 33]

The final element of initial trauma patient evaluation in the setting of spinal GSI is exposure of the patient and assessment for entry and exit wounds. All patients with a wound — and all spinal GSI patients have at least one wound — should be assessed for history of tetanus prophylaxis. A history of greater than three doses of tetanus toxoid vaccine and less than five years since the last dose requires no further action.[34] For patients with unknown tetanus prophylaxis history or fewer than three doses of tetanus toxoid, both tetanus immunoglobulin and a tetanus toxoid containing vaccine should be given. Patients with a history of three or more doses of tetanus vaccine, but greater than five years since the last dose, should be given only a tetanus toxoid containing vaccine.

Antibiotic Prophylaxis

The presence and location of a wound can also assist in two other important manners: evaluation for associated injury to other body systems, and the assessment for potential risk of infection. Concomitant injuries sustained with cervical and thoracic spinal GSI will typically be identified during the initial evaluation of airway, breathing, and circulation given the critical nature of those injuries. Injuries to the abdominal viscera occur more commonly than other associated injuries following thoracolumbar spinal GSI.[15] These injuries would be treated by an appropriately trained

abdominal or trauma surgeon. The impact of a visceral injury on the evaluation and treatment of the spinal GSI is the potential for spinal infection (Figure 1), although high-level evidence to guide antibiotic selection and duration is sparse. It has been accepted practice to prescribe broad-spectrum antibiotics to cover both Gram-positive and Gram-negative bacteria at the time of penetrating abdominal injury regardless of spinal involvement and before surgical intervention because of evidence suggesting that preoperative antibiotic use can reduce the rate of infection to 7–11% compared with a rate of 30% in patients receiving antibiotics only during or after surgery.[35] For spinal GSI and penetration of the abdomen, standard practice has been to continue antibiotics for 2–3 days if no visceral penetration was identified and for 5–14 days for visceral injury.[20, 36–38] The empirical evidence for this practice, however, is mixed.[39] Kumar and colleagues reported that antibiotic prophylaxis for at least seven days reduced the risk of spinal infection regardless of the organ perforated.[36] Roffi and colleagues reported spinal or paraspinal infection in 7% of 42 patients treated for spinal GSI and associated visceral perforation even after a minimum of six days of prophylactic antibiotics.[38] In contrast, Kihtir and colleagues reported no spinal infections in 21 patients with spinal GSI and transperitoneal penetration following irrigation of the missile track and only 48 hours of antibiotics.[40] Recently, Rabinowitz and colleagues reported only one paraspinal psoas infection in 51 patients (2%) with spinal GSI with visceral injury and concluded that antimicrobial prophylaxis of 24–48 hours is sufficient for the prevention of most infections in this population.[41] Thus, although high-quality data do not exist to conclusively guide a decision, sufficient evidence does support the use of preoperative antibiotics with continuation for 24 hours for prevention of infection in spinal GSI with visceral perforation.[39] This recommendation appears to provide adequate prophylaxis while avoiding the prolonged courses of antibiotics associated with the development of drug-resistant organisms, fungal and *Clostridium difficile* superinfections, and the healthcare costs associated with treating them.[41–43]



Figures 1A-B. Preoperative CT scan in the sagittal **(A)** and axial planes **(B)** of a patient with a spinal GSI at the L3 level traversing the large bowel and pancreas before entering the spine. Surgical intervention was performed when the patient developed clinical signs of spinal and psoas infection.

Definitive Management of Spinal GSI

Secondary Survey and Evaluation

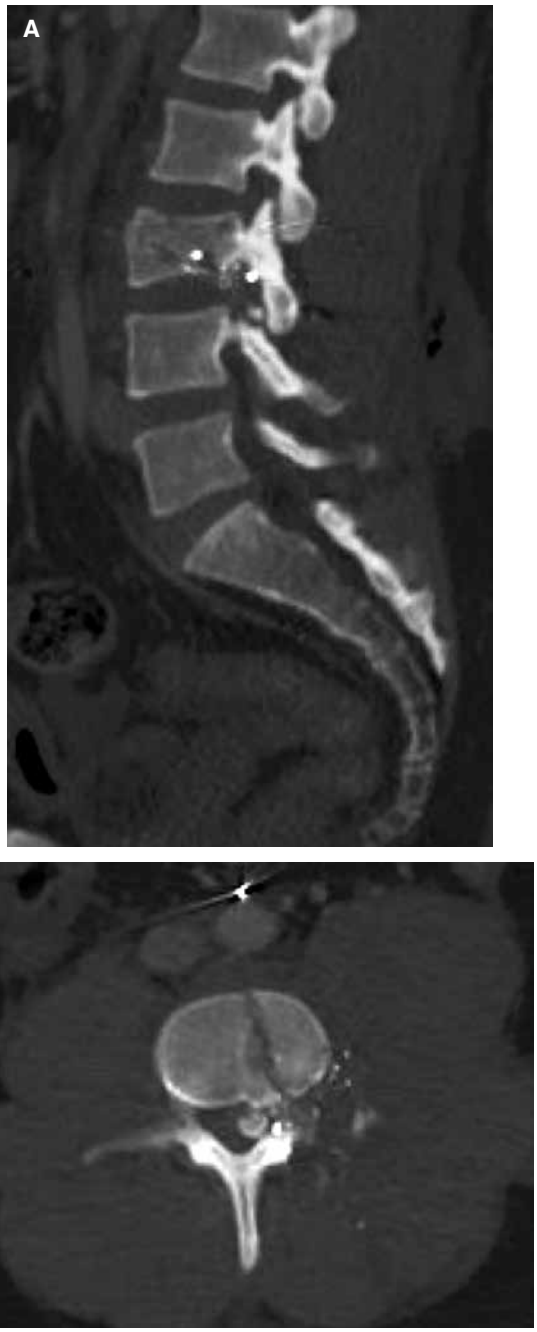
The definitive management of spinal GSI is determined by neurologic function, mechanical spinal stability, associated spinal injuries including cerebrospinal fluid (CSF) leak, and injuries to other body system. These factors should be assessed following the immediate stabilization of the patient. A neurologic examination should be repeated hourly in patients with incomplete neurologic injuries so that any change in function can be rapidly determined and action taken. An assessment of mechanical stability of the spine should be aided by radiographic imaging. Computed tomography of the neck, thorax, abdomen or pelvis can typically be performed rapidly to assess for fractures of the vertebral bodies and posterior elements. The anatomic region should be chosen based on the neurologic deficit and location of entrance and exit wounds. MRI can be used to evaluate the ligamentous and neural structures but can theoretically induce migration of bullet fragments. A detailed discussion of the use of MRI after spinal GSI is included below.

Indications for Surgery

The overarching goals of surgical treatment of spinal GSI are to optimize the potential for recovery of neurologic function and to minimize the occurrence of complications. The specific procedures should be chosen rationally by the specific problems to be addressed surgically and should follow the manner in which decisions are made for treatment of other spinal conditions. Compression of neural elements is addressed by spinal decompression. Segmental instability is addressed using instrumentation and fusion for reconstruction and stabilization. Disruption of sagittal and coronal balance is addressed using the principles of spinal deformity surgery. The discussion below will outline the surgical decision-making factors to spinal GSI. Because surgery for stable, complete neurologic deficits has not been shown to improve sensory or motor recovery,[25, 44–46] patients without clear indications for surgical intervention should treated without surgery. Furthermore, surgical treatment has been shown to result in a higher incidence of complications (21%) compared to patients treated without surgery (7%).[23]

Loss of Neurologic Function

A progressive loss of neurologic function with radiographic evidence of neural compression has been considered an absolute indication for surgical intervention[20, 47–50] particularly for worsening radicular function following lumbar spinal GSI (Figure 2).[14, 51] A preponderance of the available data appears to support this indication for surgery although no large, well controlled studies have been performed to make this recommendation with a high level of evidence. Duz and colleagues performed surgery on 15 patients with progressive deficits after spinal GSI and showed significant neurological improvements compared to those with stable deficits.[52] In a review of seven patients with progressive decline, Simpson and colleagues reported that three patients (43%) showed improved function following surgery.[45] Similarly, Beaty and colleagues reported that, from a larger series of 144 cervical spinal GSI, two patients had progressive deficits and both improved one ASIA grade after decompression.[10] Finally, it should be noted, and patients appropriately counseled, that bowel and bladder function, if compromised by spinal GSI, often remains impaired regardless of intervention.[14]



Figures 2A-B. Preoperative CT scan in the sagittal **(A)** and axial planes **(B)** of a patient with a spinal GSI at the right L3-4 facet severing the L3 nerve root and causing progressive dysfunction of the cauda equina.

Bullet Removal

Bullet fragments and intact bullets often remain within the spinal canal following spinal GSI (Figure 1). As with neural compression of any other etiology, the goal of bullet removal is neural decompression with the hope that decompression will allow for optimal restoration of neurologic function.[20, 51] Specific clinical factors can indicate that removal of the fragments may be beneficial and contribute to restoration of neurologic function. As discussed above, a progressive neurological deficit or incomplete SCI in the setting of radiographic evidence of neural compression are well supported indications for surgical intervention,[2, 13, 14, 20, 25, 47–51] including for removal of bullet fragments in the cervical, thoracic, and lumbar spine. Removal of bullet fragments for complete, static SCI, however, has not been reported to show significant restoration of neurologic function.[13, 25, 51] Additionally, fragment removal from spinal segments cranial to T12 has been reported to be less likely to restore function than has removal of fragments from T12 and caudal, possibly related to the preponderance of complete cord lesions associated with cervical and thoracic GSI.[25, 48, 51] At best, restoration of

one to two levels of function can be expected after bullet removal.[20, 25]

Bullet fragment removal has also been reported to be beneficial for patients in whom fragments have migrated within the spinal canal following injury.[53–59] Fragment migration may occur as a result of gravity or variation of body position following patient mobilization and may occur early after injury,[57] or following even a substantial delay.[53, 55, 58] All patients treated for delayed neurologic symptoms reported restoration of neurologic function following bullet fragment removal. Although the evidence for bullet fragment removal for migration is comprised only of sporadic case reports, the possibility should be considered in the neurologically intact patient following spinal GSI whose function changes over time.

If removal of bullet fragments is to be undertaken, the surgical approach to the spine should be chosen logically and can often be dictated by the position of the bullet fragment. A transoral, posterior, or posterolateral approach can provide safe access to the atlanto-axial complex.[33, 60] Laminectomy can be performed to access bullet fragments positioned dorsally in the spinal canal and anterior corpectomy for fragments positioned ventrally or for surgery performed in conjunction with stabilization of vertebral body fractures when necessary.

The presence of bullet fragments in the spinal canal is not associated with an increased risk of infection, regardless of visceral penetration prior to entering the spinal canal.[38, 40, 61] Prevention of infection, therefore, should not be used as an indication for exploration and removal of bullet fragments following spinal GSI.

Spinal Instability

Compromised spinal stability has been suggested as an indication for surgery on patients with spinal GSI.[10] Although spinal GSI typically do not compromise spinal stability, injuries with significant vertebral body comminution, bilateral pedicle or facet fracture, or posterior ligamentous disruption can lead to compromised sagittal and coronal balance as well as frank translational displacement which would require surgical stabilization.[21, 52, 62] Iatrogenic instability can also result from wide decompressive laminectomy and has been suggested to be the main reason for instability following spinal GSI.[46, 63] Similar to the discussion above, a preponderance of evidence suggests that stabilization be performed for compromised spinal stability (injury to all three spinal columns) with reports concluding that surgical stabilization can either lead to frank improvements in neurologic function,[52] or facilitate rehabilitation by allowing earlier mobilization, even if neurologic improvements are not realized.[10]

Repair of CSF Leak

Dural tears have also been identified as indications for surgery in patients with spinal GSI.[20, 38, 64] In the setting of blunt trauma, ligamentum flavum disruption on MRI or vertical laminar fracture suggests a high likelihood that a dural tear will be discovered at the time of surgery.[65] With spinal GSI, however, any bullet or fragment that traverses the spinal and directly damages the spinal cord or cauda equina will, by default, disrupt the dura. Symptomatic dural tears must be sought out through clinical signs and symptoms typical of CSF leak: persistent and abundant serous drainage from the wound, positional headaches, diplopia, photophobia, nausea. Once identified, these defects should be repaired to reduce the risk of persistent CSF fistula, meningitis, and loss of neurological function. Repair of dural tears in the cervical spine can be problematic due to poor visualization of the ventral thecal sac. The application of fibrin glue on the defect, placement of a submuscular drain, and maintaining patients in an upright position effectively treated cervical CSF leaks in one small series.[65] In the lumbar spine, laminectomy and dural repair, either primarily or by use of a graft, is an appropriate treatment. A subarachnoid drain can be placed for persistent CSF leaks.

Timing of Surgery

The optimal timing for surgical intervention in patients with any spinal injury has been a source of much debate over the past few decades.[66–68] In patients with blunt injury to the spinal cord, the most current reports suggest that surgical intervention within 24 hours of injury may offer more neurologic benefit than if surgery is delayed.[68] In addition to the potential for improved restoration of neurologic function, early surgery has been reported to reduce the risk of complications as well.[52, 69–71] This includes a lower risk of pneumonia, fewer days on a ventilator, fewer infections, and shorter ICU stay. Patients who underwent surgery more than two weeks following injury have also been reported to develop arachnoiditis or spinal abscess at a higher rate than if surgery were performed earlier in the course of treatment.[48] Recommendations for the timing of surgical treatment of patients with spinal GSI are lacking and can only be inferred from those regarding the treatment of blunt spine and spinal cord trauma.

Role of Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) following GSI can potentially induce migration of any ferromagnetic metal retained inside the body just as it can to such metals outside the body in the vicinity of the magnet. Materials used in the manufacturing of bullets and shotgun pellets are often copper or lead and, unlike steel, are nonferromagnetic and are therefore theoretically safe for MRI.[72] Some bullets do, however, show ferromagnetism *in vitro,* purportedly from steel impurities. Nonetheless, clinical use of MRI in patients with retained bullet fragments has been reported to be safe.[10, 73–76] In all reports, no neurologic sequelae resulted from performance of up to 1.5 Tesla MRI on patients with retained frag-

ments. Image distortion was reported and was related to the size of the metallic foreign body. All reports thus far have been of small sample sizes and without knowledge of the metallic content of the missile fragments, thereby compromising the generalizability of the findings. The decision to proceed with MRI following spinal GSI with retained bullet fragments should therefore be made on a case-by-case basis with the patient duly informed of the risk of the procedure and the empiric evidence for its safety.[10]

Metal Toxicity

Lead toxicity, known as plumbism, results from the effects of lead at the cellular level, including inhibition of neurotransmitter release, competition with calcium, and dysregulation of cellular metabolism.[77, 78] Consequences of toxicity include anemia, abdominal pain, anorexia, nephropathy, lethargy, encephalopathy, and motor neuropathy. Symptoms can occur intermittently as lead is released from bone marrow during the hematopoietic activity of a stress response.[79] Lead intoxication has been reported in case series of retained bullets within joint spaces and intervertebral discs.[80–83] Bullet location is the most important predictor of symptom development.[79] Intraarticular missiles more commonly cause systemic toxicity because synovial fluid dissolves lead, which enters the circulatory system via lymphatics. The onset of symptoms may be acute but are more typically insidious, developing even up to 40 years after exposure.[84] Missiles in soft tissues or bone are typically asymptomatic because they become encased in fibrous tissue and limit the dissolution of lead.

Copper, on the other hand, produces toxic effects on tissues by direct contact by interacting with carboxylic acid, amides, and amines, ultimately resulting in protein degradation.[4, 85, 86] Although copper applied experimentally on to neural tissue has been shown to induce neurolysis, myelinolysis, and other local tissue necrosis,[78, 86, 87] systemic copper toxicity following spinal GSI has not been reported. Some authors have advocated the removal of metal fragments from the spinal canal to avoid such toxicity and tissue necrosis.[78, 88]

Summary

Spinal GSI is can be a devastating event that leads to considerable morbidity and mortality of a patient from both the neurologic injury as well as the concomitant injury to other body systems. Definitive treatment of the spinal injury depends on the mechanical stability of the spine, the level of neurologic impairment, and change in neurologic function over time. The outcome of surgical intervention for spinal GSI has been shown to be better for patients with incomplete neurologic injuries and injuries to T12 and caudal. The overall management of a patient with a spinal GSI requires a multidisciplinary approach utilizing the ATLS protocol, emergency physicians and trauma surgeons, neck, chest, and abdomen surgeons, spine surgeons, and rehabilitation specialists.

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Original Research

Autologous Bone Graft Harvesting: A Review of Grafts and Surgical Techniques

Andre M. Jakoi, MD;[1] Justin A. Iorio, MD;[2] Patrick J. Cahill, MD[3]

[1]*University Orthopedic Institute at Hahnemann, Philadelphia, PA;* [2]*Department of Orthopaedic Surgery, Temple University Hospital, Philadelphia, PA;* [3]*Shriners Hospital for Children, Philadelphia, PA*

Introduction

Bone grafting is a necessary aspect of spinal fusion. The "gold standard" bone graft is autologous. Autologous bone grafting for spinal surgery increases fusion rates and can provide structural stability. The ideal bone graft has the following features to optimize fusion potential: osteogenesis, osteoinduction and osteoconduction. Additionally, the graft should be non-immunogenic, biomechanically stable, and avoid disease transmission. *Osteogenesis* refers to the native capacity to form bone via living stem cells within bone marrow. This process is accomplished by osteoblasts under the influence of many factors, such as bone morphogenetic protein (BMP). Osteoinduction, via growth factors, induces the differentiation of mesenchymal cells to become osteoprogenitor cells and, ultimately, osteoblasts. *Osteoconduction* refers to the structural composition of a bone graft that serves as a scaffold for new bone formation and vascular ingrowth. Allograft, in contrast to autograft, is devoid of bone marrow and therefore lacks osteogenic potential. Instead, allograft augments the healing process primarily through osteoconduction.[1, 2] Although autograft is considered superior for its fusion potential, harvesting requires technical expertise and is associated with surgical time, postoperative pain, infection, hematoma, neurovascular injury, and cosmetic deformity at the site of graft extraction.[3–5] Since first reported in 1911,[6] different methods of acquiring and using bone graft have been developed. There are several areas from where bone graft can be harvested and the decision is dependent upon surgeon comfort, amount of required graft, purpose (i.e., structural vs. onlay), and level of spine surgery (cervical, thoracic, or lumbar). Each bone graft donor site has distinct advantages and disadvantages. This review will discuss the different graft types and appropriate surgical technique for harvesting of each.

Types of Bone Graft

Cancellous Graft

Cancellous bone graft from an autologous source is an excellent medium for fusion.[7] It is often harvested from the iliac crest (anteriorly or posteriorly) but can also be obtained from the distal radius, distal femoral metaphysis or proximal tibia. Cancellous graft is primarily osteoconductive but is also osteoinductive and osteogenic, thus demonstrating all key properties. The greater osteoconductive properties are a reflection of the survival of osteoblasts and endosteal lining cells on the graft surface during transplant; many of the marrow cells, which are responsible for osteogenesis, undergo cell death.[1, 8] Growth factors and cytokines involved in osteoinduction are released during graft resorption.[1] When obtained for fusion of the cervical spine, purely cancellous bone is most often used to pack a strut graft or as onlay material for posterolateral arthrodesis. Cancellous bone alone is unable to provide stability and should not be used as a structural element in a surgical construct. However, cancellous autograft revascularizes within several weeks, induces more bone formation than cortical graft, and is replaced by host bone and marrow within one year.[1, 9, 10]

Cortical Graft

Cortical grafts are used when structural integrity is the primary concern. Harvest sites include the fibula, ribs and iliac crest. These grafts can be harvested either with or without their vascular pedicle. They are most often used as a strut graft in vertebral reconstructions in the setting of a corpectomy. Although cortical grafts can be harvested from various sites, knowledge of the advantages of each graft source is required for appropriate surgical planning. Iliac crest autograft, for example, is suboptimal for multilevel corpectomies because it cannot resist large axial stresses, its harvest produces a large bony defect, and the curved shape confers difficulty with graft insertion into the cervical spine.[11] A fibular graft is a more popular choice in this situation. The primary purpose of the strut is support and osteoconduction; however, some osteogenesis may be provided by osteoblasts within the graft.[12] The center of the graft can be filled with cancellous bone to add osteogenic and inductive properties to the graft.

Corticocancellous Graft

The combination of the structural integrity of cortical bone and the osteogenic properties of cancellous bone make corticocancellous grafts popular choices. Per unit weight, bone morphogenetic protein, which is osteoinductive, exists in cortical bone in higher concentrations than cancellous bone, thus providing important factors for graft incorpora-

tion.[13] This type of graft may be harvested from the iliac crest, fibula, ribs, or laminae (during routine cervical, thoracic, or lumbar laminectomy). Corticocancellous bone obtained from the anterior iliac crest is preferable to bone obtained from the posterior pelvis if early load-bearing of the graft is a concern because anterior pelvic bone is able to support greater axial loads.[14] Iliac crest graft can be harvested from either the inner or outer tables of the ilium; bone removal from the inner table is preferable if maintaining abductor muscle function is a primary concern.[15] The fibula, although stronger than iliac crest graft, lacks the abundant cancellous bone which is present in the pelvis.[14] If used as an onlay graft, stability is achieved though dorsal fixation.

Autograft Types

Local Bone

Bone graft material can be obtained from vertebral bodies at the time of anterior decompression. The drilled bone that remains after the endplates are prepared can be collected and utilized for grafting. The center of a strut or allograft ring can then be filled with this bone graft without the need for a separate incision. Saving the posterior elements removed during laminectomy is a simple method of obtaining bone graft. Kho and Chen[16] found that 94.9% of lumbar spondylolisthesis patients obtained solid fusion on radiographs with laminectomy bone alone. A disadvantage of laminectomy bone, however, is the small amount of bone volume. In addition, the high ratio of cortical to trabecular bone means that there is a relatively low number of osteogenic cells.[17] This graft is best utilized by separating the bone from soft tissues and grinding the graft into a heavy paste. When collected appropriately, this material may be enough to avoid a second incision for remote autograft harvesting. In a prospective study, Niu et al.[18] found that when laminectomy bone is combined with bone marrow aspirate, which is both osteoinductive and osteogenic, one-level fusions were achieved at a similar rate to those achieved by autogenous iliac bone crest graft.

Iliac Crest

Despite the associated donor site morbidity, increased blood loss, operating time and hospitalization time, iliac crest autograft is considered the gold standard because of the associated excellent fusion rates.[19, 20] Studies have reported fusion rates as high as 92% with the use of autologous iliac crest bone grafts (ICBG).[21, 22] Autologous ICBG is more commonly used for multi-level fusions and L5-S1 decompressions compared to other types of bone grafting because fusion rates for multi-level surgeries are improved with ICBG compared to other graft options, and pseudarthrosis at L5-S1 is a known concern.[19, 20]

Anterior

The anterior approach to the iliac crest is used for anterior reconstructive procedures. Cancellous or corticocancellous grafts can be obtained with this method. This approach may be preferable during a procedure in which the patient is already supine, but a disadvantage is the lower volume of obtainable bone. Harvesting from the anterior iliac crest should be used only if less than 20–30 cc of bone is required.[1] The patient is positioned supine with a bump under the ipsilateral gluteal region to accentuate the anterior superior iliac spine (ASIS). The incision is made parallel to the hip and a wide area should be sterilely draped. At least 3 cm of the ASIS needs to be kept intact to avoid injury to the insertion of the sartorius muscle and inguinal ligament.[4, 15] The lateral femoral cutaneous nerve may have an anomalous course in this region and should be avoided.[4, 15] The integrity of the ASIS should not be compromised or a stress fracture can result from the forces of the sartorius and rectus femoris musculature.[4, 15]

A 3–6 cm curved incision is placed 3–4 cm lateral to the ASIS. The incision, which runs superiorly and posteriorly, is made over or just below the crest to minimize postoperative pain. The fascia should be opened carefully to facilitate proper closure at the end of the procedure. Inadequate fascial closure increases the risk of hernia. The periosteum is incised and elevated from the ilium, thus exposing cortical bone which can be perforated with a Rongeur or osteotome. The iliac tubercle, located 5 cm posteriorly from the ASIS, contains a large amount of cancellous bone for harvesting. Once the cortex at the brim of the ilium has been violated, curettes are used to remove the inner graft material. Wolfe and Kawamoto[23] reported their technique, in which an osteotome is used to enter the iliac crest obliquely, thus separating the inner and outer tables from a central graft, which provides a block of bone up to 10 by 8 cm in size. The muscle and periosteum are left attached to the outer ridge of the iliac crest. Wire or sutures are used to reapproximate the inner and outer ilium. Tricortical grafts require more dissection. A 6 cm incision is followed by subperiosteal dissection of the inner and outer tables of the ilium. Bone graft is harvested at least 3 cm posteriorly from the ASIS by using parallel saw blades to enter the tables of the ilium. An oscillating saw is preferable to an osteotome because of the graft weakening that may occur with osteotomes.[24] The peritoneal cavity, which lies medially, should not be violated. Careless dissection of the iliacus from the inner wall can injure the iliohypogastric or ilioinguinal nerves, femoral nerve, deep circumflex iliac artery, and iliolumbar arteries (Figure 1).[4] Once the iliac crest is fully exposed, the size of the graft should be measured carefully in all three dimensions. The graft is fashioned with a reciprocating sagittal saw. Final removal of the bone may require the use of osteotomies to free the bone from attachments in the inferomedial region. Hemostasis of the exposed bony surfaces may be achieved using several techniques which include bone wax or other hemostatic agents. If necessary, a drain may be left in place to avoid formation of a seroma.[4]

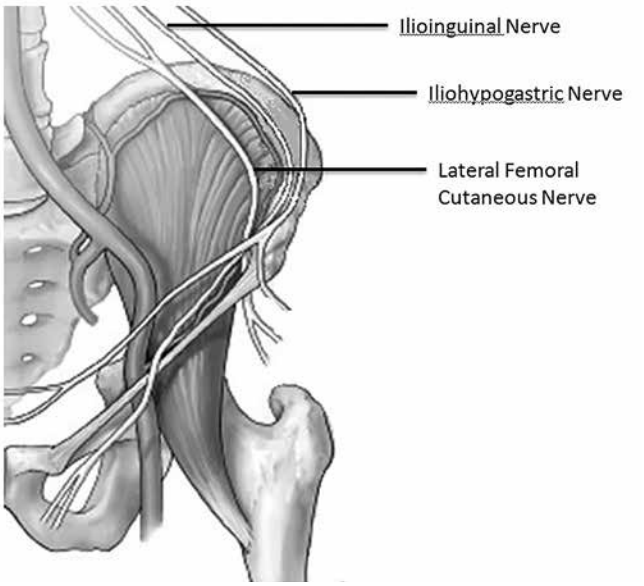

Figure 1

Posterior

For posterior procedures, onlay graft material may be needed to supplement the fusion construct. Dorsal spinal surgeries do not require structural graft because dorsal instrumentation is typically implanted. The advantage of dorsal iliac crest grafts is the large volume of available bone. Two approaches are available: bone can either be harvested through the midline lumbar incision that has been made for the current spinal decompression, or a separate incision can be made lateral to the surgical site.[11] If graft is to be harvested from the midline lumbar incision, a fascial incision is made approximately 6 cm laterally from the site of decompression. Dissection risks injury to the superior cluneal nerves, which exit from the lumbodorsal fascia and course as close as 6 cm lateral to the PSIS.[15] The fascia over the PSIS is incised and elevated from the ilium with electrocautery and a Cobb elevator. Dissection should be at least 4 cm lateral to the PSIS to avoid iatrogenic injury to the sacroiliac joint and neurovascular structures exiting from the greater sciatic notch.[1] Externally, the sciatic nerve, superior gluteal nerve and branches of the superior gluteal artery travel cephalad after exiting the greater sciatic notch. Internally, the superior gluteal artery and the ureter are of concern (Figure 2). An opening in the cortical surface, directed caudally, is made with an osteotome. Cancellous bone can be obtained using curets or gouges. Bone bleeding is controlled by packing the area with sponges and applying bone wax or hemostatic agents. The defect can be filled with allograft.

If a separate incision is required for bone graft harvesting, a vertical incision is made over the posterior superior iliac spine (PSIS) with the patient in the prone position. The alternative transverse incision, if used, should be made cautiously so as to avoid laceration of the cluneal nerves. Dissection through the fascia and graft removal occurs as described above.

To obtain a corticocancellous graft, a longer exposure is used. The incision for the exposure of the posterior iliac crest should not exceed 8 cm from the PSIS to avoid injury to the superior cluneal nerves, which course over the crest. The fascia over the crest is exposed and opened. The musculature is elevated using subperiosteal technique. The dissection should not extend too inferiorly to avoid jeopardizing the structures in the region of the sciatic notch.

The subcrestal approach is an alternative method for obtaining bicortical and cancellous graft. An incision 1 cm lateral to the PSIS allows exposure as described above. Instead of simply perforating the surface of the cortex, however, a unicortical window can be cut with osteotomes or a saw. Additional cancellous bone can then be harvested through the same opening. Care should be exerted during closure of the fascial layer to avoid damage to the gluteal musculature. With meticulous hemostasis, a postoperative drain is unnecessary.

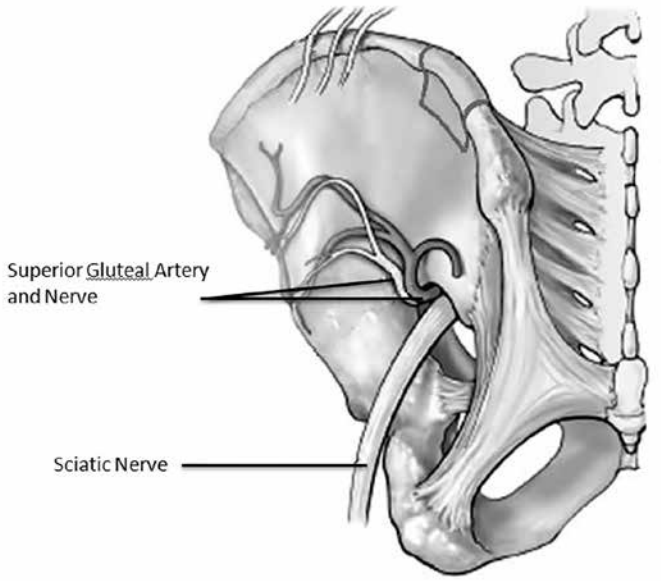

Figure 2

Fibular Strut Graft

Harvesting of autogenous fibula has been associated with morbidity, but high rates of arthrodesis have been reported[15, 25, 26] and fibular graft provides strength and a long construct length. In cases of failed fusion, vascularized graft can be used.[27] Compared to nonvascularized cortical grafts, vascularized grafts heal rapidly at the site of insertion and are stronger during the first six weeks after surgery because they do not undergo resorption.[28] The patient can be placed prone, lateral or supine. A straight lateral incision followed by dissection between the posterior and lateral compartments allows access to the middle third of the fibula. Proximally, the peroneal nerve is at risk at the level of the fibular neck. Distally, 10 cm of bone should be maintained above

the ankle joint to avoid producing ankle instability. As much as 18 cm of fibula can be harvested.

An incision is made between the peroneal and soleus muscles. Dissection is carried through the lateral intermuscular septum. The plane is dissected sharply until bone can be palpated. The fibular surface is covered in muscle origins that can be dissected free using a subperiosteal technique. An oscillating saw is preferable for bone removal because osteotomes can fracture the graft. Meticulous hemostasis is then achieved. The fascia is not closed to avoid the possibility of compartment syndrome and often a drain is placed. The fibula carries as much as 15% of the axial load and is the origin of many muscles of the leg. Consequently, walking may be uncomfortable for up to one year postoperatively.[15]

Rib

Rib autograft is an excellent adjunct for occipitocervical as well as subaxial fusions.[29] Sawin et al.[29] performed a comparative analysis of 600 patients who received either autologous rib or iliac crest bone graft for posterior cervical fusion. They reported excellent fusion rates in both groups (rib, 98.8% vs. iliac crest, 94.4%; $p = 0.056$), but significantly less donor site morbidity in those who received rib autograft (3.7% vs. 25.3%; $p < 0.001$) even after chronic pain was removed from the iliac crest group. Autologous rib graft can be used to span large defects, such as after cervical laminectomy, and is ideal for patients with large or abnormally-shaped occiputs (rendering iliac graft placement difficult).[30] Rib autograft is also easily harvested during thoracic spine surgeries. The graft is corticocancellous, strong, readily available, and has a variable shape (flatter posteriorly and more curved anteriorly) that can be harvested to fit the lordotic curvature of the occipitocervical spine. The flatter, medial rib is convenient for procedures of the atlantoaxial and subaxial spine.[29] An additional advantage of rib compared to iliac crest graft for the cervical spine is multiplanar stability; rib graft has circumferentially intact cortices and thus better resists bending and rotational forces of the upper spine.[29] Complications of harvesting include pneumothorax and chest wall neuralgia.[31]

The patient is placed in the prone position as needed for a posterior spinal operation and the thorax is included in the surgical field. An oblique incision is made over the rib to be removed. The overall length, shape, and sagittal contour of the rib that is required is determined by the area of arthrodesis.[30] The tissues are dissected in-line with the incision until the periosteum is reached. A circumferential subperiosteal dissection will expose the bare surface of the rib and release all of the soft tissues. Care should be taken near the inferior aspect of the rib to avoid the neurovascular bundle as well as the pleural space (Figure 3). A rib cutter may be used to incise the rib both proximally and distally for removal. An oscillating saw or high-speed drill is preferred because a rib cutter can splinter the rib adjacent to the cut surface. Sufficient bone should be removed to provide both structural and morselized autograft.[30] The parietal pleura should be irrigated and inspected for an air leak by hyperinflation of the lungs. Small defects in the pleura can be repaired primarily. Structural graft is placed on both sides of the dorsal spine and secured by wires followed by packing of morselized bone onto the fusion site. The wound is closed in layers. Postoperatively, a chest radiograph is obtained to monitor for pneumothorax.

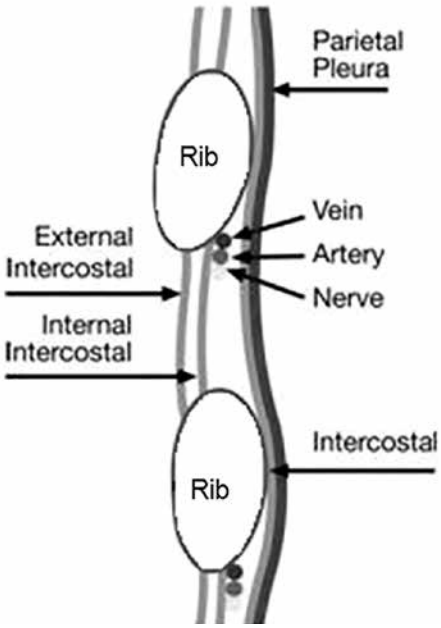

Figure 3

Outcomes

Autogenous iliac crest bone graft has excellent fusion rates and is the standard to which all others are compared. Sengupta et al.[20] compared clinical and radiographic outcomes of autogenous local bone versus ICBG in 76 patients with spinal stenosis who underwent decompression and posterior spinal fusion. Overall fusion rates for local bone (65%) and ICBG (75%) were similar ($p = 0.39$); however, ICBG achieved significantly greater fusion rates (66%) than local bone (20%) for fusions involving at least two levels ($p = 0.029$). Clinical outcomes were independent of fusion rates and were similar between groups. Other studies of local bone graft have similarly reported excellent fusion rates.[32–34] Radcliff et al.[19] performed a subgroup analysis of the Spine Patient Outcomes Research Trial (SPORT) to evaluate the outcomes of posterior ICBG versus non-ICBG bone graft, which included both autologous and allogeneic substitutes. At four-years follow-up, no differences in complications (including hematoma and infection), subsequent surgical operations, or clinical outcomes were found. Autogenous fibular grafts have additionally shown good results.[25, 26] In a series of 145 patients (324 levels) who underwent anterior

cervical fusions, 84% of three-level and 93% of two-level fusions achieved union.[25] A fusion rate of 100% has also been reported in patients who underwent anterior fibular strut grafting for correction of thoracic kyphosis.[35] Autogenous rib graft for cervical procedures has shown fusion rates similar to ICBG, but with less morbidity.[29]

Donor-Site Morbidity

Acute and chronic donor-site pain affecting up to 60% of patients after ICBG has been reported.[36–39] An advantage of using local bone, rib, or fibular autograft is the lower rate of donor-site pain compared to ICBG. The incidence of donor-site pain after fibula harvesting varies from less than one-percent to 15%[25, 40] and in Sawin et al.'s[29] large series of rib autograft harvesting, no patient experienced postoperative chest wall pain. Fibula and rib harvesting are associated with other complications, however. Muscle weakness, compartment syndrome, and neurovascular injury may occur from fibula harvesting[5, 15] while harvesting of ribs may result in pneumonia and pneumothorax.[29, 31, 41]

Reconstruction

Pain after ICBG harvesting is believed to result from elevation of the abductors from the ilium, penetration of the outer iliac cortex, and injury to the lateral femoral cutaneous, ilioinguinal, and cluneal nerves.[4, 42, 43] Thus, minimizing injury to these structures will reduce discomfort. Continuous infusions of local anesthetics are an acceptable treatment for reducing perioperative pain. In a prospective, randomized, double-blind trial of 0.5% bupivacaine versus placebo, patients who underwent ICBG harvesting and received 48 hours of local anesthetic reported significantly less acute and chronic pain at four-years follow-up than those who received the placebo. Morphine injections into the harvest site have also decreased acute postoperative pain for up to 24 hours.[44]

Recently, strategies to minimize graft related complications have been under investigation. The graft site can be reconstructed by several different methods.[27, 45–47] For anterior graft sites that have had only cancellous bone removed, the empty cavity of the iliac crest can be filled with allograft cancellous expander. This choice may promote internal healing and may help the crest to regain a more normal density. Backfilling the harvest site with coralline hydroxyapatite reduced pain and demonstrated increased bony ingrowth compared to controls in a series of spine patients.[48] Another study of iliac crest backfilling showed significantly fewer medullary defects with hydroxyapatite-calcium triphosphate compared to controls on postoperative CT scans.[49] The defect left after a strut is removed is a more difficult problem. A large defect can leave a painful and aesthetically unpleasing deformity. Such deformities can be addressed with a variety of reconstructive techniques. The gap can be filled with polymethylmethacrylate or other ceramic material which is molded to recreate the anatomy of the iliac crest.[45] Recent approaches combine absorbable mesh with bone cement to remodel the iliac crest. This material provides a lattice against which new bone may form. The bioabsorbable nature of the mesh obviates concern about implanting another foreign body. Preliminary results using this technique have been promising.[47] However, with the advent of osteoinductive materials like BMP, the need for iliac crest reconstruction techniques may be short lived.

Conclusion

The use of harvested autograft in spinal fusion is well established and frequently used. Autograft is osteogenic, osteoinductive, and osteoconductive, thus making it an ideal graft material for spinal arthrodesis. The decision to harvest bone graft from a specific donor site is based upon ease of access, surgeon comfort, size and shape of surgical field, goals of fusion (structural vs. non-structural, primarily osteoconductive vs. osteogenic, etc.), and patient's acceptance of donor site morbidity. Knowledge of the pros and cons of donor sites (iliac crest, fibula, spine, or rib) and appropriate surgical techniques can provide excellent outcomes and minimize complications.

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Medical Student Research Project

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Pharmacological Management of Concussions: Current Concepts

ANDREW PORTER, BA; JOSEPH S. TORG, MD

Department of Orthopaedic Surgery, Temple University School of Medicine, Philadelphia, PA

Abstract

The majority of athletic-induced cerebral concussions are successfully managed with rest, observation and rehabilitation. However, some patients exhibit protracted concussion symptoms, generally defined as those lasting longer than three weeks, and may require pharmacological intervention. In this review, the current evidence-based pharmacological intervention is examined. Current therapy is largely symptom based, and often divided into four specific categories: 1) somatic, 2) sleep disturbance, 3) emotional fragility, and 4) cognitive function. The pharmacological therapy will be summarized for each of these classes, along with the most commonly utilized medications and the efficacy of current treatments. It has been demonstrated that pharmacological intervention can be successful in combatting symptoms of protracted concussion, but the results of treatment is variable, and there is no therapy that treats the underlying pathophysiology of concussion.

Introduction

The Centers for Disease Control and Prevention (CDC) has stated that there are approximately 1.4 million cases of traumatic brain injury per year, of which 75–90% are considered to be mild traumatic brain injuries (mTBI), also referred to as cerebral concussions. The CDC also estimates that a large number of concussions go unreported, and the actual number per year is 1.6–3.8 million.[1] Concussions are a growing issue in the United States, and we are only beginning to understand their true severity and the lasting effects that they can have. In addition, while management of concussions has improved over the last decade, is no agreed-upon form of pharmacological, psychological, or optimal period of rest treatment protocol.

The most comprehensive definition of concussion comes from the CDC which uses the term mild traumatic brain injury (mTBI) interchangeably with the term concussion. An mTBI or concussion is defined as a complex pathophysiologic process affecting the brain, induced by traumatic biomechanical forces secondary to direct or indirect forces to the head. mTBI is caused by a blow or jolt to the head that disrupts the function of the brain. This disturbance of brain function is typically associated with normal structural neuroimaging findings (i.e., CT scan, MRI). mTBI results in a constellation of physical, cognitive, emotional and/or sleep-related symptoms and may or may not involve a loss of consciousness (LOC). Duration of symptoms is highly variable and may last from several minutes to days, weeks, months, or even longer in some cases.[1]

The majority (80%) of concussions resolve spontaneously within several weeks[2] and are treated initially with physical, mental and cognitive rest. If symptoms do not resolve within three weeks, which occurs in about 20% of patients, pharmacological intervention may be considered.[2] To be emphasized, there is no pharmacological "cure" for concussion, and treatment is largely symptom based. These symptoms can be categorized in a number of ways, the most widely utilized characterization grouping being: 1) sleep disturbance, 2) somatic (primarily headache), 3) emotional, and 4) cognitive.[3] Many different drugs have been examined in hopes of finding the "golden bullet" for concussion treatment, but the search for the definitive agent remains elusive.[4] The purpose paper is to outline the current pharmacological therapy being utilized in the management of concussions, and most importantly, how therapy aids in improving symptoms in patients with protracted concussions.

Pharmacology in Concussion Management

Pharmacological treatment is never the first step in management of concussions. Physical, emotional, and cognitive rest, along with patient education regarding symptoms and risk factors, have proven to be very effective forms of initial treatment. Until very recently, it was believed that patients should refrain from all activities and rest extensively in the days following a concussion. However, Nygren-de Boussard et al. have recently shown that returning to activity as soon as possible, at an appropriate level, may actually improve recovery.[5, 6] The reasoning behind this finding is believed to be that excessive rest may cause other health issues, as well as deconditioning.[5] Further investigation needs to be conducted regarding this claim, but it is something to consider when treating patients.

Unfortunately, for some patients, symptoms do not resolve spontaneously and other treatments, namely pharmacological intervention, may be indicated. Meehan suggests that medication should only be used in treatment of concussion if the following three conditions are met: 1) the athlete's symptoms have exceeded the typical recovery period for a sport-related concussion, 2) the symptoms are negatively affecting the patient's life to such a degree that the possible benefit of treatment outweighs the potential risks of the medication being considered, and 3) the clinician caring for the athlete is knowledgeable and experienced in the assessment and management of sport-related concussion or concussive injury in general.[3] When the decision is made to introduce medication into the patient's treatment plan, Wortzel et al. encourages an approach of "start-low, go-slow, but go."[7] Wortzel is also careful to point out that patients must be closely monitored for side effects, benefits, and drug-drug interactions.[7]

Currently, no drugs are proven to be effective in treating the underlying pathophysiology of concussion and thereby decreasing recovery time. In fact, there are no available medications that have been shown to decrease recovery time by any mechanism.[3] Therefore, the current use of medication in management of concussion is entirely symptom based and many of the drugs that have shown to effectively reduce various symptoms are used in an off-label manner. However, to improve the ability to treat concussions pharmacologically, more research is necessary to identify drugs that will aid in treating the underlying pathophysiology.

As stated, when discussing various symptoms manifestations of cerebral concussion, we propose dividing them into four general categories: sleep, somatic (i.e., headache), dizziness, etc., emotional, and cognitive. When determining which medication to prescribe, it is extremely important to consider all aspects of the patient profile, as current drug therapy is highly specific. Another aspect to consider when discussing pharmacological management of concussion is when the patient should be allowed to resume regular activity. To be emphasized, before a patient resumes their normal daily and athletic activities, they must be both symptom and medication free. This ensures that the medication is not masking any adverse reactions a patient may have while returning to activity.[6] To be discussed are the four different categories of symptoms, as well as the medications that have proven to be effective and are commonly found being utilized in the clinical setting.

Somatic Symptoms

The most common complaint following a concussion is headache, occurring in more than 90% of all patients.[8] Most headaches resolve spontaneously within several weeks, but some can persist for months, years, or even remain permanently.[3] Headaches can be managed in the short-term with the use of acetaminophen.[8] The use of NSAIDs is generally avoided in the acute phase because they are prone to cause bleeding and other complications.[8] In addition, while acetaminophen and NSAIDs may be effective in short-term treatments, rebound headaches often occur, making these drugs unsuitable for long-term treatment.[3] In treating headaches, just as with other symptoms of protracted concussions, it is essential to obtain a detailed patient history to determine the exact nature of the headaches in that some headaches may be secondary to another underlying condition, and it is best to focus pharmacological therapy on a diagnostic basis rather than attempting to treat the headaches specifically. Primary headaches following concussion are often separated into two different categories: tension-type and migraine-like. The drug amitriptyline, an anti-depressant, has been shown to be effective in treating both of these categories.[2, 3, 8] Also, amitriptyline also exhibits some sedative effects and can be useful in treating patients who also suffer from sleep disturbances, to be discussed in greater detail.[3] Another class of drugs, triptans, has also shown to be effective in treating patients with post-traumatic headaches.[2, 9] Erikson performed a study with military troops who suffered from post-traumatic headaches either due to blast or non-blast injuries, and found triptans to be effective in significantly decreasing the frequency of headaches. More research needs to be done to further examine these findings, but it looks to be a very promising treatment, especially for those suffering headaches due to a blast injury, which have been historically difficult to treat.[9]

Other common somatic symptoms of concussion, such as vertigo — a condition in which the patient perceives motion due to dysfunction of the vestibular system — as well as vomiting, vision impairments and hearing dysfunction, generally resolve naturally and require no further treatment.[10] For persistent dizziness or disequilibrium, there are currently no pharmacological agents that have been shown to be effective. Vestibular rehabilitation is indicated in these patients.[8] Ocular impairments are not treated pharmacologically, and physical therapy is recommended for these patients as well. In patients suffering from nausea, it is important to determine any triggers or underlying pathology before prescribing antiemetics.[8]

Sleep Disturbances

Sleep disturbance is a common complaint of patients suffering from cerebral concussion. This includes difficulty falling asleep, staying asleep, and insomnia.[8] Proper sleep hygiene is the first line of treatment that should be considered for these patients.[3, 8] The premise behind sleep hygiene is to create a sleeping environment devoid of any stimulation. This means removing all televisions, phones, etc. from the patient's bedroom to eliminate any distractions.[3] The patient should be lying down in a dark and quiet room, free from any stressors. Additionally, the patient should be directed to minimize caffeine, nicotine, alcohol, and daytime naps.[3] Resuming a regular daytime schedule with regards to physical and mental activities will help the patient develop a

normal rhythm and further work to combat any sleeping difficulties.[8]

If the patient persists in having issues with sleep despite the use of these behavior modifications, pharmacological intervention may be considered. The first line of pharmacological therapy is melatonin.[3, 8] Petraglia et al. suggest beginning with a low dose, 0.3 mg prior to bed, and slowly increasing the amount until an effective dosage is found.[8] Melatonin is a safe and efficacious drug that exhibits very few side effects, thereby making it the best candidate for sleep disturbance treatment.[11] Trazodone is another drug that has recently been used in treating concussion patients who experience difficulty sleeping.[3, 8] Trazodone is a serotonin antagonist and re-uptake inhibitor with minimal side effects. Ambien is also commonly used in treating patients with trouble sleeping. Benzodiazepines, while a seemingly logical choice, should be avoided to prevent potential deleterious effects on the central nervous system.[2, 3] As mentioned previously, amitriptyline has also been shown to have some sedative effects and can be beneficial in treating those with concussion.[3]

Emotional Fragility

Emotional symptoms are another problem that many concussion patients experience and can include increased agitation, aggression, and especially depression. It is estimated that 60% of patients suffering from the long-term sequelae of mTBI will develop some degree of depression within 12 months.[12] It is thought that depression in mTBI patients is triggered not only by the neurochemical imbalances that follow a concussion, but also by the restrictions that are placed on them both physically and cognitively, as well as other symptoms they may be experiencing that are negatively influencing their quality of life.[3] The initial treatment for these conditions is generally non-pharmacological and usually consists of assisting the patient to develop the proper coping strategies, ensure there is a proper support system in place, and visiting with a psychologist if necessary.[3] Ideally, any emotional symptoms a patient is experiencing will resolve in a matter of weeks. If that is not the case, pharmacological intervention is then considered.

When deciding which drug to prescribe, it is important to consider any other symptoms the patient may be experiencing. Traditional antidepressant drugs such as tricyclic antidepressants and selective serotonin reuptake inhibitors have been used, but the data surrounding their success is inconsistent.[13] Methylphenidate has been shown to be the most successful pharmacological treatment and also aids in treating a number of other symptoms.[12, 14, 15] Methylphenidate has proven to be effective in treating depression, as well as reducing combativeness and improving the overall psychosocial outcome.[12] In addition, methylphenidate has proven to be beneficial with regard to cognitive outcomes, such as increasing memory, attention, and mental processing[14] and will be discussed in greater detail. Finally, methylphenidate aids in reducing daytime sleepiness, perhaps contributing to its role in improving cognitive functioning.[14] However, many patients are weary to take methylphenidate, more commonly known as Ritalin, so often the other drugs discussed below are prescribed as the first line of pharmacological treatment.

Table 1. Summary of Drugs Used to Treat Various Concussion Symptoms

Medication	Symptoms Targeted	Mechanism of Action	Suggested Starting Dose	Possible Adverse Reactions
Melatonin	Sleep disturbance	Unclear; endogenous hormone produced by pineal gland	0.3–5 mg prior to bed	Nausea, next-day grogginess, irritability, reduced blood flow, hypothermia
Trazodone (Desyrel, Oleptro, Trialodine)	Sleep disturbance	Serotonin antagonist and reuptake inhibitor	25–50 mg/day	Sedation, orthostatic hypotension, mania, cardiac arrhythmia, priapism
Acetaminophen (Tylenol)	Headache	COX-2 inhibitor	PRN	Skin reaction, nausea, stomach pain, loss of appetite, jaundice
Amitriptyline (Elavil, Endep, Levate)	Headache	Serotonin-norepinephrine reuptake inhibitor	10–25 mg/day	Drowsiness, dizziness, dry mouth, blurred vision, constipation, weight gain, trouble urinating
Triptans (Axert, Frova, Maxalt, Imitrex, Treximet, Zomig)	Headache	Serotonin receptor agonist	Varies depending on brand	Recurrence of migraine, dizziness, dry mouth, muscle aches, nausea, vomiting
Sertraline (Zoloft, Lustral)	Depression	SSRI	25 mg/day	Sleepiness, nervousness, insomnia, dizziness, nausea, skin rash, headache, diarrhea, dry mouth, weight loss
Methylphenidate (Concerta, Methylin, Ritalin, Equasym XL)	Emotional and cognitive symptoms	Inhibitor of dopamine and norepinephrine reuptake	10 mg/day	Nervousness, trouble sleeping, loss of appetite, weight loss, dizziness, nausea, vomiting, headache
Amantadine (Symmetrel)	Cognitive functioning	Increases the release of dopamine and inhibits reuptake	200 mg/day	Nervousness, difficulty concentrating, headache, irritability, loss of appetite, nausea, blotchy skin, trouble sleeping
Donepezil (Aricept)	Cognitive functioning	Acetylcholinesterase inhibitor	5 mg/day	Bradycardia, nausea, diarrhea, anorexia, abdominal pain, vivid dreams

The other drug that has been well documented to treat depression in concussion patients is sertraline.[3, 13–15] While sertraline appears to be a good choice for treating depression, its effects on other aspects of concussion symptomology are questioned. Meehan claims that sertraline has cognitive benefits in addition to its positive effects on depression,[3] whereas Lee et al. argue that these cognitive benefits are less effective when compared to methylphenidate, and sertraline may in fact play a role in hindering natural cognitive recovery.[14] With regard to other post-concussive symptoms, such as headache, irritability, sleep disturbance and blurred vision, Fann et al. state that sertraline helps to decrease their incidence,[13] and Wheaton et al. contend that it can actually precipitate them.[15] Most agree that sertraline is a good choice when trying to manage depression in patients suffering from concussion. The other side effects and benefits require more clinical research.

Amitriptyline, discussed earlier in reference to its benefits in treating headaches and sleep disorders, is also an effective treatment of primary depression, but has been shown to be ineffective in treating depression in mTBI patients.[3, 8, 12] The mechanism behind this is unclear, and it cannot be recommended as first-line treatment.

Cognitive Function

Cognitive symptoms of concussion are the most complex and difficult to treat. These include issues with memory, decreased concentration, slower processing speed, and decreased overall cognitive functioning.[3] Computerized neuropsychological testing has now made these deficits readily identifiable and measureable, but treatment remains challenging.[3] Cognitive deficits are very common in the first hours to days following a concussion, but most resolve spontaneously within a matter of days or weeks.[8] If symptoms persist for longer than 3–4 weeks, treatment intervention is generally recommended.[15, 16] Cognitive rehabilitation is an option, but its efficacy remains questionable.[3, 7] Pharmacological treatment is the next viable option, and different drug regimens are being experimented with to determine which, if any, provides relief to the patient.

The most studied drug for treating cognitive symptoms of concussion is methylphenidate.[2, 3, 8] Methylphenidate, mentioned earlier when discussing emotional symptoms, has also been shown to increase attention, speed of processing, and general cognitive functioning.[3, 8] Conversely, methylphenidate also lowers the seizure threshold, and therefore must be used with great caution.[3]

Amantadine is another drug that has recently been shown to improve cognitive functions in concussion patients.[2, 3, 8, 16] Reddy et al. conducted a study that showed amantadine significantly increased verbal memory, as well as reaction time. However, no increase in visual motor or visual processing was reported.[16] Furthermore, treatment with amantadine resulted in fewer overall symptoms[16] and a study by Petraglia et al. described an increase in total executive functioning.[8] Amantadine is a very promising agent, and further study is necessary to determine its true efficacy.

Another drug commonly used in management of cognitive symptoms of concussion is donepezil,[3, 8, 15, 17–19] which has been shown to increase attention, short- and long-term memory, as well as overall cognitive function.[15, 19] Much of the current published data regarding the use of donepezil for cognitive treatment is centered around patients suffering from moderate to severe TBI, and more data is necessary to confirm its use in patients with mTBI.

Conclusion

This review has outlined the evidence-based pharmacological intervention currently being utilized to treat concussion patients. While the vast majority of concussion cases can be successfully treated with rest and rehabilitation, some patients with protracted symptoms of concussion require pharmacological intervention. Current treatment is entirely symptom based, and these symptoms are often categorized into four classes: somatic, sleep disturbance, emotional fragility, and cognitive function. The pharmacological treatment for these various symptoms, while proven to be effective, remains relatively variable amongst clinicians and the medications utilized are often done so in an off-label manner. Further clinical experience and research is needed to truly identify the efficacy of current medications, as well as identify others that can be used to treat the underlying pathophysiology of concussion.

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Athletic Induced mTBI and Catastrophic Intracranial Injuries: Determining Helmet Efficacy and Predisposing Injury Profiles — A Systematic Review

Paul Navo, MPH;[1] R. Dawn Comstock, PhD;[2] Dustin Greenhill, MD;[1]
Barry Boden, MD;[3] Joseph S. Torg, MD[1]

[1]*Temple University, Philadelphia, PA;* [2]*University of Colorado, Denver, Aurora, CO;*
[3]*Orthopedic Center, Rockville, MD*

Abstract

Concussion has been identified as the "signature American football injury of the 21st Century."[1] Since the advent of tackle football in 1869, both mild traumatic and catastrophic brain injury have occurred at a sustained and persistent rate. Of the numerous published studies on athletic induced head/brain trauma, only a few have attempted to associate concussion with helmet technology. The purpose of this report is to perform a systematic review of the literature and data analysis to answer the following questions: 1) Does advanced helmet technology protect or prevent the brain from mild traumatic brain injury (mTBI) or intracranial edema/hemorrhage, and 2) Do past and currently documented central nervous system injury patterns resulting from football indicate the presence of identifiable susceptibility profiles and, if so, what are the possible component combinations?

Data from the reports of Guskiewicz, McCrory, Boden, Collins, and Bartsch were analyzed with regard to helmet technology and injury prevention, and injury profile susceptibility. This data consisted of 1,398 concussion injury reports collected from the National High School Sports-Related Injury Surveillance System (NHSS-RISS).

This data suggests that neither advanced football helmet technology nor helmet condition protect high school players from mTBI or intracranial edema/hemorrhage. However, improperly fitted helmets and those lined with air-bladders increase the risk of head injury. Team physicians, athletic directors, coaches, and athletic trainers should be aware of these findings and ensure proper oversight for their student-athletes.

Additionally, we propose that brain injuries resulting from football may have an identifiable susceptibility profile. The next phase of concussion research should aim to categorize components within this profile.

Introduction

Cerebral concussions are one of the most common yet complex athletically-induced injuries in contact sports. A concussion, often referred to as mild traumatic brain injury (mTBI), occurs when an abrupt force to the head results in a disturbance of brain function. Severity of symptoms can range from transient alteration in brain function to persistent memory problems, depression, and dementia.

Recently, there is a worthy concern regarding concussions in high school athletes. It is estimated that between 1.7 and 3.8 million mTBIs occur every year in the United States.[2] Adolescents between the ages of 10 and 19 years old are at the greatest risk of concussion.[3] Data from a national high school registry in 2012 revealed that concussions comprised 13.2% of all reported injuries.[4] This statistic reveals an alarming upward trend from 5.5% and 8.9%[4] in 1999 and 2007, respectively. Among all high school sports, football is consistently a major contributor. However, the role of football helmets with regard to brain injury in high school football is unknown.

Acceleration and deceleration (A/D) forces as well as direction of force have long been considered important factors in the generation and severity of mTBI. However, other studies have shown that concussions can also occur via indirect, rotation forces.[5, 6] In fact, rotational forces have been reported to cause the most severe injuries with lateral (side-to-side) forces resulting in injuries with the most severe symptoms, such as persistent coma and severe disability, and poorer recovery prognosis.[7] Gaetz et al.[7] reported that neurons have inherent characteristics that may make them more susceptible or resistant to diffuse injury. Characteristics that may predispose to more severe injury include axons that change direction, larger caliber neurons, and axons at locations where a change in tissue density occurs.[7] Gaetz also reported that the depth of lesion increases with increased force and thereby produces a more severe disturbance of consciousness.

History

Bartsch has identified concussion as the "signature American football injury of the 21st Century".[1] Bartsch has developed the following chronology, which we have expanded upon:

Princeton and Rutgers played the first organized intercollegiate game on November 8, 1869. From then on, violence prevailed, injuries occurred, and concern mounted.

Becoming known as much for violence as for tactics and performance, the governing authorities banned the dangerous "flying wedge" formation in 1893 that apparently was responsible for many injuries.

The first protective headgear was introduced in 1896 and consisted of a pair of earmuffs supported by leather straps. At the end of the 19th century, the president of Harvard University and the other Ivy League universities spearheaded profuse opposition to the game. In 1905, 18 football fatalities were recorded as a result of the game. Although the incidence of death was not reported, the fact that football was only played by seven Ivy colleges and a few other schools, demonstrates the high risk of catastrophic injury. Under intense pressure to prohibit the game, President Teddy Roosevelt summoned the involved athletic directors to Washington, D.C. and recommended the formation of the National Collegiate Athletic Association in an attempt to make the game safer.

In 1984, the second impact syndrome was described as a second impact to the brain, prior to recovery from the first impact, which often results in diffuse cerebral bleeding and death.[8] The condition emphasized the necessity of close follow-up, a CT scan to rule out intracranial edema/bleeding, and prohibiting a symptomatic player from returning to activity until he/she is asymptomatic, neurologic negative and has return of full neurocognitive function. The recent advent of psychometric/neurocognitive testing has been a marked addition to the management of concussion and minor traumatic brain injury. This clinical adjunct assists the clinician in evaluating brain recovery and reducing the occurrence of repeat concussion and the post-concussion syndrome. More recently, McGee has reported on autopsy findings of former boxers and football players diagnosed as having chronic traumatic encephalopathy (CTE) with tau protein deposition in brain substance in a perivascular distribution.

Chronic Traumatic Encephalopathy (CTE)

Since the advent of tackle football in 1869 and despite the efforts of President Teddy Roosevelt and the advances in helmet technology, both catastrophic and mTBI have occurred at a sustained and persistent rate. Reports by Dischinger et al.[9] and McKee[10, 11] identified chronic sequela of mTBI. Dischinger refers to mTBI as a "silent epidemic" because the problems associated with these injuries are often not visible but may be associated with profound consequences such as long-term mental, physical or occupational sequela. McKee has described specific changes in brains of a number of former football players who had been diagnosed as having had CTE. In addition to McKee's findings that repetitive concussions may result in chronic traumatic encephalopathy, in 2010 she reported four cases of former and current players who committed suicide and whose brains demonstrated tau protein deposition at autopsy.[11]

A systematic review of the literature reveals four categories of athletic induced head/brain trauma:

1) Skull fracture — This is extremely rare in that helmets must meet NOCSAE standards for skull tolerance to impact.

2) Mild mTBI — A common a metabolic event characterized by neuron deformation with potassium flowing out and calcium in the cell.

3) Subdural hematoma/cerebral edema — An extremely uncommon a vascular event characterized by increased intracranial pressure.

4) Chronic traumatic encephalopathy — Occurrence not well defined, but tau protein deposition in the brain has been implicated.

The purpose of this report is to perform a systematic review of the literature and an analysis of data in order to answer the following questions.[12–17]

1) Has advanced helmet technology protected or prevented the brain from mTBI or intracranial edema/hemorrhage?

2) Do past and currently documented brain injuries from football suggest the presence of identifiable susceptibility profiles? If so, what are the possible components worth researching?

3) Recent clinical laboratory evidence clearly indicates the likelihood of a genetic predisposition to the problematic prolonged concussion syndromes. Is this genetic predisposition a sole risk factor or is it a component of an identifiable susceptibility profile?

Methods

Data from concussion injury reports in high school football were obtained from the National High School Sports Related Injury Surveillance System (NHSS-RISS).[18–24] The NHSS-RISS collected prospective surveillance of high school athletics exposures and injuries during the school years from 2005–2006 through 2011–2012 using the computerized RIO™ (reporting information online) system. All eligible schools had a certified athletic trainer and participating schools were selected based on stratification into geographic areas and school enrollment size. Athletic trainers at participating institutions were offered a $300 honorarium for completing weekly reports of athlete exposures and injury reports for injuries resulting in either time lost or head/face trauma. The NHSS-RISS is conducted under approval of the IRB at the Ohio State University. In each concussion report, athletic trainers were asked a variety of questions including the demographics of the athlete, athlete position, type of

play, characteristics of the helmet, symptoms of concussion, and time lost before return to play. Also included were the age of the helmet (new vs. reconditioned), type of padding in the helmet and whether or not the athletic trainer believed the helmet fit correctly at the time of injury. The finding of helmet fit was queried with a yes/no question. Assessment of equipment fit was included in the required educational competencies for all certified athletic trainers at CAATE accredited education programs.

Data from the above-cited reports of Guskiewicz et al.,[25] McCrory et al.,[26] Boden et al.,[27] Collins et al.,[28] and Bartsch et al.[1] were analyzed with regard to helmet technology and injury prevention. Studies reported by McKee et al.,[10, 11] Terrell et al.,[29] and McDevitt et al.[30] are revised to support the premise of injury profile susceptibility.

Results

Reports of 1,398 concussions, collected by NHSSRISS, were examined using loss of consciousness (LOC) and amnesia as separate end points. LOC incidence was 49/1398 = 0.040 and amnesia incidence was 300/1398 = 0.2414. Multivariate odds ratios were calculated for helmet fit, inner helmet padding, helmet condition as new vs. reconditioned and athlete age. Athletes wearing properly-fitted helmets, as reported by team certified athletic trainers, were 82% less likely to experience LOC (OR = 0.182, –95% CI 0.057–0.587, p = 0.0043). Helmet age and condition (new vs. reconditioned) were not significant predictors of amnesia of LOC.[18–24] As participant age increased, so did the risk of amnesia (OR = 1.386, 95% CI 1.214–1.541, P = 0.001). Helmet lining (foam, air, gel) had no significant effect on amnesia or LOC. From the existing literature, the rate of the occurrence of mTBI in the national high school football population of 1.2 ± 0.1 million participants per year over a 30-year period has, with two exceptions, persisted between four and six percent despite presumed improvement in helmet technology. We believe that this strongly suggests a profile commonality of those predisposed to mTBI or those who experience a protracted recovery and brings into question the protective effect of presumed improved helmet technology.

An analysis of the Boden/Mueller data on the yearly number of "catastrophic" head injuries per 1.2 million high school and college football players over the 20-year period 1990–2010 reveals, with two exceptions, a yearly incidence of between four and 10 injuries. When this data is viewed as incidence per 100,000 high school and college participants over the 20-year period 1989–90 to 2001–02, it demonstrates a relatively flat line between 0.04 and 0.85 injuries per 100,000. Thus, again, over the recent 20-year period, there has been a constant rate of "catastrophic" intracranial injuries in high school and college football players. With a million plus participants sustaining numerous impacts to their heads each season, the question of why only an extremely small group experience an intracranial hemorrhage needs to be addressed. Clearly, this observation strongly suggests a profile or genetic susceptibility of those predisposed to intracranial injury and question the efficacy of advanced helmet technology.

As indicated above, air bladder helmet liners have been associated with loss of consciousness. Boden reports, on the basis of unpublished data, the association of an increased risk of "catastrophic" intracranial brain injury with air bladder lined helmets. That is, 84% of these injuries that occurred from 1989 to 2001 involved air helmets.

Bartsch et al. recently reported on laboratory impact test comparisons of 20th and 21st Century American football helmets.[1] They compared modern football helmets, widely believed to improve protection by reducing head impact doses and head injury risk, with vintage leather helmets or 'leatherheads.' In their injury biomechanics laboratory, they performed impact tests using helmeted head forms inducing near and sub-concussive head impact doses on par with approximately the 95th percentile of on-field collision severity. They also calculated impact dose injury risk parameters common to laboratory and on-field traumatic neuromechanics. The results of this study were that in many instances, the head impact doses and head injury risks while wearing the vintage leatherheads were comparable to or better than those while wearing several widely-used 21st Century varsity helmets.

Discussion

Helmet Fit

In the 1960s, the Gadd severity index (GSI) was developed to determine the likelihood of skull fracture based on acceleration during impact. The National Operating Committee on Standards for Athletic Equipment (NOCSAE) then used the newly-developed GSI to establish "pass/fail" helmet standards. Helmet technology has evolved with the development of the polycarbonate outer shell and a variety of air bladder, air bladder and foam, and foam inner systems. While the number of skull fractures in football has dramatically decreased with new helmet design, both mTBI and catastrophic occurrences have persisted at concerning rates.

Our findings identify helmet fit as a factor related to increased risk for concussion. Also, loss of consciousness and helmet lining (air bladder) are strongly associated with intracranial injury. Helmet age (new vs. reconditioned) and athlete age were not found to be significant risk factors for concussion with LOC or amnesia. The observation that each increased school grade level for the student marked a 35% increased risk of concussion with associated amnesia raises the question of whether this was a function of increased exposure to trauma or due to endemic factors. The increased risk of intracranial injury, as per Boden[27] with air-bladder helmet suspension, may be related to decreased maintenance of the helmets. Air-bladder systems are prone to leaking, and

helmet fit may be compromised with an insufficiently filled air bladder.

Among the numerous published studies dealing with athletically-induced head trauma, only two have asserted that helmet technology may decrease the rate of concussion.[28, 31] Notably, neither study specifically mentions helmet fit. Moreover, each study includes limitations. The Collins[28] study in 2006 was funded by the helmet manufacturer, Riddell. Only 136 concussions were reported, with 62 concussions in the experimental group, raising questions about the power of these findings. Additionally, the study failed to control for athlete exposures and age of the helmet.[28] The more recent study by Rowson et al.[31] was subject to concerns regarding equipment bias and underreporting.

Benson et al.[32] reviewed 51 studies of protective equipment across all sports and traumatic brain injuries. Twenty-nine of these articles focused on athletic headgear, with 19 epidemiological studies and 10 biomechanical studies. The authors concluded there is insufficient evidence to suggest helmets are protective against concussion.[17] NOCSAE has reported that an older helmet scores lower on the Severity Index, and is therefore less protective than a new helmet. The Severity Index was developed to establish protection against skull fractures and no data has been published to validate the Severity Index relative to concussion injury.

Boden et al.[27] suggests that helmet fit may be a factor to consider during brain injury analyses, but this explicit variable was not included in their data collection.[26, 27] At the 2008 International Conference on Concussion in Sport, of the 145 of the 148 references cited by McCrory et al.,[26] none specifically mentioned helmet fit. Also to be noted, the 2012 annual report by Mueller[33] documents football fatalities and "catastrophic" head injuries since 1945, without including an analysis of the relationship of these injuries to protective headgear or of the existence of preexisting susceptibility injury profiles.

Genetics

Repetitive head injury has been associated with the development of CTE,[10] characterized by several pathological disease markers, such as the build-up of tau protein within brain cells that can only be seen upon autopsy. Another such protein is TAR DNA-binding protein 43 (TDP-43), which deposits on the surface of the brain, around the ventricles, and within the brainstem in CTE. McKee et al.[11] correlated repetitive head trauma with the development of lower motor neuron diseases seen in Amyotrophic Lateral Sclerosis (ALS) and is a fatal progressive degeneration of motor neurons in the spinal cord and brain. However, there has been significant resistance to this relationship in the scientific community. Furthermore, concussions have been associated with emotional and neuropsychological disturbances including depression and other mental abnormalities. There is growing evidence of the detrimental effects of concussions on brain function later in life that could be due to structural changes brought about by mTBI.[11]

In an attempt to understand what is occurring on a molecular level, recent research has focused on several biomarkers to determine the presence and severity of mTBI. Following mTBI, the Blood-Brain Barrier (BBB) is often disrupted allowing for the diffusion of larger water-soluble molecules that are normally unable to travel from the brain to the cerebrospinal fluid (CSF) and general circulation. The S100 calcium binding protein B (S100B) is one such molecule that has been shown to accurately indicate both osmotic and physical BBB dysfunction within the first 12 hours after mTBI and can be used to determine the functional status of the BBB.[34] Proteolysis of MAP-tau, a neuronally-localized intracellular protein, to cleaved-tau (C-tau) also appears to be related to the pathophysiology of neuronal damage that commonly appears with mTBIs. Initial C-tau serum levels have been shown to be a significant predictor of intracranial pressure and determination of clinical outcome. C-tau serum levels have particular sensitivity for identifying severe mTBI patients with good clinical outcomes.[35] Elevated C-tau levels have been associated with poor clinical outcome. While both S100B and C-Tau have been shown to indicate initial common clinical features of mTBI, both markers have also been found to be poor predictors of clinical outcome even three months after mTBI.[36]

Genetics may play a role in recovery time following mTBI. A 2014 publication by McDevitt et al.[30] studied the effect of polymorphisms to the repeated GT sequence within variable region of the promoter region of the GRIN2A gene between concussion recovery time or concussion severity scores. Genetic variations in the N-methyl D-aspartate (NMDA) glutamate receptor NR2A subunits were found to modulate the severity and/or recovery from mTBI. The GRIN2A gene produces the NR2A subunit; therefore, genetic variability within the GRIN2A promoter region may be associated with recovery time following mTBI. McDevitt et al. found a significant association between the GT variable region tandem repeat (VNTR) within the promoter region of GRIN2A and recovery time following a concussion. Specifically, it was observed that there was a four-time greater chance of prolonged recovery time in individuals who were homozygous for long GRIN2A alleles, where long alleles were defined as an alleles with >25 dinucleotide repeats in the GT tract.[30] These findings suggest that there are genetic factors that contribute to long-term recovery from concussion and that genetic polymorphisms within the GRIN2A promoter region can be a useful predictive marker of susceptibility to concussion and brain trauma.

A 2008 publication by Terrell et al.[29] studied the associations of Apolipoprotein (APOE), APOE promoter (G-219T), and tau protein exon polymorphisms ($^{His}47^{Tyr}$ and $^{Ser}53^{Pro}$) and the history of self-reported concussion in college athletes. Terrell et al. found that the APOE promoter TT geno-

type, relative to the GG genotype was associated with a nearly three-fold increased risk of a history of all concussions combined, and with a four-fold increased risk of a history of concussions with loss of consciousness.[29] These findings suggest additional genetic factors that may show athletes with increased risk for having a history of concussions, especially more severe concussions.

Advancing the risk profile of concussion injuries in tackle football may contribute to risk reduction for one of the most popular sports among America's youth. The number of individuals engaged in high school and college football each year is in the order of 1.2 ± 0.1 million, yet the percentage of those sustaining a reported concussion (4 to 6%) is relatively small and the number of those experiencing the post-concussion syndrome or a protracted recovery is even smaller. The odds of sustaining an intracranial injury (four to eight per season, or 0.6 per 100,000) is extremely rare. As the data indicates, helmet fit and lining are associated with both concussion and severe intracranial injuries respectively. It is well recognized that air bladders deflate on a regular basis and helmet fitting, particularly in the high schools, is haphazard. Yet many thousands of youngsters with poorly fitting helmets and/or deflated bladders receive multiple head impacts without injury. Therefore, it is hypothesized that the athletes with brain injuries have an injury susceptibility profile of multiple factors. Thus, an athlete with a poorly fitted helmet and a deflated air bladder receives multiple heads impact without sequela while another athlete with a similar helmet condition has associate multiple predisposing factors and experiences an intracranial hemorrhage. It is purposed that the next phase of research dealing with athletic-induced intracranial injuries investigates susceptibility profiles for both mTBI and intracranial injuries (see Table 1).

The following factors are proposed as possible components of the mTBI or intracranial injury profiles:

Table 1. Possible Components of the mTBI or Intracranial Injury Profiles

Helmet type or fit	Age
Environmental	Prior Concussion
Dehydration	Anatomic factors
Depression	Gender
Fatigue	Genetic
Hormonal disturbance	Attention Deficit Hyperactive Disorder (ADHD)
Psychiatric	Migraine Headache
Metabolic	History of previous head injury
Position	Body Mass Index (BMI)
Viral illness	Others to be identified
Medications	

Conclusions

1) Advanced football helmet technology and design is not protective against mTBI or intracranial edema/ hemorrhage.

2) Current data indicates that helmet fit and air bladder lining are associated with both mTBI and intracranial edema/ hemorrhage. It is the responsibility of the Athletic Director and Head Football Coach to see: 1) that provisions are made to ensure that each player has a properly fitted helmet and that 2) a responsible adult supervises and oversees that helmet air bladders are properly inflated on a weekly basis.

3) The first and currently unappreciated step in resolving both acute brain injury problems is to identify the components of the susceptibility profiles and implement changes to disrupt the predisposing injury combinations.

4) Importantly, future research is mandatory to support the concept of genetic predisposition to development of chronic sequelae and possible chronic traumatic encephalopathy.

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Medical Student Research Project

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Predictive Risk Factors and Reasons for an Adverse Event Following Total Knee Arthroplasty

Mark Bundschuh, BS;[1] Frederick Ramsey, PhD;[2] Pekka Mooar, MD[3]

[1]*Temple University School of Medicine;* [2]*Department of Clinical Sciences, Temple University School of Medicine;* [3]*Temple University Hospital, Department of Orthopaedic Surgery, Philadelphia, PA*

Background

In 2009, more than 600,000 total knee arthroplasties (TKA) were performed in the United States.[10] Indeed, it is one of our country's most effective procedures in terms of cost and patient satisfaction.[3, 6] TKA procedure volumes continued to increase by 6% during the economic downturn from 2009 to 2010, with the Centers of Medicare and Medicaid Services (CMS) paying for the majority of cases.[10, 11] With an increasingly aging and obese population, TKA procedure volumes and their associated cost will continue to rise.

In order to improve patient safety and curb the high cost of healthcare in the United States, a major initiative of the CMS is to reduce the number of costly readmissions in many medical specialties. In orthopaedic surgery, the CMS has proposed a shift from reimbursement via a fee-for-service structure towards an episode-based bundled payment structure.[4, 7] This fixed reimbursement will cover the TKA, postoperative hospitalization, and any subsequent readmissions within 30 days of the surgical procedure. Thus, 30-day readmission rate has become an important marker of patient safety and hospital care.

A large body of literature has investigated the predictors of readmission following TKA. The two most consistent predictors of readmission following TKA are increased age[2, 5, 9, 13, 14, 16, 17] and obesity.[2, 5, 8,14] Moreover, an increased number of medical comorbidities[2, 15] and some specific comorbidities including diabetes milletus,[14] coronary artery disease,[9, 12, 14] congestive heart failure,[9, 12] and postoperative anemia[9, 12] have shown to be independent risk factors for readmission following TKA. Other recent studies have also demonstrated a significant association between increased length of stay and readmission following TKA.[2, 12, 15, 17] In addition to studying the predictors for readmission following TKA, several studies have also examined the leading causes of readmission. The most common reasons for readmission following TKA are infection,[1, 2, 5, 9, 13, 14, 15] cellulitis,[2, 9, 14, 15] and joint stiffness.[1, 14, 17]

With a shift to an episode-based bundled payment structure, hospitals will be required to utilize healthcare resources more efficiently as extended lengths of stay, emergency visits, and readmissions can all reduce a hospital's profitability. It is also important to understand the reasons that cause these events to occur. As such, our study examines not only the 30-day readmission rate, but also emergency visits and extended lengths of stay and combines them into a composite outcome, called adverse events. Thus, the goal of our study was to determine the risk factors associated with and causes of adverse events following TKA in order to identify at-risk patients and reduce future adverse events.

Methods

After Institutional Review Board (IRB) approval was obtained, a retrospective chart review was conducted at a tertiary academic hospital in a low income region. The study examined adverse events following 306 total knee arthroplasties performed between January 1, 2011 to December 31, 2012 (two years). International Classification of Disease, Ninth Revision (ICD-9) codes 715.16 (OA) and 81.54 (TKA) were used to identify patients with osteoarthritis of the leg who underwent total knetabe arthroplasty.

Only patients over the age of 18 were included in the study. Readmissions were included only if they were unplanned and occurred within 30 days of the index admission. Emergency visits were also only considered within 30 days of the index admission. Emergency visits that resulted in a readmission were considered a readmission only. Length of stay was measured from the day of admission for surgery until the day of discharge. Patients that had a stay of greater than or equal to 10 days were considered to have had extended lengths of stay. In this study, the three outcomes — readmission, emergency visits, and extended lengths of stay — were mutually exclusive among all patients. Reason for an adverse event was also documented.

This study utilized several different variables: patient demographics, pre-operative combordities, pre-operative laboratory values, operative variables, and post-operative variables. Pertinent patient demographics included age, gender, and race/ethnicity. There were many pre-operative comorbidities: body mass index (BMI), dyslipidemia —

defined as high cholesterol, high triglycerides, and/or high low-density lipoprotein (LDL), hypertension, diabetes milletus, congestive heart disease, coronary artery disease, number of comorbidities, and current smoker. Pre-operative laboratory values included hemoglobin and albumin. Relevant operative variables included blood loss, operative time, tourniquet time, type of anesthesia, the American Society of Anesthesiologists (ASA) physical status classification, and bilateral knee replacement. Notable post-operative variables included deep vein thrombosis (DVT) prophylaxis, discharge disposition, and length of stay (LOS) for the index admission.

Descriptive statistics were calculated for both categorical and continuous variables. Data was presented as mean with standard deviations or percentages. All variables were then compared between the no adverse event and adverse event groups using univariate statistical analysis. Specific data analysis methodologies were dependent on whether the data was expressed as categorical or continuous. Discretization of selected continuous variables into multiple categories was performed after inspection of the data and analytical judgment. Association of variables and an adverse event were tested using a standard student's t-test for continuous variables and a chi-squared test (or the Fisher's exact test, where appropriate) for categorical variables, and the P-values of those associations were reported. Bootstrap resampling was used to adjust P-values for intra-variable comparisons.

For multivariate analysis, logistic regression was performed to identify independent predictors of an adverse event. Results were reported as adjusted odds ratios with 95% confidence intervals. The reason of an adverse event was determined retrospectively by the researcher. Statistical significance was defined as $P < 0.05$. All reported P-values are two-sided. Given the comparatively small sample size, careful consideration was applied relative to an overly strict and exclusionary application of this limit. In selected circumstances, P-values that exceeded 0.05 were considered or evaluated. Data were analyzed using SAS® 9.3 for Windows.

Results

306 patients that underwent total knee arthroplasty during our two-year study period were included in this study analysis. Following TKA, there were 42 adverse events (17 readmissions, 20 emergency visits, and five extended lengths of stay). The rate of an adverse event following TKA was 13.7%, and the 30-day readmission rate following TKA was 5.9%. Patient characteristics of TKA patients were reported in Table 1. The average age of the study cohort was 64.6 ± 9.7 years. Nearly 75% of the group was female and over 50% identified their race as Black. The average patient was classified as obese, with a mean body mass index of 34.5 ± 7.5 kg/m^2. In general, the population had a high incidence of comorbidities including dyslipidemia (35%), hypertension (77.5%), and diabetes milletus (31.7%). The most commonly used type of anesthesia was general (61.4%), and most patients had an ASA physical status classification of three (79.4%). 11.8% of patient underwent bilateral procedures.

Table 1. Patient Characteristics of TKA Patients

Variable	Description of Sample
Age (years)	64.6 ± 9.7
Gender (%)	
Female	73.9
Male	26.1
Race/Ethnicity (%)	
Black	53.9
White	27.8
Hispanic	13.7
Unknown	2.6
Asian	2.0
Body Mass Index (kg/m^2)	34.5 ± 7.5
Hypercholesterolemia (%)	35.0
Hypertension (%)	77.5
Diabetes Mellitus	31.7
Congestive Heart Disease (%)	7.2
Coronary Artery Disease (%)	10.5
Number of Comorbidities	2.3 ± 1.2
Current Smoker (%)	21.9
Blood Urea Nitrogen (mg/dL)	15.6 ± 6.7
Hemoglobin (g/dL)	12.8 ± 1.3
Blood Loss (mL)	187 ± 114
Operative Time (minutes)	126 ± 49
Tourniquet Time (minutes)	70 ± 25
Type of Anesthesia (%)	
General	61.4
Spinal	30.7
Epidural	24.2
ASA Class (%)	
2	18.3
3	79.4
4	2.3
Bilateral Procedure (%)	11.8
DVT Prophylaxis (%)	
Coumadin	88.9
Coumadin and Lovenox	10.1
Lovenox	1.0
Discharge Disposition (%)	
Skilled Nursing Facility	52.4
Home	38.1
Acute Inpatient Rehabilitation	9.5
Length of Stay (days)	3.5 ± 1.4

Data is expressed as means ± standard deviation or percentages.

Table 2 shows the univariate analysis of TKA patients with and without an adverse event. Body mass index ≥35 ($P = 0.0209$) and diabetes milletus ($P = 0.0423$) were associated with an adverse event following total knee arthroplasty. There was no association between race/ethnicity and an adverse event following TKA. However, based on additional analysis of race/ethnicity and emergency visits, it was observed that race/ethnicity was associated with an emergency visit following TKA ($P = 0.0485$ for Black and $P = 0.0930$ for Hispanic, as compared to White). There were two marginally significant variables: number of comorbidities ($P = 0.0711$) and blood loss ($P = 0.0806$). Presented in Table 3, subsequent multivariate logistic regression analysis identified both body mass index ≥35 (OR 2.15, 95% CI 1.11–

Table 2. Univariate Analysis of TKA Patients With and Without an Adverse Event

Variable	No Adverse Event (n = 264)	Adverse Event (n = 42)	P Value
Age (years)	64.6 ± 9.8	64.9 ± 9.4	0.822
Gender (%)			0.994
Female	73.86	73.81	
Male	26.14	26.19	
Race/Ethnicity (%)			0.351
Black	51.89	66.67	
White	29.55	16.67	
Hispanic	13.64	14.29	
Unknown	2.65	2.38	
Asian	2.27	0.00	
Body Mass Index (kg/m^2)			*0.021
<35	57.20	38.10	
≥35	42.80	61.90	
Hypercholesterolemia (%)	33.71	42.86	0.248
Hypertension (%)	77.27	78.57	0.852
Diabetes Mellitus (%)	29.55	45.24	*0.042
Congestive Heart Disease (%)	6.82	9.52	0.520
Coronary Artery Disease (%)	11.36	4.76	0.279
Number of Comorbidities	2.3 ± 1.2	2.6 ± 1.2	0.071
Current Smoker (%)	20.83	28.57	0.260
Blood Urea Nitrogen (mg/dL)	15.6 ± 6.5	15.9 ± 8.5	0.834
Hemoglobin (g/dL)	12.9 ± 1.4	12.7 ± 1.1	0.547
Blood Loss (mL)	191.4 ± 115.7	158.3 ± 97.2	0.081
Operative Time (minutes)	126.9 ± 49.9	123.2 ± 46.0	0.651
Tourniquet Time (minutes)	70.3 ± 24.7	70.4 ± 26.5	0.981
Type of Anesthesia (%)			
General	62.50	54.76	0.339
Spinal	29.55	38.10	0.265
Epidural	23.48	28.57	0.475
ASA Class (%)			0.210
2	19.32	11.90	
3	78.79	83.33	
4	1.89	4.76	
Bilateral Procedure (%)	12.12	9.52	0.799
DVT Prophylaxis (%)			0.537
Coumadin	87.88	95.24	
Coumadin and Lovenox	10.98	4.76	
Lovenox	1.14	0.00	
Discharge Disposition (%)			0.687
Skilled Nursing Facility	48.29	52.38	
Home	36.50	38.10	
Acute Inpatient Rehabilitation	15.21	9.52	

Data is expressed as means ± standard deviation or percentages.
*p < 0.05

Table 3. Multivariate Logistic Regression for Predictors of an Adverse Event Following TKA

Variable	Adjusted Odds Ratio (95% Confidence Interval)
Body Mass Index (kg/m^2): ≥35 vs. <35 (reference)	2.15 (1.11–4.22)
Diabetes Mellitus	1.95 (1.00–3.81)

4.22) and diabetes milletus (OR 1.95, 1.00–3.81) as independent predictors of an adverse event following total knee arthroplasty.

The reasons for an adverse event following total knee arthroplasty were reported in Table 4. The most common reason was leg pain (10 patients, 23.8%). Other frequent reasons for an adverse event following TKA included cellulitis (seven patients, 16.7%) and deep vein thrombosis and/or pulmonary embolism (seven patients, 16.7%). One patient (2.4%) had an adverse event following TKA due to Ogilvie Syndrome, a rare gastrointestinal disorder that can occur after major surgery.

Table 4. Reasons for an Adverse Event Following TKA

Rank	Reason	N	Frequency (%)
1	Leg Pain	10	23.8
2	Cellulitis	7	16.7
2	DVT and/or PE	7	16.7
4	Joint Infection	3	7.1
5	Abnormal INR	2	4.8
5	Anemia	2	4.8
5	Multiple	2	4.8
8	Acute Renal Failure	1	2.4
8	Bleeding	1	2.4
8	Chest Pain	1	2.4
8	Edema	1	2.4
8	Fall	1	2.4
8	High Blood Pressure	1	2.4
8	Internal Derangement of Knee	1	2.4
8	Nausea and Vomiting	1	2.4
8	Ogilvie Syndrome	1	2.4
		42	100.0

Discussion

The present study utilized a two-year sample from a tertiary academic hospital to examine the risk factors associated with and the causes of an adverse event following total knee arthroplasty. The principle findings of study were that both body mass index ≥35 and diabetes milletus were independent predictors of an adverse event following total knee arthroplasty. Leg pain, cellulitis, and deep vein thrombosis and/or pulmonary embolism were the most common reasons for an adverse event following TKA. These findings (1) confirm the results of many other studies, (2) provide valuable information to orthopaedic surgeons, and (3) support the initiation of future, related studies.

Multiple studies have reported body mass index[2, 5, 8, 14] or diabetes milletus[14] as an independent predictor of 30-day readmission following TKA. Interestingly, there are several studies that have found no association between body mass index/obesity[9, 12, 13, 15, 17] or diabetes milletus[2, 9, 12, 13] and 30-day readmission following TKA. Of our three most common reasons for adverse event following TKA, cellulitis was the most common finding in related studies.[2, 9, 14, 15]

There is some lack of consensus regarding the risk factors and causes of adverse events following total knee arthroplasty. Part of this may be attributable to different study populations simply having different susceptibilities for comorbidities and adverse reactions following major surgery. Our study contained a patient population with two unique factors: first, our study contained a Black race majority (53.9%) and White race minority (27.8%). In contrast, Clement et al., Mesko et al., and Pugely et al. all performed studies that had White race majorities over 65%. Second, our patient population had a high incidence of comorbidities

including dyslipidemia (35%), hypertension (77.5%), and diabetes milletus (31.7%).

There were several limitations in the current study. Some patient records lacked consistency and clarity; some information was illegible or missing. This made data collection more error-prone. Also, the reason for an adverse event following total knee arthroplasty was retrospectively determined from the patient record. However, in an effort to reduce bias, related diagnoses were grouped together into broader definitions such as "joint infection." Another limitation was the inability to capture all adverse events. Although patients have strict instructions to follow-up and come in for an emergency visit if any problems arise, it is possible that some patients may have presented to other regional hospitals for adverse events.

In conclusion, adverse events following total knee arthroplasty are both detrimental to patient wellbeing and expensive for payers. As the number one payer of total knee arthroplasty, it is likely that the Centers of Medicare and Medicaid Services will shift the payment model to place more of the financial risk on hospitals. Future studies with larger sample sizes are necessary to validate current findings and to potentially discover additional risk factors that could not be seen with this study's limited power. Gaining further understanding of the predictive risk factors and reasons for an adverse event following total knee arthroplasty will help a hospital better uphold its moral and financial obligations.

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Medical Student Research Project

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Understanding the Mechanism and Chemical Properties of Tranexamic Acid and its Applications in Orthopedics, Specifically Trauma Patients

Chava Blivaiss, BA; Christopher L. Haydel, MD; Anastassia Persidsky, MD

Department of Orthopaedic Surgery, Temple University School of Medicine, Philadelphia, PA

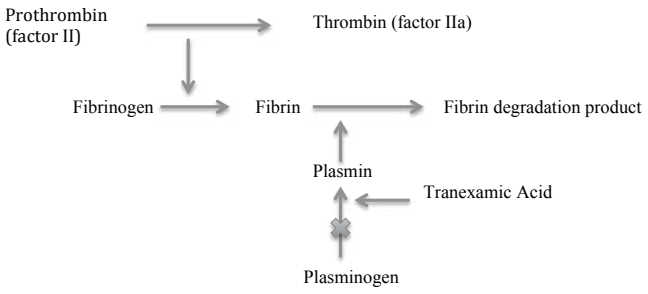
Introduction/Background

Worldwide, traumatic bleeding kills around two million people each year.[1] Surgeons are continuously searching for ways to improve surgical outcomes, minimize blood loss, and decrease the need for transfusion during surgery. A simple and cost-effective manner to do so is with antifibrinolytic drugs such as tranexamic acid (TXA). Tranexamic acid, an antifibrinolytic agent, has been utilized for decades during surgical procedures to minimize blood loss.[2] In March 2011, TXA was added to the World Health Organization list of essential medicines and that listing it might reduce deaths from hemorrhage.[3] It is a synthetic lysine amino acid derivative that acts by reversibly binding to plasminogen and preventing interactions with fibrin. This inhibits the breakdown of fibrin clots. Lysine residues on fibrin facilitate its binding to lysine on plasminogen. Tranexamic acid binds with high affinity to one of these lysine-binding sites and with low affinity to the other four or five binding sites. In doing so, it blocks plasminogen from binding to fibrin. Although plasminogen can still be converted to plasmin in the presence of a plasminogen activator, once it binds with tranexamic acid, it can no longer act with and digest fibrin (Figure 1). The lack of fibrinolysis is exhibited through reduced concentration of D-dimer (a small protein breakdown product of fibrin).[4] Another hypothesis is that TXA diminishes the body's natural anti-inflammatory response to hemorrhage.[5] TXA has a reputable safety and efficacy profile.[6] As opposed to other methods, studies show tranexamic acid is more cost efficient, helps increase the number of positive outcomes from surgery, and decreases the need for blood transfusion.

Other comparable antifibrinolytics and blood products have been observed in more depth and received more focus than TXA but are less cost effective or potent. In comparison to TXA, Apoprotein is a bovine product that leads to risks of allergic reaction and potential for disease transmission in patients.[7] Epsilon aminocaproic acid (EACA), another antifibrinolytic drug, is not only more costly but is approximately 7–10 times less potent than TXA.[8] Alternatively, allogenic blood transfusions have been correlated with postoperative infection and add additional costs to surgery, so any methods to minimize its use would be beneficial.[9] The superiority of TXA in cost, potency, and fewer potential interactions furthers the need for more study and inquiry into TXA's many potential uses.

Studies and reviews have established tranexamic acid's ability to reduce bleeding in patients undergoing elective orthopedic surgery, such as total knee replacement and total hip replacement, without any evidence of increased risk for thromboembolic events. Also notable is its ability to decrease the need for blood transfusion by one-third in these patients.[8, 10, 11] Two major studies — the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) and Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study — both explore the use of TXA in trauma settings. Studies and reviews have examined the use of tranexamic acid in trauma patients and orthopedic patients as separate entities, but this paper serves to review all those resources available simultaneously and assess their applications to orthopedic trauma patients. We hope to suggest further avenues of research in the field.

Figure 1. Fibrinolysis Cascade and Tranexamic Acid



Methods

A systemic computerized search of online databases PubMed and OVID was conducted using the key words: *tranexamic acid OR TXA AND trauma OR orthopedics*. After reviewing titles of the studies, we reviewed the

abstracts and chose those studies, reviews and meta-analyses that were potentially relevant. Similar data such as reduction in blood loss, patient demographics, and incidence of thrombolytic events were collected from all sources.

Discussion

CRASH-2

The CRASH-2 trial evaluated the efficacy of tranexamic acid and its cost effectiveness among 20,211 trauma patients admitted to 270 hospitals in 40 countries. The average age of participants in the trial was 35 years and 85% were male.[12] Patients were included only when the physician was uncertain whether or not to treat with TXA.[13] Prior to CRASH-2, only one randomized control trial of antifibrinolytic agent in trauma patients had been conducted with 70 randomized patients; therefore, it is clear that there is insufficient evidence to support the clinical significance of TXA treatment and more research must be conducted.[14]

CRASH-2 deduced that the usefulness of tranexamic acid in reducing the risk of death by hemorrhage is time sensitive. Therefore, early administration within three hours of injury is advantageous and those patients derive the most benefit from treatment. Out of the criteria analyzed — time from injury in hours, systolic blood pressure, GCS, and injury type — the only time TXA did not have a lower risk ratio than those treated with placebo was when it was administered greater than three hours after injury. As seen in Figure 2, overall in all patients analyzed in the study, TXA was statistically significant in preventing mortality regardless of other subcategory criteria. One subcategory in particular yielded interesting results. Patients were categorized as having blunt injuries, which included those with both blunt and penetrating injuries and those with only penetrating injuries. Of those patients given TXA (n = 10,093), 6,812 (67.5%) were categorized as blunt trauma and the other 3,281 (32.5%) with penetrating. Of the blunt trauma, 1,134/6,788 (16.7%) died of their injuries while only 329/3,272 (10.1%) of the penetrating trauma did. Of the 10,114 patients given the placebo, 6,843 (67.7%) had blunt trauma and 3,271 (32.3%) penetrating. Of those patients with blunt trauma treated with placebo, 1,233/6,817 (18.1%) died of their injuries while 380/3,250 (11.7%) with penetrating trauma died. In blunt trauma patients, the relative risk for those receiving TXA verses placebo was .92 (0.83 to 1.02) and for penetrating trauma 0.86 (0.72 to 1.03) with 99% CI. $\chi^2 = 0.791$, p = 0.37.[12]

Figure 2. Crash-2 Study Mortality Rates for Those Allocated TXA Versus Placebo and Accompanying Risk Ratio

All Patients	Mortality Post TXA Administration	Mortality Post Placebo Administration	Risk Ratio (99% CI)
20,211	1,463/10,060 (14.5%)	1,613/10,067 (16.0%)	0.91 (0.85 to 0.97) **2p = 0.0035**

In reviewing the data presented, we performed a chi-squared analysis to test response rates as seen in Figure 3. If the cumulative difference between the expected and observed is large enough, then the difference is significant. The null hypothesis (H_0) that we are testing is that the response rate (death) between the two groups (blunt/penetrating and penetrating) is equal. Based on these chi square analysis results, we reject the null hypothesis (H_0) and conclude there is a significant difference in the incidence of death between the two groups at a 0.0001 (or smaller) level of significance. There is only a one in 10,000 chance that the observed differences are due to random chance. Based on the data provided, there is a statistically significant difference in death associated with blunt trauma as compared with penetrating trauma. This potentially indicates that TXA is more efficacious in cases of penetrating trauma than blunt trauma or combined trauma and is worthy of further research and study.

Figure 3. Mortality of Blunt and Penetrating Trauma Patients (Where Both Groups Are Given TXA)

The FREQ Procedure			
Table of Trauma by Outcome			
Trauma	**Outcome (Death)**		
Frequency Row Pct	**Yes**	**No**	**Total**
Blunt	1,134 (16.65)	5,678 (83.35)	6,812
Penetrating	329 (10.03)	2,952 (89.97)	3,281
Total	1,463	8,630	10,093
Statistics for Table of Trauma by Outcome			
Statistic	**DF**	**Value**	**Prob**
Chi-Square	1	78.2921	<.0001
Likelihood Ratio Chi-Square	1	82.7147	<.0001
Continuity Adj. Chi-Square	1	77.7589	<.0001
Mantel-Haenszel Chi-Square	1	78.2843	<.0001
Phi Coefficient		0.0881	
Contingency Coefficient		0.0877	
Cramer's V		0.0881	
Fisher's Exact Test			
Cell (1,1) Frequency (F)	1,134		
Left-sided Pr ≤ F	1.0000		
Right-sided Pr ≥ F	6.542E-20		
Table Probability (P)	5.208E-20		
Two-sided Pr ≤ P	1.294E-19		

Sample Size = 10,093

Further results of the study proved that early administration of TXA to trauma patients minimized all causes of mortality with no evidence of increase in vascular occlusive events (although the possibility of some increase cannot be excluded). It was a double blind study ensuring that clinicians had no foreknowledge of allocation. As opposed to other studies, they did not find a substantial decrease in those

receiving blood transfusions or the amount of blood transfused; however, they found TXA is still able to reduce the risk of bleeding to death by approximately one-third. The study showed no significant differences between those patients in the TXA group that were given high or low doses. The fixed dose chosen was both successful in larger patients (>100 kg) and in smaller patients (<50 kg) without adverse effects. Beyond the positive attributes of TXA when administered in early proximity to time of injury, CRASH-2 found that late administration could increase the risk of death due to bleeding. It is best administered within three hours of initial injury and for those patients arriving several hours post injury, the clinician must use caution as TXA may not only be less effectual but even detrimental to the patient's recovery.[12]

CRASH-2, while critically important for discovering the efficacy and cost effectiveness of TXA, leaves many questions to be researched. Most of the hospitals in the study are located in developing countries. Of the patients randomized in the trial, 4,816 were in Africa, 7,366 in Asia, 2,218 in Europe/Australia/North America, and 5,807 in Caribbean/Central and South America. In order to assess the validity and generalizability of the results, a similar study should be conducted in the United States in urban trauma centers to see if the same results are present. Additionally, with all the other anti-coagulants, methods of blood preservation, and safety of blood transfusions, is TXA necessary in the urban trauma center?

MATTERs

In 2010, major hemorrhage protocols in England changed the basis of TXA administration from the clinical judgment of the attending physician to administration for patients with signs of hyperfibrinolysis or in need of blood products. The standard dose of 1 g intravenous bolus was given at intervals decided by the physician.[15] The MATTERs Study was a retrospective observational cohort study done reviewing the use of TXA in combat injuries at a single surgical hospital at Camp Bastion in Afghanistan.[16] Although they had the results from CRASH-2 to reference, they found them ungeneralizable to military purposes because the civilian hospitals in which the study was conducted lacked many of the modern trauma practices available in military situations.[16]

Of the 896 patients received at the camp with combat injuries requiring transfusion, 293 received a mean intravenous dose of 2.3 g TXA (SD 1.3 g) within one hour of injury (Figure 4). The TXA group had higher injury severity score upon admission, higher percentage of patients with severe extremity injury, lower revised trauma score, and a greater percentage of people with lower Glasgow coma scale and hypotension.[16] Upon plotting a Kaplan-Meier survival curve of the overall cohort of those patients receiving TXA versus no TXA, the group receiving TXA had better 30-day survival (P = .006).[16] Many of the findings matched those of CRASH-2; however, the findings of the MATTERs study

Figure 4. Study Profile for Overall Cohort and Study Groups of MATTERs Study

Total patients admitted to Camp Bastion with combat injuries requiring transfusion	**896**
Received TXA	293
Received TXA and massive transfusion	125
Did not receive TXA	603
Did not receive TXA but did receive massive transfusion	196

went a step further showing that not only does TXA reduce mortality in hemorrhage and trauma patients but it suggested a stronger efficacy in those more severely injured as evidenced in a 6.5% reduction in mortality in those patients requiring TXA and an operation.[16] MATTERs found the CRASH-2 study to introduce a "conservative bias" against the "TXA effect" due to the lighter nature of the injuries presented in the civilian hospital versus those seen in combat. It found that TXA was most effective in the massive transfusion group, as seen in Figure 5, reducing mortality within this group by 13.7% (n = 231). The CRASH-2 study's number needed to treat with TXA was 67 but only seven patients in the MATTERs study, which shows the impact extent of injury has on efficacy of TXA. It is important to note that the prospective randomized aspect of the study was stopped due to the benefits observed in using TXA to reduce inflammation. The TXA group showed higher rates of deep vein thrombosis (DVT) and pulmonary embolism (PE) but this is most likely due to the more extensive nature of injuries of those treated in this cohort and can be linked to increased thrombolytic events; however, it is possible the increased thrombolytic events may be caused by TXA and this must be further investigated. The overall findings paralleled those of CRASH-2 indicating the use of TXA with additional blood components improve patient outcomes, and that early administration of TXA with patients susceptible to hemorrhage should become protocol, especially those in the most dire situations (massive transfusion).[16]

Elective Orthopedic Procedures: Total Hip Replacement/ Total Knee Replacement

As opposed to trauma uses, there have been many studies, reviews and meta-analyses on the uses of TXA in elective orthopedic surgery, specifically total knee and hip arthroplasty. In a 2013 meta-analysis performed by Gandhi et al.,[8] they analyzed 33 randomized controlled studies to assess the efficacy of TXA in total knee arthroplasty (TKA) and total hip arthroplasty (THA) in regards to total blood loss, patients receiving allogenic transfusions, and occurrence of DVT. They found that for total blood loss during TKA, there was a combined weighted mean difference of –1.149 ($p < 0.001$, 95% CI –1.298, –1.000) representing statistically significantly less blood loss in those patients given TXA compared to the control; however, there was a high level of heterogeneity between studies ($p = 0.000$, $I^2 = 85.710$). For THA, the

Figure 5. Development of Thrombolytic Events and All Cause Mortality Rates in MATTERs Study

	Overall			Massive Transfusion		
	Given TXA (n =293)	No TXA (n = 603)	P Value	Given TXA (n = 125)	No TXA (n = 196)	P Value
Developed Pulmonary Embolism	8 (2.7%)	2 (0.3%)	.001*	4 (3.2%)	0	.01*
Developed Deep Vein Thrombosis	7 (2.4%)	1 (0.2%)	.001*	2 (1.6%)	1 (0.5%)	.32
Mortality within 24 hours	293 (9.6%)	603 (12.4%)	.20	125 (9.6%)	196 (14.8%)	.17
Mortality within 48 hours	264 (11.3%)	507 (18.9%)	.004*	112 (10.4%)	160 (23.5%)	.003*
In hospital mortality	264 (17.4%)	603 (23.9%)	.03*	125 (14.4%)	196 (28.1%)	.004*

*Statistically significant values of $p < .05$

weighted mean difference of total blood loss was −0.504 ($p < 0.001$; 95% CI −0.672, −0.336) representing statistically significantly less blood loss in those patients given TXA compared to the control group with only moderate heterogeneity between studies ($p = 0.006$, $I^2 = 58.000$). The combined odds ratio (OR) for patients receiving allogenic blood transfusions undergoing TKA was 0.145 ($p < 0.001$; 95% CI, 0.094, 0.223) signifying the number of patients requiring transfusions was statistically significantly less for those given TXA than the control and there was no heterogeneity between studies ($p = 0.801$, $I^2 = 0.000$). The combined OR for patients receiving allogenic blood transfusions undergoing THA was 0.327 ($p < 0.001$; 95% CI, 0.208, 0.515) signifying the number of patients requiring transfusions was statistically significantly less for those given TXA than the control but there was moderate heterogeneity between studies ($p = 0.135$, $I^2 = 34.089$). The combined OR for patients developing DVT after TKA and THA were 1.030 and 1.070 respectively, indicating that in both surgeries, those patients given TXA had no increased incidence of DVT than those in the control groups and there was no heterogeneity between studies in either surgery. The results demonstrated statistical significance in TXA's ability to reduce total blood loss, number of patients requiring transfusions, and did not increase instances of DVT in TKA and THA, the effect being even greater in the former.[8]

Meta-analyses on the use of TXA in TKA and THA separately come to consistent conclusions on its ability to reduce blood loss. Zhou et al.'s 2013 meta-analysis of 19 randomized controlled trials on the use of TXA in THA containing 1,030 patients, found that TXA reduced total blood loss by an average of 305.27 mL ($p < 0.001$; 95% CI, –397.66 mL, –212.89 mL) compared to placebo groups. They also found that the number of patients requiring allogenic blood transfusion was 28% less in the TXA group than placebo ($p < 0.001$; 95% CI, 0.19, 0.42). A dose effect relationship was analyzed in 11 of the studies and found a correlation between increased TXA dose and decreased total blood loss ($p = 0.0033$, $r = –0.7258$). From their analysis, they found that intravenous administration of 10–20 mg/kg of TXA pre-incision and subsequently followed by 10–20 mg/kg 3–12 hours post-operation would be effective, while administering it only after operation may not be as efficacious. Like other studies, they also found no increased incidence of DVT in the TXA group. Yang et al.[17] 2012 meta-analysis on the safety and efficacy of TXA reducing blood loss in TKA, although only 15 randomized controlled studies were analyzed, the results once again exemplified the beneficial use of TXA in surgery. They found the amount of blood loss per patient was significantly less in the tranexamic acid group compared with the placebo group by an average of −504.90 mL ($p < 0.00001$; 95% CI, −620.89 mL, −388.92 mL). They too found the rate of patients who required transfusion during TKA was significantly less in the tranexamic acid group compared with the placebo group with an OR = 0.16 ($p < 0.00001$; 95% CI, 0.10, 0.25). There was no increased incidence of DVT or PE in the TXA group as their odds ratios were 0.75 and 0.65 respectively. These results, although slightly differ surgery-to-surgery, are consistent in overall meta-analysis despite the heterogeneity of studies.

In Huang et al.,[18] meta-analysis of 46 randomized controlled studies on the use of TXA to reduce blood loss and transfusion in major orthopedic surgery found similar results to the previous reviews. In terms of total blood loss, the weighted mean difference for all patients was completed and those patients given TXA had significantly reduced blood loss by an average of 408.33 mL compared to controls ($p < 0.00001$; 95% CI, –505.69, –310.97). Additionally, intraoperative bleeding was reduced in TXA patients by a mean of 125.65 mL ($p < 0.0001$; 95% CI, –182.58, –68.72). They found that TXA reduced the probability of needing a blood transfusion by 49% (relative risk 0.51; $p < 0.00001$; 95% CI, 0.46, 0.56). The use of TXA reduced the blood units transferred per patient, reduced the blood transfusion volume, and did not increase the incidence of DVT compared to controls.

Orthopedic surgeons commonly utilize a pneumatic tourniquet to reduce blood to the surgical field during total knee arthroplasty, which increases fibrinolysis and increased bleeding postoperatively. Studies have shown that applying 1.5–3 g TXA topically at the end of total knee arthroplasty decreased total blood loss post-operatively compared to placebo but had no effect on transfusion requirements.[19] A systematic review of randomized clinical trials on the use of intravenous TXA in elective and emergency surgery, performed by Ker et al.,[20] found that TXA reduced the probabil-

ity of blood transfusion by 38%. They also found that TXA given after incision had a greater impact on blood loss but the difference between pre- and post-incision was small. Despite differences in questions, methodology and surgery type, all reviews and meta-analyses seem to come to analogous conclusions as we hypothesized that the benefits and efficacy of TXA merit its use and further studies.

Conclusion

In conclusion, we find TXA leads to statistically significant decrease in blood loss in both trauma and orthopedic settings and could be beneficial in the field of trauma orthopedics. From the many studies, it seems that TXA is most efficacious when given within an hour of injury and to those patients with more severe injuries with the highest concern for hemorrhage and hyperfibrinolysis. Further studies should probe whether the results of both the MATTERs and CRASH-2 studies can be applied and replicated in urban first-world hospitals with orthopedic trauma patients using the parameters from the CRASH-2 study or use guidelines set forth in the *Journal of Trauma Acute Care Surgery* by Napolitano et al., "In adult trauma patients with severe hemorrhagic shock (SBP ≤ 75 mm Hg), with known predictors of fibrinolysis, or with known fibrinolysis by TEG (LY30 > 3%); and only administer TXA if less than three hours from time of injury; and TXA administration: 1 g intravenously administered over 10 minutes, then 1 g intravenously administered over eight hours."[21] Based on the success of its use in elective orthopedics procedures, this would be a valid prediction.

Currently, the PATCH (Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Hemorrhage) Trauma study is taking place in Australia and New Zealand. It is a randomized control trial that will determine the effect of early administration TXA compared with placebo on mortality and favorable outcomes at six months in severely injured adults at high risk of acute traumatic coagulopathy. The results of this study should be taken into account when designing future studies as it is more applicable to the major urban trauma/orthopedics setting than the CRASH-2 or MATTERs studies.[22]

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Original Research

Association Between *GRIN2A* Promoter Polymorphism and Recovery from Concussion

Jane McDevitt, PhD;[1] Ryan Timothy Tierney, PhD;[1] Jacqueline Phillips, MS;[1]
John P. Gaughan, PhD;[2] Joseph S. Torg, MD;[3] Evgeny Krynetskiy, PhD[4]

[1]*Temple University, Department of Kinesiology, Philadelphia, PA;* [2]*Biostatistics Consulting Center,*
[3]*Temple University School of Medicine, Department of Orthopedic Surgery, Philadelphia, PA;*
[4]*Temple University School of Pharmacy, Philadelphia, PA*

Abstract

Objective: To determine genetic variability within the *GRIN2A* promoter and its association with concussion recovery time. The hypothesis tested was that there would be a difference in allele and/or genotype distribution between two groups of athletes with normal and prolonged recovery.

Methods: DNA was extracted from saliva collected from a total of 87 athletes with a diagnosed concussion who completed a concussion evaluation. The (GT) variable number tandem repeats (VNTR) within the promoter region of *GRIN2A* was genotyped. The long (L) allele was an allele with ≥25 VNTR, and the short (S) allele was an allele with <25 VNTR in the GT tract. Participants' recovery time was followed prospectively, and was categorized as normal (≤60 days) or prolonged (>60 days).

Results: L allele carriers were found more frequently in the prolonged recovery group ($p = 0.048$). Additionally, LL carriers were 1.65 times more likely to recover longer than 60 days following the concussive event (odds ratio 1.030, 95% CI 1.030–2.653, $p = 0.0372$).

Conclusion: Determining genetic influence on concussion recovery will aid in future development of genetic counseling. The clinical relevance of genotyping athletes could improve management of athletes who experience concussion injuries.

Introduction

Cerebral concussion is defined as a traumatically-induced transient disturbance of the brain and involves complex pathophysiological processes.[1] Each year, an estimated 1.6 to 3.8 million sports-related concussions occur,[2] resulting in billions of dollars in healthcare costs.[3] This is likely an underestimate since many concussions are probably missed and true incidence is unknown.[2, 4] Eighty to 90% of athletes are returned to play within 7–14 days[5, 6] but some athletes do not return to play for 14,[7] 21 days after injury[8] to 30 or more days after injury.[9] However, there is no specific definition of what qualifies as prolonged recovery. Several risk factors that could contribute to a greater risk of prolonged recovery have been reported and include age, sex,[6] reporting specific signs and symptoms (s/s) such as dizziness[8] or headache[10] at the time of injury, history of previous concussions,[11] and playing specific activities (e.g., football).[12] Recovery time is also likely to be influenced by genetic variability in the genes involved with the cell's resistance and response to mechanical stress.[13]

During a head impact, an external force causes head acceleration resulting in brain cell strain or deformation.[14–15] This mechanical strain alters cell structure, and induces changes in biochemical environment, e.g., the indiscriminate ion flow through protein channels, and the release of the excitatory amino acid glutamate.[17, 18] Extracellular glutamate binds to several receptors within the n-methyl-d aspartic acid (NMDA) channel, which exacerbates the Ca^{2+} ion influx and prolongs neuron dysfunction.[17] Following a concussive event, Ca^{2+} levels may increase beyond normal levels,[19] and can remain elevated for up to 14 days.[20] Variations in the NMDA structure or polypeptide level influence the magnitude of neuron cell dysfunction following a traumatic mechanical event, and are considered contributing factors to variability of concussion duration. Genetic polymorphism within the promoter region of the *GRIN2A* gene modulates expression of NMDA subunit NR2A.[21] The length of (GT)n repeat has been associated to *GRIN2A* expression level, with longer alleles (≥25 repeats) correlating with poorer outcomes in several brain-related diseases such as bipolar disease and schizophrenia.[21–23]

Several studies aimed to test an association of genetic factors with incidence and/or recovery from concussion in high school and college athletes.[24–28] Previous studies examined genetic and environmental factors such as polymorphisms within *APOE* gene and concussion history, which led to poor outcome in concussion recovery.[24–28] A definite answer to the question about the contribution of genetic factors to concussion susceptibility and recovery still remains to be found.

In the current study, we tested the hypothesis that genetic variability within the *GRIN2A* promoter region is associated with concussion recovery. The variable number of GT repeats (rs3219790; VNTR) within *GRIN2A* promoter was

determined, and statistical analysis for association with concussion severity and recovery was performed.

Materials and Methods

Participants

A case series study design was utilized to test 87 (23 females, 64 males; 19.47 ± 6.02 years old) athletes with a diagnosed concussion from a hospital concussion program (September 1, 2011 to February 1, 2013). Athletes suspected of concussion were referred to the center by a coach, parent, other physician, or certified athletic trainer. All patients enrolled in the study had a concussion verified by the center's physician during the initial evaluation. A concussion case for this study was defined as the patient having a pathomechanical event followed by signs and symptoms (e.g., headache, dizziness) within the next 48 hours.[6] All participants with a diagnosed concussion from an athletic event who volunteered to be in the study, and returned for follow-up and return-to-play care were included in the study. All concussions from a non-athletic event (e.g., a fall, car accident) were excluded from the study. All candidates who agreed to participate in the study had the study explained to them to ensure a complete understanding of the study's purpose and the methodologies utilized. The athletes were free to withdraw consent and to discontinue participation in the project or activity at any time without prejudice. The athletes also signed informed consent or assent forms before participation. The University's Institutional Review Board approved this study.

Enrolled participants provided salivary samples for isolation of DNA. The number of (GT) VNTR (rs3219790) within the promoter region of *GRIN2A* was genotyped. The long (L) allele was defined as an allele with ≥25 dinucleotide repeats in the GT tract. The short (S) allele was defined as an allele with <25 dinucleotide repeats in the GT tract. The same technique to determine the cut-off point was used in other *GRIN2A* promoter (GT)n VNTR studies, where the average GT repeat in this study was 24.5.[21–23] Based on the results of genetic analysis, participants were genotyped as LL homozygotes, SS homozygotes, or LS heterozygotes.

Athlete's recovery time was followed prospectively until the full return-to-play (RTP) clearance date determined by the treating physician. Participant's recovery time was categorized as normal (≤60 days) or prolonged (>60 days). The current cohort recovered in approximately 56 days after injury onset. Utilizing this cutoff point, 67 athletes were placed in the normal recovery group with an average of 20.84 ± 10.93 days to recover and 20 athletes were placed in the prolonged recovery group with an average of 172.64 ± 117.77 days to recover.

Concussion Assessment Battery

Patients completed a standardized initial evaluation where the following parameters were assessed: concussion injury characteristics including the date and time of injury, mechanism of injury, acute (e.g., loss of consciousness, dizziness), patient history including self-reported prior concussion history, migraine, attention deficit disorder/hyper-attention deficit disorder, and psychiatric history (e.g., depression). Initial evaluation was followed by an objective screening, which included the vestibular ocular assessments, the BESS test, and an ImPACT.

DNA Collection, Purification, and Estimation

Salivary samples for genotyping and DNA isolation were collected using Oragene DNA Self Collection Kits (DNA Genotek, Ottawa, ON, Canada). DNA was extracted according to manufacturer's instructions. Purified DNA was quantified using a Quant-it PicoGreen dsDNA assay kit (Invitrogen, CA; Parkman et al., 2003). The DNA region surrounding position (–975 to –776) in the promoter of *GRIN2A* was amplified by polymerase chain reaction (PCR) with the forward (FWD) or 5'-FAM-labeled forward (FAM-FWD), and reverse (REV) primers (Operon, AL). Primer sequences were as described earlier.[21–22] PCR reaction mix contained 20 to 40 ng genomic DNA, 0.1 μM each primer, and 1.25 units of AmpliTaq Gold DNA polymerase (Applied Biosystems, CA) in 3.5 mM $MgCl_2$ at pH 8.5. The cycling conditions were 94°C for two minutes, 35 cycles (94°C for one minute, 55°C for two minutes, 72°C for one minute), followed by incubation at 72°C for seven minutes.

Purification of the Reaction Mix and Genotyping

The PCR products (5 μl) mixed with 2 μl of ExoSAP-IT reagent (Affymetrix, CA) were incubated at 37°C for 15 minutes followed by thermoinactivation at 80°C for 15 minutes. The reaction mix was analyzed by capillary electrophoresis (Genewiz, NJ). Fragment length polymorphism analysis (FLP) was performed by measuring the migration time of a PCR product, and extrapolation to the known fragments in the DNA standard ladder using Peak Scanner software v1.0 (Applied Biosystems, CA) using internal standards. The number of GT dinucleotide repeats was calculated using the following equation: n(GT) = (L – 167)/2, where L is the length of the PCR fragment estimated in base pairs. The genotyping success rate was 100%.

The amplification products were inserted into pCR4-TOPO cloning vector (Invitrogen, CA). The recombinant constructs were used for transformation of bacterial strain TOP10. The identity of amplified products was confirmed by sequence analysis.

Pedigree Analysis of (GT)n Polymorphism

To validate the analytical method for (GT)n repeat genotyping, a pedigree analysis of (GT)n alleles in a three-generation family was performed (Figure 2). To this end, saliva was collected from six members of the three-generation family, and genotyping analysis was performed using the established protocols described above. The pedigree chart

1 GAAGGAAGCATGTGGGAAATGCAGATGTCTTTGCTTTTAGGATTCTGGCT CCCTGAGATC
61 AGAGGAGTGGGTTCCCGTACGGGGGTGGCGAGGCACAGGGAGAAGCATTGGAGCAGACTC
21 **TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTG**TCGGCGCGCCTGTGCGTGGA
181 GGGGGATAACTGTACCCAGC

Figure 1. *GRIN2A* Promoter Fragment Located at Chromosome 16. The sequence corresponds to position 10217386 – 10217585 of contig GRCh37.p10 (NT_010393.16). Primers used for PCR analysis are underlined. Polymorphic GT repeat region is shown in bold font.

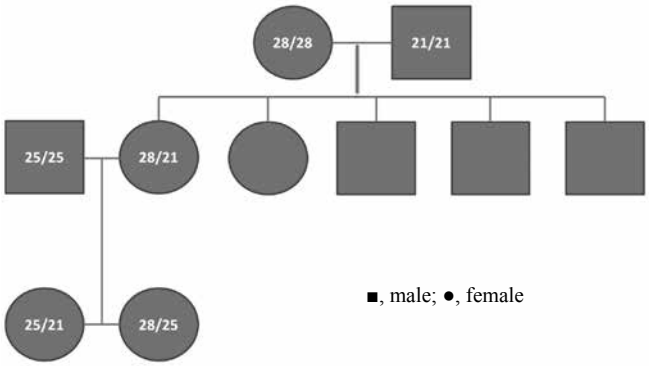

Figure 2. Pedigree Analysis of (GT)n Repeat Alleles in a Three-Generation Family. Six members were genotyped in respect to the number of GT repeats in the *GRIN2A* promoter region. The number of repeats is indicated for each genotyped individual.

analysis confirmed that the protocol established in this work accurately detected the presence of allelic variants both in homo- and heterozygous individuals, and that the corresponding alleles are inherited according to the Mendel's laws. Therefore, the pedigree analysis validated the protocol for (GT)n genotyping both in homo- and heterozygotes.

Statistical Analysis

The genotype groups were analyzed using dominant (LL + LS versus SS), recessive (LL versus LS + SS), and co-dominant (LL versus LS versus SS) genetic models. The variation between (GT)n VNTR, the L and S frequencies and the duration of recovery (normal versus prolonged) were assessed using two-tailed, Chi-Square association test. Univariate logistic regression analysis was used to estimate the extent to which VNTR and non-genetic factors contributed to prolonged recovery. Non-genetic factors included were age, sex, race, concussion history, migraine history, and history of dizziness and balance issues at time of injury. Differences in concussion severity utilizing the dominant, recessive, and co-dominant genetic models were analyzed using a two-tailed t-tests. SAS v 9.2 (SAS Institute, Cary, NC) was used for all analyses. The alpha level was set at $p \leq .05$.

Results

The clinical characteristics of the 87 participants are presented in Table 1, and the descriptive data by group is presented in Table 2. There were no significant differences in descriptive data between recovery groups. The athletes in the normal recovery group were examined on average within 7.06 ± 6.64 days after concussion injury. Participants in the prolonged recovery group were examined within 90.25 ± 124.31 days following injury. This cohort demonstrated significantly poorer scores on initial evaluation compared to

Table 1. Characteristics of 87 Athletes Enrolled in this Study

Age	19.47 ± 6.02 (SD) yr
Sex n (%)	23 (26) females, 64 (74) males
Race n (%)	45 (52) Caucasian, 12 (14) African American, 3 (0.03) Hispanic/Latino, 1 (0.01) Native American, 2 (0.02) Asian/Pacific Islander, 2 (0.02) mix, 22 (25) did not report
Hx Migraine	10
Hx Learning Disability	12
Hx Depression	2
Prev Conc n (%)	19 (22) with 1 previous, 13 (15) with 2 previous, 5 (0.6) with 3 previous, 1 with 4 (0.01) previous, 1 with 5 (0.01) previous, 1 with 6 (0.01) previous, 1 with 7 (0.01) previous, 1 with 9 (0.01) previous

Note: SD (standard deviation), yr (year), Hx Migraine (history of migraines or 15+ headaches per month), Hx Learning Disability (history of attention deficit disorder or hyper-attention deficit disorder), Hx Depression (diagnosed with depression), Prev Conc (number of previous concussions).

Table 2. Descriptive Data by Recovery Group

Variables	Prolonged Recovery n (%) n = 20	Normal Recovery n (%) n = 67	*p*
Sex n (%)			0.150
Male	12 (14)	52 (60)	
Female	8 (0.09)	15 (17)	
Race			0.411
Caucasian	10 (24)	11 (26)	
African American	4 (10)	4 (10)	
Hispanic/Latino	0 (0)	2 (5)	
Native American	0 (0)	1 (2)	
Asian/ Pacific Islander	0 (0)	1 (2)	
Not Reported	6 (14)	3 (7)	
Migraine			0.825
Hx	2 (0.02)	8 (0.09)	
No Hx	18 (21)	57 (61)	
Learning Disability			0.659
Hx	0 (0)	12 (14)	
No Hx	20 (23)	53 (48)	
Depression			0.495
Hx	1 (0.01)	1 (0.01)	
No Hx	19 (22)	63 (72)	
Genetic Factors			0.094
LL	7 (0.08)	11 (13)	
LS	11 (13)	37 (43)	
SS	2 (0.02)	19 (22)	
Age Mean (SD)	18.17 (2.87)	23.75 (10.24)	0.249
Prev Conc	1.43 (0.01)	0.93 (1.65)	0.169

Note: M (mean), SD (standard deviation), n (number), Hx (history), ADHD (attention deficit disorder), Prev Conc (number of previous concussions). **p* value Fisher's exact test.

return to their return-to-play evaluation for each of the concussion assessments (Table 3).

Validation of (GT)n Genotyping Analysis

Sequence analysis of cloned fragments was in agreement with the results of FLP analysis by capillary electrophoresis. The PCR products were not homogenous, because of a well-known phenomenon of slippage of Taq polymerase on a monotonous template.[29] The presence of several peaks on the electrophoregram did not impede the analysis of homozygous genotypes, because the strongest signal clearly identified the major product, and was used for calculating the number of GT repeats. The pedigree chart analysis confirmed that the protocol established in this work accurately detected the presence of allelic variants both in homo- and heterozygous individuals, and that the alleles are inherited according to the mendelian inheritance pattern. The pedigree analysis validated the protocol for (GT)n genotyping both in homo- and heterozygotes.

Table 3. Differences in Initial and Return-to-Play Evaluation Scores

Test	Mean	SD	t	df	*p*
Initial VOR	0.56	0.50	6.80	40	0.000*
RTP VOR	0.02	0.16			
Initial BESS	15.54	7.17	2.68	38	0.011*
RTP BESS	12.54	7.46			
Initial Verbal	80.80	18.76	–4.21	39	0.000*
RTP Verbal	90.95	10.83			
Initial Visual	67.60	15.77	–4.07	39	0.000*
RTP Visual	75.18	15.96			
Initial Motor	37.85	9.51	–4.12	38	0.000*
RTP Motor	41.03	8.38			
Initial s/s	27.07	21.92	7.66	39	0.000*
RTP s/s	7.08	16.00			

Note: SD (standard deviation), RTP (return to play), *significance at $p \leq .05$.

Allele Distribution and Recovery Time

The mean repeat number of (GT)n was 24.5, and the GT repeat number ranged from 19 to 36. We categorized all allelic variants into two groups: long allele L ($n \geq 25$), and short allele S ($n < 25$), in accordance with previous publications.[21–23] Therefore, all participants were classified as homozygous carriers of long allele (LL, 21%), homozygous carriers of short allele (SS, 24%), or heterozygotes (LS, 55%). No deviation from the Hardy-Weinberg equilibrium was detected (Table 4). There was significant variation between the frequencies of L and S alleles of the normal (L= 59, S = 75) and prolonged (L = 25, S = 15) recovery time groups ($p = 0.048$, odds ratio = 2.11, Wald $\chi^2 = 4.209$), where the L allele carriers were two times more likely to be found in the prolonged recovery group compared to those carrying the S allele. The variation between long or normal recovery with different (GT)n genotypes showed no significant differences among genotypes (Table 5). However, there was a trend in the codominant model demonstrating that LL genotype was over represented in the prolonged recovery group

Table 4. Hardy-Weinberg Equilibrium

Genotypes	Observed #	Expected #
Homozygote reference	21	23.3
Heterozygote	48	43.4
Homozygote variant	18	20.3
Variable allele frequency	0.48	
C^2 = 0.954829932		
C^2 test *P* value = 0.328493		1 degree of freedom

Table 5. Test for Association Between Recovery and Genetic Model

Model	Normal	Prolonged	*p* (Fisher's Exact Test)
Recessive			0.137
LL	19	2	
SS + LS	48	18	
Dominant			0.112
LL + LS	56	13	
SS	11	7	
Codominant			0.094
LL	11	11	
SS	19	19	
LS	37	37	

Note: LL (homozygous long alleles), SS (homozygous short alleles), LS (heterozygous long allele and short allele), *p* (alpha level), *df* = 1.
*Significance at $p \leq .05$.

($p = 0.094$). Utilizing different cut points at 40 ($p = 0.109$) and 50 ($p = 0.094$) illustrated a trend, where those carrying the L allele and LL genotype were more likely to have prolonged recovery. This trend was not seen when shorter recovery times were used (10–30 days).

Recovery data were used in univariate analysis of participants carrying the LL, LS, or SS genotypes as independent variables (Table 6). Each predictor was analyzed using univariate logistic regression. There were no significant associations found. However, there was a trend found between recovery and the dominant genetic model (LL versus SS + LS; odds ratio 0.365, 95% CI 0.119–1.122, $p = 0.079$). Finally, a single variable logistic regression predicted that those carrying the LL genotype were six times more likely to take longer than 60 days to recover from a concussion injury (odds ratio 1.030, 95% CI 1.030–2.653, $p = 0.0372$).

Discussion

This was the first study to investigate the effect of VNTR polymorphism (rs3219790) in the promoter region of *GRIN2A* on concussion recovery time, and we found an association with both allele and genotype. Carriers of the L allele and those having LL genotype are more likely to take longer than 60 days to recover. As no universal definition of prolonged recovery duration exists, different authors defined it as an injury persisting over ten,[5] 14,[7] 21,[8] or 30 days.[9] In our study, 23% of concussed population took greater than 60 days to recover. Compared to previous research, where 80% typically recover in less than 10 days,[1, 6, 20] a larger majority of the current studies' population took greater than 60 days

Table 6. Univariate Regression Analyses of Risk Factors for Prolonged Recovery

Parameter	Wald χ^2	Wald *p*	Odds Ratio	95% CI
Age	3.29	0.070	1.30	0.98–1.71
Sex	2.38	0.122	0.43	0.15–1.25
African American	0.02	0.879	1.21	0.2–4.88
Caucasian	0.12	0.725	1.29	0.31–5.44
Hx Prev Concussion	2.82	0.093	2.43	0.86–6.87
Ac Dizziness	0.37	0.542	0.73	0.26–2.02
Ac Balance	2.01	0.156	0.22	0.07–5.94
LOC	2.69	0.101	0.23	0.04–1.33
Hx Migraine	0.13	0.718	1.26	0.37–4.30
Recessive	2.56	0.109	0.28	0.06–1.33
Codominant	0.72	0.397	1.31	0.70–2.47
Dominant	3.10	0.079	0.37	0.12–1.12

Note: Hx (history), N_Prev (number of previous concussions), Ac Dizz (reported acute symptom of dizziness immediately following concussion), Ac Balance (reporting acute symptom of balance issue immediately following concussion), LOC (loss of consciousness), Migraine (reporting a history of migraine problems), Est (estimate), Std Error (standard error), χ^2 (chi-square), p (alpha level), CI (confidence interval), Recessive (LL versus LS + SS), Dominant (LL + LS versus SS), and Co-dominant (LL versus LS versus SS).
*Significance at $p \leq .05$.

to recover. This may be due to the current population being recruited from a hospital concussion program. Athletes that have a problem recovering after a concussion are more likely to seek attention at a concussion program.

Using the known pathophysiology pathway of the recovery process, we selected the candidate gene, *GRIN2A,* which codes for the NR2A subunit within the NMDA channel. *GRIN2A* expression is modulated by (GT)n VNTR in the promoter region.[21, 23, 30] The (GT)n VNTR in the promoter region had been earlier associated with altered expression level of *GRIN2A.*[21, 23, 30] The length of (GT)n repeat modulates *GRIN2A* expression level, with longer alleles (≥25 repeats) associated with lower transcription of GRIN2A mRNA. The results of our study demonstrated that the carriers of the L allele are two times more likely to recover in 60 or more days. Our findings suggest that the expression level of NMDA channel plays an important role during neuronal recovery, and this hypothesis is currently under investigation in our lab.

Previous research has also attributed the GRIN2A L allele to be associated with poor brain outcomes. This may be due to decreased transcription of *GRIN2A* to produce the NR2A subunit within NMDA channel. This suggests that the NR2A subunit is necessary for NMDA functioning following a concussive event. Similar to this study's findings, previous research has demonstrated that polymorphisms in this gene may be a contributing risk factor for increased susceptibility to schizophrenia and bipolar disorder.[20, 21, 22] It has also been attributed to decreased volumes of hippocampal and amygdala regions.[23]

Promoter repeat polymorphisms are known to modulate gene expression, and often result in an altered phenotype.[31] Besides *GRIN2A,* there are several other genes containing the (GT)n VNTR, and the short (GT)n alleles (<25 repeats) manifest higher levels of expression compared to the long (GT)n alleles (≥25 repeats). These differences in expression level are also reflected in distinct phenotypes. Carriers of the short alleles in the promoter of *HO-1* have an increased risk of rheumatoid arthritis (OR = 0.80, 95% CI = 0.70–0.90, p = 0.019), compared with the carriers of the long alleles.[32] The (GT)n repeat within *HMOX1* promoter modulates the transcription activity, and those carrying the long alleles (≥25 repeats) have an increased risk for type II diabetes compared to those carrying the short alleles (<25 repeats; OR = 1.25, 95% CI 1.02–1.24, p = 0.02).[33] Importantly, the relationship between the genotype and mechanical brain stress response was demonstrated for other genes, e.g., *APOE.*[24–28] Our study in college athletes with a concussion history showed that individuals who carry three APOE variant alleles were 10 times more likely to report a concussion.[27]

This was the first study to analyze the effect of VNTR in the promoter region of *GRIN2A* with concussion recovery and concussion severity. The method used to analyze VNTR in this study is applicable to other genes that also contain dinucleotide (GT)n repeat polymorphisms. Importantly, the functional significance of (GT)n polymorphism on gene expression remains to be elucidated. This work contributes to further characterization of gene expression regulated by (GT)n-containing promoters. It should be noted that there were several limitations in this study. First, some athletes were not seen at the time of injury, which might have been the reason we did not see much difference in severity scores between recovery groups. Next, one gene and one polymorphism were examined; however, concussions are multifactorial injuries and most likely influenced by several genes and numerous polymorphisms. Future research using hypothesis-free technique such as genome-wide analysis could help identify additional predictive risk factors contributing to recovery rate.

Conclusion

In summary, the L allele carriers as well as those carrying the LL genotype were more likely to experience prolonged recovery following a concussion, presumably due to decreased transcription of *GRIN2A.* This suggests that the level of NR2A subunit is important for NMDA functioning following a concussive event. On the basis of these observations, we conclude that genetic factors contribute to long-term recovery from a concussion. Our results suggest that genetic polymorphisms in *GRIN2A* promoter region are a useful predictive marker of athlete susceptibility to concussion and brain trauma. Clinically, the prospective genotyping of athletes before the sport season could help improve monitoring and management of athletes who experience concussion injuries. Furthermore, genetic markers can assist in the management of concussions post-injury.

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Original Research

Concussion Occurrence and Perception Survey for Athletes (COPSA)

Jane McDevitt, PhD, LAT, ATC, CSCS; Ryan T. Tierney, PhD, LAT, ATC; Eugene Komaroff, PhD

Temple University, Philadelphia, PA

Abstract

Context: Underreporting of concussions is a problem in high school athletics. Additionally, little is known as to what factors influence the athletes' unwillingness to report concussive signs and symptoms (s/s).

Objective: Identify athletes' perception, reporting values, and occurrence of concussive s/s.

Design: Survey.

Setting: Urban high schools.

Participants: 302 athletes participating in a 2010–2011 sport.

Interventions: An anonymous survey was constructed for the study. Athletes were grouped into high concussion risk sport (HRS), low concussion risk sport (LRS), or both (B).

Main Outcome Measure(s): Athletes responded to demographic information and concussion s/s data across four domains (knowledge, concern, report, and occurrence).

Results: Over half LRS athletes and 20% HRS athletes reported they did not have any concussion knowledge (p = .002). Least concerning s/s were extra sad (42%), noise hurts my head (34%), and nervous (33%). Signs and symptoms least likely to be reported were grumpy (36%), nervous (30%), and extra sad (27%).

Conclusion: Urban high school athletes are concerned and would report s/s that are overtly detrimental to their health, but those s/s that occur most often after a head impact, athletes are less concerned about and may not report those s/s.

Introduction

Concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces, such as a blow to the head or body.[1] The occurrence of concussions has been increasingly recognized to affect almost 20% of the athletic population (i.e., high school, college, elite athletes) and seems to have deleterious effects later in life.[2] Among high school athletes, concussions account for upwards of 13% of reported injuries.[3, 4] In addition, players with a history of at least one concussion are five times more likely to have subsequent concussions,[5] and can experience long-term adverse neuropsychological changes[6] such as depression.[7] Sports-related concussions account for 20% of all head injuries in the U.S., but interestingly, many athletes (12–34%) do not seek medical attention.[4, 5, 8]

Part of a concussion evaluation as well as return-to-play measures are based around self-reported signs and symptoms (s/s). This self-reporting system increases the difficulty of identifying and treating a concussion. Concussed athletes can self-report one or more of the following symptoms post-impact: headache, nausea, vomiting, dizziness/balance problems, feeling "slowed down," fatigue, difficulty sleeping, drowsiness, sensitivity to light or noise, loss of consciousness, blurred vision, difficulty remembering, and difficulty concentrating.[9] Overwhelmingly though, high school athletes fail to either recognize the mechanisms and/or the seriousness of their mild traumatic brain injuries and tend not to report them.[8, 10–13] Shockingly, some even accept them as part of their sport.[11] Due to the potential short- and long-term damage that could occur from a concussion, it is imperative for athletes to be cognizant of their injury status so that they may act accordingly (e.g., report the injury in order to receive appropriate treatment).

It has previously been estimated that 50% of concussions in the high school setting go unreported.[10, 14, 15] This underreporting may be due in the athletes' failure to recognize the s/s as a potential concussion. In one study, over a quarter (26%) of the athletes did not recognize a potential concussion injury.[12] There is little research evaluating which s/s athletes may not be concerned about occurring, and thus do not report having them. To date, researchers have not developed diagnostic tests with adequate sensitivity and/or specificity that would detect masked s/s.[16] Furthermore, during sideline evaluation of concussions, athletes may not report their s/s to sports medical staff typically because the athletes did not believe they are serious enough to report.[10, 11] Therefore, the study's purpose was to identify high school athletes' concussion s/s knowledge, concern, reporting habits, and occurrence. There is awareness among athletic trainers that underreporting and masking of concussive s/s occurs,[9] but there is little research as to which s/s this would most likely occur and why. Our goal was to provide information

that aids in concussion evaluation. Concussion evaluation has proven to be a cumbersome task for sports-medicine team professionals, especially when athletes mask or do not report s/s after a head impact.[8]

Methods

Design

Fifteen hundred surveys were distributed to urban high schools, and 304 student athletes participating in a 2010–2011 sport returned the surveys (~20% response rate). Prior to data collection, we obtained approval from the Institutional Review Boards of all involved institutions. Due to the anonymity of the survey, informed consent/assent was not required. No follow-up measures could be taken due to the anonymity of the surveys. The survey was distributed to each of the urban high schools. This cohort was chosen due to no full-time athletic trainers are staffed at the high school. Athletes who chose to complete the survey did so with no accompaniment from the authors.

Participants

The athletes were between the ages of 13–19, and consisted of 55% male and 45% female (Table 1). Two hundred and seventy-six athletes stated they did not have a history of concussion, 15 reported that they did have a history of a concussion, and 11 omitted their concussion history. Athletes were grouped into high concussion risk sport (HRS), low concussion risk sport (LRS), or both (B). Thirty-two percent reported that they played sport(s) that were considered low concussion risk (i.e., track/cross-country, cheerleading, baseball, softball). Forty percent reported they played sport(s) that were considered high concussion risk (i.e., football, basketball, and soccer). Twenty-eight percent reported that they participated in both a high and low concussion sport. We defined HRS as those sports with a high incidence/prevalence of concussion, and LRS as those that have reported low incidence/prevalence of concussions. Marar et al.[4] found that football reported the most concussions at the high school level at a rate of 6.4 per 10,000 athletic events (A-E) followed by boys' ice hockey (5.4 per 10,000 A-E), boys' lacrosse (4.0 per 10,000 A-E), girls' lacrosse (3.5 per 10,000 A-E) and girls' soccer (3.4 per 10,000 A-E).[4] Athletes were grouped into the B category if they participated in both a high and low concussion risk sport. There were no exclusionary criteria.

Procedures

A single survey served as the instrument for the study. The COPSA paper and pencil survey (Table 2) was designed by the author using a content validation process, which addressed the athletes' knowledge, perception of concerning s/s, reporting habits, and occurrence of concussions and associated s/s. The instrument's was pretested for face validity by three concussion content experts as well as two survey study experts. The Flesch-Kincaid program (Microsoft Co., Redmond, WA) was utilized to ensure that the wording of the questions and vocabulary of the concussion s/s itself were not above a 6th grade reading level.

The survey collected demographic information and concussion s/s data across four main domains (i.e., knowledge, concern, reporting habits, and occurrence). Concussion knowledge was assessed via three questions: "I know about sports-related head injuries and concussion." "Sports-related head injuries are a problem in the sport(s) I play." and "There are things I can do to prevent/minimize sports related head injuries." The concussion s/s data collection included 24-items with three (concern, reporting habits, occurrence) items containing a list of 19 s/s assembled from previously published list of concussion 27 s/s.[7] These s/s fall within five domains: 1) symptoms: somatic (e.g., headache), cognitive (e.g., feeling like in a fog) and/or emotional symptoms (e.g., irritability); 2) physical signs (e.g., loss of consciousness, amnesia); 3) behavioral changes (e.g., irritability); 4) Cognitive impairment (e.g., slowed reaction times); and 5) sleep disturbance (e.g., drowsiness).[9] The term "dinged' was listed as a s/s due to its common use to indicate a concussion. Athletes indicated their concern (very concerned, maybe concerned, or not concerned), reporting habits (definitely report, maybe report, or definitely not report), and occurrence (always,

Table 1. Demographics from the Concussion Occurrence and Perception Survey for Athletes (COPSA) — 2008 (Number, Percent)

Gender	Male 155/304 (51%)	Female 126/304 (41%)				
Age (years)	13–14 54/304 (18%)	15–16 31/304 (10%)	17–8 93/304 (47%)	19 and over 3/304 (1%)		
Height (ft)	Under 5' 8/304 (3%)	5'0–5'5 114/304 (38%)	5'6–6'0 119/304 (39%)	Over 6'0 25/304 (8%)		
Weight (lbs)	Under 100 10/304 (3%)	100–125 69/304 (23%)	125–150 91/304 (30%)	151–176 49/304 (16%)	176–200 27/304 (9%)	Over 200 24/304 (8%)
Sport	HHIS 97/304 (32%)	LHIS 78/304 (25%)	B 68/304 (22%)			
Game time	Entire 74/304 (24%)	Most 86/304 (28%)	Some 28/304 (9%)	Little 15/304 (5%)	None 33/304 (11%)	

Note: HHIS = high head impact sport, LHIS = low head impact sport, B = both high and low impact sports. Percent's reported are valid percent's and take into consideration missing data. All totals may not equal 100% due to rounding.

Table 2. Sample Questions from the Concussion Occurrence and Perception Survey for Athletes (COPSA) — 2008

Concussions and other sports-related head impact injuries have been receiving increased attention lately. We are asking you to complete this survey to help us learn two things. First, we would like to find out what high schools students know about the subject and how concerned they are. Second, we would like to learn how often these injuries occur, the most common symptoms, and who students tell when they experience symptoms.

No names will be collected. Everything will be kept in a locked office and no individual information will be shared with people outside the research team.

Thank you for your participation!

We are interested in ***sports-related head injuries only.*** For our study, a *sports-related head injury* is defined as a bump to the head that occurs during a sports game (or practice session) that involves one or more symptoms of a concussion. Some examples are listed below.

Sports-related	Non Sports-related
Hitting head when going up for a "header"	Hitting head on dashboard in a car accident or on floor in bus accident
Getting kicked/punched in head during a football game	Getting punched in the face during a fight
Landing on head after going up for a catch in baseball	Hitting your head when you trip down the stairs
Hitting head on wall during a flip turn when swimming	Falling from a tree

KNOWLEDGE

	Quite a lot	Somewhat	Not at all
1. I know about sports-related head injuries and concussions.	◯	◯	◯
2. Sports-related head injuries are a problem in the sport(s) I play.	◯	◯	◯
3. There are things I can do to prevent/minimize sports-related head injuries.	◯ True	◯ False	

CONCERN

4. Please tell us how concerned you would be if you hit your head during a game or practice session and had:

	Not concerned	Maybe concerned	Very concerned
Blurry vision	◯	◯	◯
Dinged/bell rung	◯	◯	◯
Dizzy	◯	◯	◯
Drowsy	◯	◯	◯
Easily tired	◯	◯	◯
Slowed down/in a fog	◯	◯	◯
Headache	◯	◯	◯
Grumpy	◯	◯	◯
Loss of consciousness	◯	◯	◯
Memory problems	◯	◯	◯
Sick to stomach	◯	◯	◯
Nervous	◯	◯	◯
Poor balance	◯	◯	◯
Poor concentration	◯	◯	◯
Ringing in ears	◯	◯	◯
Extra sad	◯	◯	◯
Light hurts eyes	◯	◯	◯
Noise hurts head	◯	◯	◯
Throwing up	◯	◯	◯

REPORTING

5. Sometimes athletes experience symptoms after hitting their head during a game or practice, but do not want to tell anyone. What are the chances you would tell an adult if you had:

	Definitely not tell	Maybe tell	Definitely tell
Blurry vision	◯	◯	◯
Dinged/bell rung	◯	◯	◯
Dizzy	◯	◯	◯
Drowsy	◯	◯	◯
Easily tired	◯	◯	◯
Slowed down/in a fog	◯	◯	◯
Headache	◯	◯	◯
Grumpy	◯	◯	◯
Loss of consciousness	◯	◯	◯
Memory problems	◯	◯	◯
Sick to stomach	◯	◯	◯
Nervous	◯	◯	◯
Poor balance	◯	◯	◯
Poor concentration	◯	◯	◯
Ringing in ears	◯	◯	◯
Extra sad	◯	◯	◯
Light hurts eyes	◯	◯	◯
Noise hurts head	◯	◯	◯
Throwing up	◯	◯	◯

(Continued on next page)

6. *When* would you tell an adult about your symptoms? *Mark all that apply.*
   ◯ During a game ◯ During a practice session ◯ After a game ◯ After a practice session ◯ Any time ◯ Never tell
7. *Who* would you tell about your symptoms? *Mark all that apply.*
   ◯ Athletic trainer ◯ Coach ◯ Parent/Guardian ◯ Teammate or Friend ◯ Doctor/Nurse/Hospital ◯ Other: _____
8. Would your reporting habits change if it were to cause loss of playing time? ◯ Yes ◯ No
9. Why do you think some students do not tell people if they have symptoms after hitting their head during a game or practice?

PERSONAL EXPERIENCE

10. Have you ever been told you had a sports-related concussion by a doctor or athletic trainer? ◯ Yes ◯ No
    a. How many sports-related concussions do you think you have had in the past year? _____
    b. How many sports-related concussions do you think you've had in your lifetime? _____
11. To what extent did you have the following symptoms after hitting your head during a game or practice?

	Never	Sometimes	Always
Blurry vision	◯	◯	◯
Dinged/bell rung	◯	◯	◯
Dizzy	◯	◯	◯
Drowsy	◯	◯	◯
Easily tired	◯	◯	◯
Slowed down/in a fog	◯	◯	◯
Headache	◯	◯	◯
Grumpy	◯	◯	◯
Loss of consciousness	◯	◯	◯
Memory problems	◯	◯	◯
Sick to stomach	◯	◯	◯
Nervous	◯	◯	◯
Poor balance	◯	◯	◯
Poor concentration	◯	◯	◯
Ringing in ears	◯	◯	◯
Extra sad	◯	◯	◯
Light hurts eyes	◯	◯	◯
Noise hurts head	◯	◯	◯
Throwing up	◯	◯	◯

12. When did you tell someone about your symptoms? *Mark all that apply.*
    ◯ During a game ◯ During a practice session ◯ After a game ◯ After a practice session ◯ Any time ◯ Never tell
13. Who did you tell about your symptoms? *Mark all that apply.*
    ◯ Athletic trainer ◯ Coach ◯ Parent/Guardian ◯ Teammate or Friend ◯ Doctor/Nurse/Hospital ◯ Other: _____
14. What made you tell someone about your symptoms?

ABOUT YOU

15. Gender ◯ Male ◯ Female
16. Age ◯ 13–14 years ◯ 15–16 years ◯ 17–18 years ◯ 19+ years
17. Race ◯ African American ◯ Asian American ◯ Latino Ethnicity ◯ Native American ◯ White, non-Latino
    ◯ Biracial/Multi-ethnic ◯ Other: _____
18. Height ◯ Under 5' ◯ 5'0–5'5" ◯ 5'6–6'0 ◯ Over 6'0
19. Weight ◯ Under 100 lbs ◯ 100–125 lbs ◯ 126–150 lbs ◯ 151–175 lbs ◯ 176–200 lbs ◯ Over 200 lbs
20. What sport(s) have you played in the past and how long did you play these sports (for example: Soccer; 4 years)?

◯ Baseball/Softball	Length of time: _____	◯ Lacrosse	Length of time: _____
◯ Basketball	Length of time: _____	◯ Rugby	Length of time: _____
◯ Boxing	Length of time: _____	◯ Soccer	Length of time: _____
◯ Cheerleading	Length of time: _____	◯ Swimming	Length of time: _____
◯ Field Hockey	Length of time: _____	◯ Track	Length of time: _____
◯ Football	Length of time: _____	◯ Volleyball	Length of time: _____
◯ Gymnastics	Length of time: _____	◯ Wrestling	Length of time: _____

    ◯ Other: _____

21. What sport(s) and position (or classes/specialties) have you played in the past **year?**

◯ Baseball/Softball	Position: _____	◯ Lacrosse	Position: _____
◯ Basketball	Position: _____	◯ Rugby	Position: _____
◯ Boxing	Class/division: _____	◯ Soccer	Position: _____
◯ Cheerleading	Position/Role: _____	◯ Swimming	Class/specialty: _____
◯ Field Hockey	Position: _____	◯ Track	Class/specialty: _____
◯ Football	Position: _____	◯ Volleyball	Position: _____
◯ Gymnastics	Class/division: _____	◯ Wrestling	Class/division: _____

    ◯ Other: _____

22. Rank your overall game playtime during this past **year** *(choose the most accurate):*
    ◯ Entire game ◯ Most of the game ◯ Some of the game ◯ Little of the game ◯ None of the game
23. Rank your level of play **last year** *(choose the most accurate):* ◯ Varsity ◯ Junior Varsity ◯ Freshman Team
24. What type of school will you attend in September 2011? ◯ Junior High ◯ High School ◯ College ◯ Other: _____

Please talk with the doctors at the Physical Day if you hit your head during a team game or practice and are having any of the symptoms listed in this survey.

sometimes, never) if they were to experience any of the listed concussion s/s following a sports-related head impact.

Statistical Analysis

To evaluate the athletes' knowledge, concern, reporting habits, and occurrence of concussion frequency, statistics were analyzed followed by chi square analyses. Three (group) by three (response) chi square analyses were used to test for associations in response options between groups (HRS, LRS, B). Alpha level was set at $p \leq .05$. Significant 3 x 3 chi-squares were followed up with pair wise 2 x 3 chi squares using a Bonferroni correction (.05/3 = .017). If significant, they were followed up with 2 x 2 pair wise chi square analysis ($p \leq .017$). All analyses were computed using SPSS 19.0 statistical program (IBM, Inc., Armonk, NY).

Results

A total of 304 high school athletes' completed the survey when 1,500 were sent out for a response rate of 20.13%. Knowledge frequency data are presented in Table 3. The knowledge chi square data are presented in Table 4. There was a significant difference between HRS and LRS athletes' within the 2 x 2 concussion knowledge chi-squares. Forty-three percent of the LRS athletes reported they knew "quite a lot" about concussions; however, 57% reported they did not have any concussion knowledge (p = .002). Seventy-nine percent of the HRS athletes reported they knew "quite a lot" about concussions, but still 21% reported they did not have any concussion knowledge (p = .002). Over half of the athletes' reported they felt they knew "quite a lot" or "somewhat" about concussions. No other significant findings were found for the knowledge data.

The data indicating the athletes' concerns about concussion s/s are presented in Figure 1. The concerning chi-square data are presented in Table 4. The most concerning s/s following a head impact were loss of consciousness (60%), memory problems (56%), throwing up (52%), and blurred vision (36%). The least concerning s/s were extra sad (42%), noise hurts my head (34%), nervous (33%), and easily tired (30%). There were several significant differences found within the concerned about balance 2 x 2 chi square calculations. Fifty-four percent of the HRS athletes' "would not be concerned" about poor balance, where 46% were "maybe concerned" about poor balance (p = .007). Seventy-one percent of the LRS athletes would only "maybe be concerned" about poor balance and 29% "wouldn't even think about being concerned" about poor balance (p = .007). There was also a significant difference between these groups and reporting "very concerned" or "maybe concerned." Seventy-two percent of the LRS athletes were "maybe concerned' about poor balance, where 28% would be "very concerned" about poor balance (p = .001). Forty-one percent of the HRS athletes reported that they would be "maybe concerned" about poor balance, and 59% reported they would be "very concerned" about poor balance. No other significant findings were found for the concerned data.

Table 3. Athletes' Response to Concussion Knowledge Questions (Number, Percentage)

	Quite a Lot	Somewhat	Not at All
I know about sports-related head injuries and concussions	74/304 (24%)	160/304 (53%)	38/304 (13%)
Sports-related head injuries are a problem in the sport(s) I play	51/304 (17%)	122/304 (40%)	95/304 (31%)
		True	**False**
There are things I can do to prevent/minimize sports-related head injuries		244/304 (80%)	23/304 (8%)

Note: Percents reported are valid percents and take into consideration missing data. All totals may not equal 100% due to rounding.

Table 4. Significant 3 x 3 Chi-square Athletes' Response by Group

	Sport			
Variable	**HRS**	**LRS**	**B**	***p***
Concussion Knowledge (N)	72	88	67	.014**
Quite a lot	18.1%	37.5%	29.9%	
Somewhat	58.3%	52.3%	61.2%	
Not at all	23.6%	10.2%	0.9%	
Concerned Poor Balance (N)	75	93	65	.006**
Very concerned	21.3%	39.8%	36.9%	
Maybe concerned	56.0%	28.0%	36.9%	
Not Concerned	21.3%	32.3%	26.2%	
Report Easily Fatigued (N)	76	88	66	.016**
Definitely report	23.7%	35.2%	19.7%	
Maybe report	59.2%	35.2%	56.1%	
Not report	17.1%	29.5%	24.2%	
Occurrence Dizziness (N)	34	52	31	.005**
Never	73.5%	69.2%	32.3%	
Sometimes	23.5%	26.9%	54.8%	
Always	02.9%	03.8%	12.9%	
Occurrence Dinged (N)	35	52	31	.065
Never	85.7%	78.8%	54.8%	
Sometimes	11.4%	17.3%	38.7%	
Always	02.9%	03.8%	06.5%	
Occurrence Tinnitus (N)	35	52	29	.036*
Never	85.7%	84.6%	58.6%	
Sometimes	11.4%	09.6%	34.5%	
Always	02.9%	05.8%	06.9%	
Occurrence Headache (N)	35	52	29	.055
Never	60.0%	55.8%	27.6%	
Sometimes	28.6%	38.5%	55.2%	
Always	11.4%	05.8%	17.2%	

Note: HRS = high concussion risk sport, LRS = low concussion risk sport, B = both high and low concussion risk sports, N = number of athlete per group, p = alpha level, *significant 3 x 3 chi square, **significant 2 x 3 chi square.

The concussion s/s reporting habits data are presented in Figure 2. The reporting habits chi-square data are presented in Table 4. Signs and symptoms most likely to be "definitely reported" after a head impact were loss of consciousness (70%), throwing up (66%), memory problems (60%), and dizzy (44%). Signs and symptoms least likely to be reported were grumpy (36%), nervous (30%), extra sad (27%), and easily tired (23%). The reporting habits for feeling easily

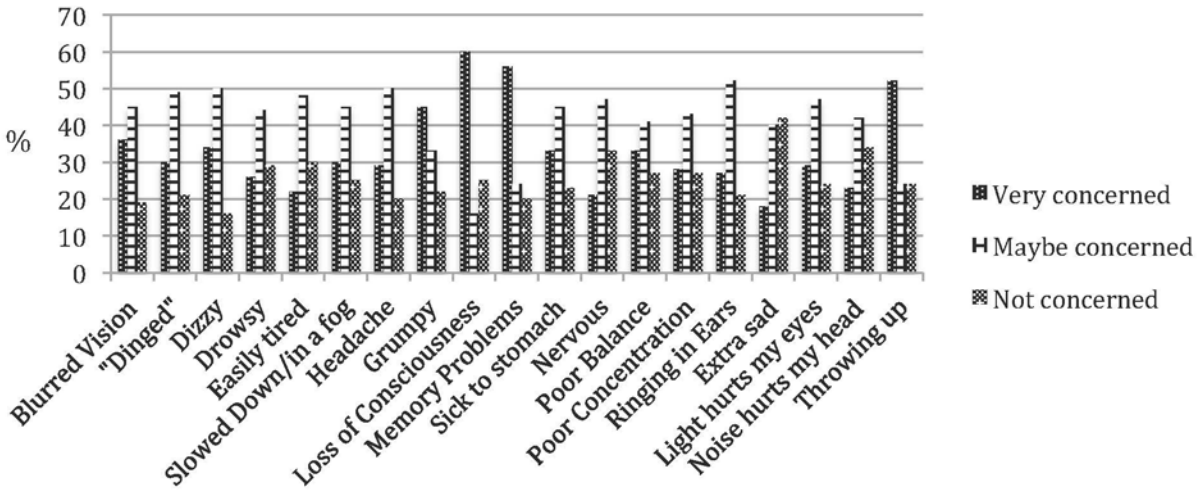

Figure 1. Percentage of athletes and level of concern of concussion s/s.

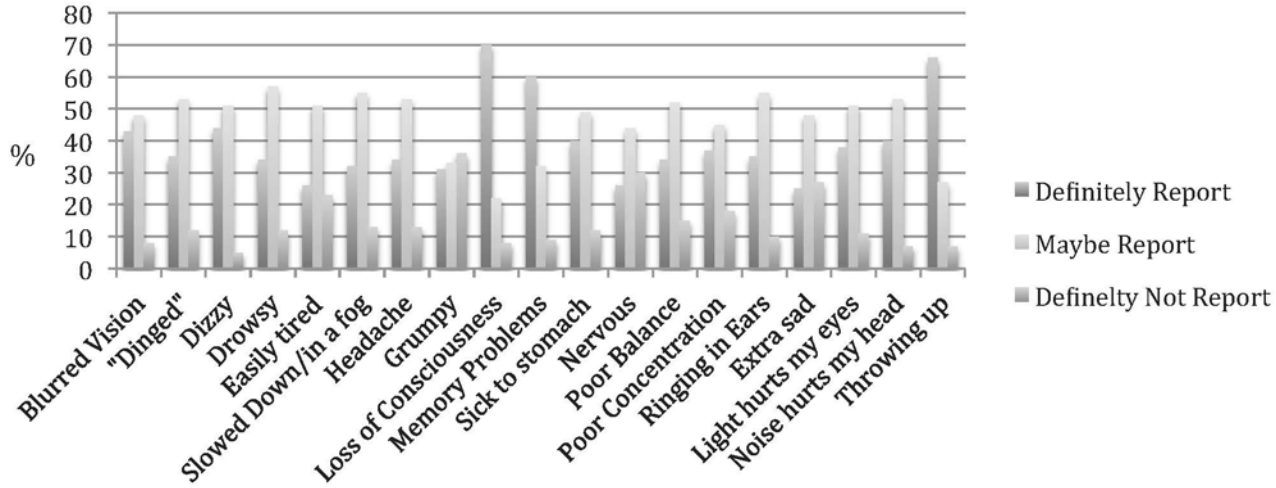

Figure 2. Percentage of athletes and reporting habits of concussion s/s.

fatigued 2 x 2 chi-squared was significant. Seventy-one percent of the LRS athletes reported that they "may report" compared to 29% reported they would "definitely report" feeling easily fatigued (p = .014). The HRS athletes were split equally, where 50% "may report" or would "definitely report" feeling easily fatigued (p = .014). No other significant findings were found for the reporting habits data.

The concussion s/s occurrence data are presented in Figure 3. The concussion s/s occurrence chi-square data are presented in Table 4. The most commonly occurring s/s that were "sometimes" or "always" occurring after a head impact were (40%, 9%), dizzy (29%, 5%), blurred vision (24%, 3%), and "dinged" (19%, 4%), respectively. The least commonly occurring s/s were loss of consciousness (90%), memory problems (88%), extra sad (86%), and throwing up (86%). Seventy-one percent of HRS athletes stated they "never" feel dizzy after a sports-related head impact, where 28% depicted they "sometimes" feel dizzy after a sports-related head impact (p = .003). Thirty-seven percent of the B group reported that they "never" feel dizzy after a sports-related head impact, and 63% "sometimes" feel dizzy after a sports-related head impact (p = .003). No other significant findings were found for the occurrence data.

Discussion

Athletes who sustain a concussion may present with acute s/s,[16] which could lead to long-term[7] effects if improperly treated (e.g., early return to play). Younger athletes are more prone to concussive injuries and prolonged recovery,[17, 18] which is supported by the physiological differences of a developing brain as opposed to an adult brain (e.g., comparison of brain water content, degree of myelination, blood volume, blood-brain barrier, cerebral metabolic rate of glucose, blood flow, number of synapse and geometry, and elasticity of the skull's sutures).[19] Research has indicated that,

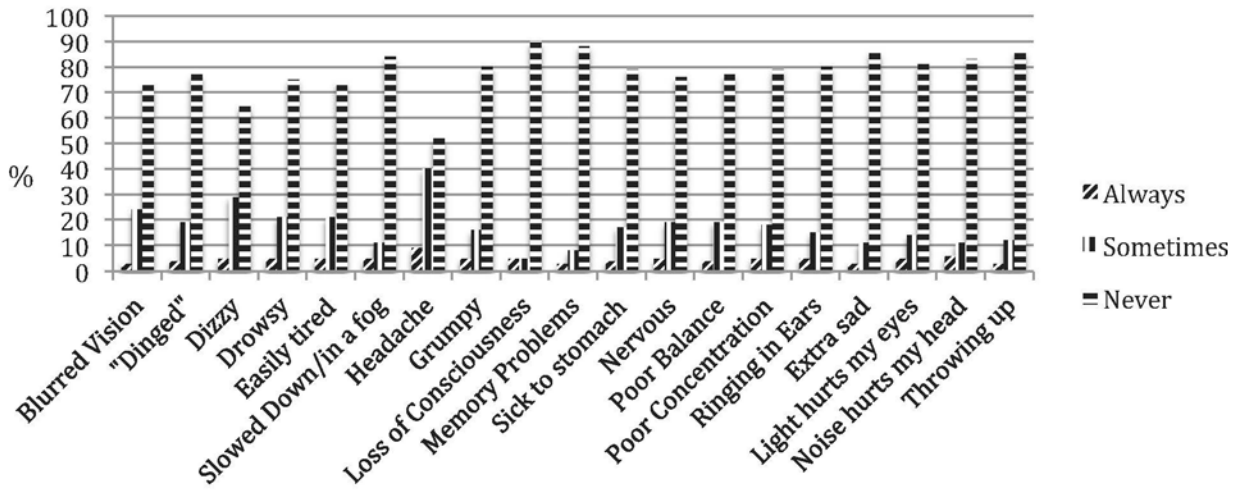

Figure 3. Percentage of athletes and occurrence of concussion s/s.

in the high school setting, an estimate of over 50% of concussions go unreported.[10, 14, 15] However, more recent reports suggest that underreporting is starting to decline, where rates range from 12%[12] to 30.5%.[8] Though this still represents a persistent minority who may not appreciate the seriousness of a concussion injury and the possible deficits later in life if a proper rest and treatment regimen is not implemented.

This under-reporting may be due in the athletes' failure to recognize the s/s as potential concussion s/s. One study in high school football players found 66% of the athletes said that they did not report their concussion because they did not believe it was serious enough. Within the same study, 41% of the football athletes recounted that they did not want to leave the game, 36% said they did not know it was a concussion, and 22% stated they did not want to let teammates down.[10] However, this study only investigated varsity high school football players, and underreporting of concussions can occur in any sport. Another study found that there is substantial under-reporting of concussions in youth ice hockey; incidence of .35 reported to 5.7 per 1,000 subjects observed, but went unreported.[20]

Athletes may not be reporting their injury is due to lack of concussion injury knowledge. One of the primary purposes of this study was to determine the athletes reported concussion knowledge, and found that nearly 73% of the athletes reported that they know very little or nothing about concussions. This finding suggests that athletes may not be reporting s/s because they may not know they sustained a concussion, or implies that athletes could be masking s/s suggesting they do not understand the severity of a concussion injury.

Based on concussion knowledge data reported, it suggests that urban high school athletes are not confidant in their concussion knowledge. We found that a majority of athletes (53%) only feel they "know somewhat" about concussions, and nearly 13% do not "know anything at all" about concussions. With that in mind, most of the athletes "think concussions are a problem in their sport" (57%), and "there are ways to prevent concussions" (91%). This suggests that the athletes know concussions are a problem, but do not have enough education to follow through with the concussion prevention and treatment protocol. Previous reports suggested that knowledge does not necessarily influence attitude and concussion-reporting habits, where the authors stated that over 40% of athletes reported a recalled concussion event without reporting their injury.[21] Therefore, there is a need to look at how concussion education can be more specific to change attitudes with what athletes should be concerned with and report.

Thus, the second and third purposes were to determine what concussion s/s athletes would be most concerned with, and which concussion s/s would the athletes report. This study established that athletes were most concerned (60%, 56%, 52%) and more likely to report (70%, 60%, 60%) explicit s/s, such as loss of consciousness, memory problems, and vomiting, respectively. However, the most common concussive s/s were not reported as most concerning such as dizziness, headache, and "dinged" (34%, 29%, 28%), respectively. They were also less inclined to definitely report these s/s (44%, 34%, 35%), respectively. The current study also found that both HRS and LRS are not concerned about poor balance nor would they definitely report becoming easily fatigued. Previous studies reported both high and low concussion risk sports do not recognize concussions specifically football, cheerleading, and cross-country (28%) were the most common sports to have their concussions go unreported.[12] In contrast to this report, a study by Llwellyn et al. found that the most unrecognized concussion symptoms were seeing stars, knocked out, and memory loss.

Additionally, the current study also found a significant finding that over half of the athletes would "definitely not be concerned" about poor balance and many would only be "maybe concerned" about having signs of poor balance after

a sports-related impact. Athletes in this study were also unsure if they would report becoming easily fatigued after a head impact. Athletic trainers should be aware of these s/s that urban high school athletes have described to be unconcerned about and do not report. Additionally, future concussion education programs should indicate that concussion s/s are not only displayed by the distinctive physical, somatic, or cognitive issues, but with behavioral and emotional changes as well.

Finally, our last purpose was to establish if any of the concussion s/s were going unreported following a sports-related head impact. Previous research has indicated several s/s that are most frequently occurring after sustaining a concussion (e.g., headache, dizziness).[15, 22] One study found that out of the 443 players surveyed, 93 reported that they had a headache during their most recent game, and only six of those were removed for reasons not given.[22] Another study found that 91 out of 152 said they never received a concussion but reported concussive s/s.[23] This survey study found similar findings where athletes reported that they either "always" (average of six athletes reported per s/s) or "sometimes" (average of 22 athletes reported per s/s) received s/s following a concussion, but only 15 athletes reported a history of a concussion. Also the most frequently occurring s/s either "sometimes" or "always" occurring after a head impact were headache (39%, 9%), dizzy (29%, 5%), blurred vision (24%, 3%), and "dinged" (19%, 4%), respectively. The high frequency of "dinged" being reported is especially alarming since it is considered a slang term for a concussion, so these could potentially be undiagnosed concussions. Previous literature has suggested banning the terms "dinged or bell rung" to describe concussions as it diminishes a potentially deleterious injury.[9] However, recent research has suggested these terms may be necessary as laymen's terms to describe the injury.[13]

This study was subject to several limitations. Firstly, the length of the survey (24-items with questions #4, #5, and #11 containing 19 s/s checklist) may have resulted in test exhaustion. Secondly, since the study design was a self-report survey, the athletes may have experienced recall bias, particularly those who reported an occurrence of s/s following a previous concussion; previous research has employed this design.[23] However, one advantage was that the wording of this study's survey was altered (from 13+ grade reading level to a 6th grade reading level) to increase readability and understanding of the s/s terminology. Also inherent with a survey study design, we assumed that the athletes were answering each question truthfully. Future research may want to investigate if understanding the concussion s/s increases using a more comprehensible terminology as well as if it has an effect on the concussion education program.

Conclusion

This study suggests that concussion education is necessary within urban high schools. Athletes understand that concussions are a problem and there are ways to prevent them; however, they are not confident in their concussion knowledge. Athletic trainers should capitalize on this notion to help educate athletes on concussions mechanisms, what s/s could occur following a concussive event, and techniques to prevent concussions (e.g., proper equipment fitting, utilizing proper techniques and rules of the sport).

Athletes are concerned and would report s/s that are overtly detrimental to their health, but those s/s that are occurring most frequently after a head impact are those s/s the athletes are less likely to be concerned about and athletes may be less likely to report these s/s. This study suggests the term "dinged" is being misused instead of being a laymen term for a concussion. There were many athletes that reported being dinged following a head impact but were not concerned about it and would most likely not report this symptom. Athletic trainers should be aware of these s/s that athletes may not be concerned about and are less likely to report and alter concussion education program to increase knowledge retainment, understanding the individual concussion s/s, and when to report a potential concussion injury.

Disclosure Statement

The author(s) declare(s) that there is no conflict of interests regarding the publication of this paper.

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Original Research

Connective Tissue Growth Factor (CTGF/CCN2) Is Essential for Secondary Palatogenesis

Joseph T. Tarr, BS;[1] Alex G. Lambi, PhD;[1] Honey Hendesi, PhD;[1]
Christina M. Mundy, PhD;[1] James P. Bradley, MD;[3] William G. DeLong, Jr., MD;[2, 3]
Steven N. Popoff, PhD[1, 2]

[1]*Department of Anatomy and Cell Biology,* [2]*Department of Orthopaedic Surgery,* [3]*Department of General Surgery, Division of Plastic and Reconstructive Surgery, Temple University School of Medicine, Philadelphia, PA;*
[4]*Department of Orthopaedic Surgery, St. Luke's University Health Network, Bethlehem, PA*

Abstract

Nonsyndromic cleft palate is a common craniofacial birth defect with an incidence of one in 700 live births. Connective tissue growth factor (CTGF/CCN2) has emerged as an essential player in normal craniofacial skeletal formation. Previous work in our laboratory identified numerous craniofacial defects such as failure of secondary palate formation in CTGF knockout (KO) mice. In this study, micro-CT and histological analyses showed that CTGF KO mice have a complete absence in midline convergence of mesenchymal tissue compared to wild-type (WT) mice. We isolated mesenchyme-derived pre-osteoblasts from crania of WT and CTGF KO mice for *in vitro* studies. CTGF KO cells exhibited decreased proliferation, adhesion to extracellular matrices and cell spreading, and reduced levels of total and activated Rac1 compared to WT cells. Since all of these cellular functions are necessary for proper formation of the secondary palate during craniofacial development, we conclude that these defects contribute to the failure of the palatal shelves to form and grow in CTGF KO mice. Future studies aimed at elucidating the precise regulatory mechanism(s) responsible for secondary cleft palate in CTGF KO mice will enhance our understanding of its etiology, and lead to the development of novel therapeutic approaches for the clinical management of this birth defect.

Introduction

Mammalian palatogenesis is a complex processes involving a tightly regulated sequence of cellular events. The mammalian secondary palate forms from palatal shelves; these are outgrowths of the oral side of the mammalian maxillary process at embryonic day (E) 11.5.[1–4] The palatal shelves grow in a vertically oriented direction lateral to the tongue in the oral cavity.[1–4] As the mandible grows inferiorly, the tongue descends, allowing for continued elongation of the palatal shelves at E13.5 and subsequent elevation to occupy a horizontal position by E14.5.[1–4] The palatal shelves continue to grow until they make contact in the midline at E15, followed by epithelium degeneration and fusion of the underlying mesenchyme to form a confluent secondary palate by E15.5.[1–4] The mesenchymal cells in the anterior portion undergo intramembranous ossification to form the hard (bony) palate,[4, 5] while those in the posterior portion differentiate into skeletal muscle to form the soft palate.[4]

The developing palate is predominantly composed of mesenchymal cells (neural crest origin), endothelial cells (mesodermal origin) and epithelium (ectodermal origin).[6] Palate formation involves the temporal and spatial coordination of cellular events including cell migration, proliferation, differentiation, and apoptosis.[1, 4, 7] Among the myriad of factors that are expressed during development of the palate, transforming growth factor beta (TGF-β) and bone morphogenetic protein (BMP) signaling pathways have been shown to be essential for palate development.[1–4, 8, 9]

Previous studies in our lab have shown that the absence of CTGF in prenatal skeletogenesis results in site-specific changes in bone microarchitecture, shape, and gene expression levels.[10] Among the most interesting of these findings were the differences found in CTGF knockout (KO) crania compared to wild-type (WT) littermates. Allometric (size-based) and non-allometric shape differences were observed in CTGF KO skulls, which were shorter and wider than their WT counterparts.[10] Specific morphologic traits seen in CTGF KO skulls included an increased curvature of the nasal bones, a serpentine shape of the mandibles, a lateral bend of the sphenoid pterygoid processes, a lateral kink in the vomer, and failure bony (hard) palate formation.[10] These results regarding formation of the secondary palate were consistent with the initial description of the CTGF KO mouse, which showed that the palatal shelves failed to elevate in E15.5 embryos.[11] What remains unclear from these studies is whether this aberrant palatogenesis represents a developmental delay or a complete failure of secondary palate formation, including the differentiation of the tissues (bone and skeletal muscle) from the neural crest-derived mesenchymal cells. A temporal analysis of palatal develop-

ment and potential cellular mechanisms contributing to aberrant palatogenesis remains to be studied.

Cleft palate is among the most common craniofacial birth defects in the United States, with an incidence of roughly one in every 700 live births.[4, 12] Children born with cleft palate typically have difficulty with feeding and talking, and therefore represent a serious need for medical intervention, which include surgical corrections within the first 18 months,[12] as well as potential lifelong medical, speech, and psychosocial therapy. In this paper, we expanded upon our previous studies of palatogenesis in CTGF KO mice by analyzing underlying soft tissue structure through micro-CT and histology. We isolated primary mesenchyme-derived cells from CTGF KO and WT mice for *in vitro* studies to assess underlying cellular defects that would contribute to delayed and/or failed palate formation. We hypothesize that a lack of CTGF in these cells will result in defects in underlying cell processes that contributes to failure of palatal shelf growth, elevation, and/or fusion. Understanding the role of CTGF in palatogenesis is expected to provide novel information with the potential for the development of new treatment strategies for the clinical management of children with cleft palate.

Materials and Methods

Source of Animals

CTGF heterozygous mice ($CTGF^{+/LacZ}$) were used as breeders to obtain CTGF KO ($CTGF^{LacZ/LacZ}$) as previously described.[13] Genotyping was determined by X-gal staining of tail clips (EMD Milipore, Billerica, MA). All animals were maintained and used according to the principles in the NIH Guide for the Care and Use of Laboratory Animals (U.S. Department of Health and Human Services, Publ. No. 86-23, 1985) and guidelines established by the IACUC of Temple University.

Phosphotungstic Acid Staining and Micro-CT Analysis

Newborn pups (P0) were euthanized and fixed in 4% paraformaldehyde (PFA) in PBS (Affymetrix, Santa Clara, CA) at 4°C for one week with PFA changed at 48 and 96 hours. Mandibles and tongues were excised to allow direct visualization of the secondary palate. Samples were washed with water for 24 hours. Skin was removed from the head and samples were placed into phosphotungstic acid, hematoxylin solution (PTAH) (Electron Microscopy Sciences, Hatfield, PA) for two weeks at 4°C. Samples were rinsed in water and scanned with a Skyscan 1172, 11 megapixel camera model, high-resolution cone-beam micro-CT scanner (Skyscan, Kontich, Belgium). Heads were scanned at a pixel size of 6.95 μm with an X-ray tube potential of 59 kV and X-ray intensity of 149 μA with each slice equal to 7 μm. A 0.5-mm aluminum filter was used to remove image noise, with a ring artifact correction of 12 and a beam hardening correction of 20%. After scanning, 3D image data was reconstructed using the SkyscanNRecon software. Images were visualized using the Skyscan CT Volume Rendering (CTvox) software.

Tissue Preparation and Histology

Animals used for this study were euthanized at birth (P0). Subsequently, tails were removed and used for X-gal staining (EMD Milipore, Billerica, MA). The remaining carcasses were fixed in 4% paraformaldehyde (PFA) in PBS (Affymetrix) at 4°C for one week. Heads were removed and decalcified in 14% ethylenediaminetetraacetic acid (EDTA Acid) (Fisher Scientific, Fair Lawn, NJ) for one week at 4°C with solution replaced every 24 hours. Heads were then dehydrated in 70% ethanol solution for 48 hours at 4°C prior to paraffin embedding. Deparaffinized sections cut at 5 μm were stained with hematoxylin (Electron Microscopy Sciences) and eosin (Thermo Shandon, Cheshire, UK) (H&E).

Isolation of Cells for In Vitro *Studies*

Primary mesenchyme-derived pre-osteoblasts from embryonic day 18.5 embryos were isolated and cultured as previously described.[14] Primary cells were isolated from the endosteal surface of parietal bones from WT and KO embryos. The cranial sutures were removed. Bones were placed in digestion media consisting of 0.1% Collagenase (Sigma)/2.5% trypsin, minced with scissors and subjected to a series of digestions of five, 15, 30, 20, 15, and 15 minutes at 37°C. The cell population enriched for pre-osteoblasts (pOBs) was obtained from the later digestions. Cells were plated in 100 mm dishes (Corning) at 5 x 10^5 cells/plate in Alpha Minimal Essential Medium (α-MEM; Hyclone, Logan, UT) supplemented with 10% fetal bovine serum (FBS; Atlanta Biologicals, Lawrenceville, GA). The cells were incubated at 37°C with 5% CO_2. The purity of the WT and KO cultures was confirmed by quantitative PCR (qPCR) to ensure that there was no cross contamination between WT and KO cells.

To produce CTGF over-expressing cells, WT pre-osteoblasts were infected with a recombinant CTGF adenovirus tagged with a green fluorescent protein (GFP) reporter dye (Ad-CTGF) one day after plating. The CTGF adenovirus was generated and provided by Dr. Tong-Chuan He.[15] Controls included uninfected cells and cells infected with adenovirus tagged with GFP only.

Cell Proliferation

Cell number was determined using the CyQUANT® NF Cell Proliferation Assay Kit (Molecular Probes) (Invitrogen, Eugene, OR) according to the manufacturer's protocol. Briefly, CTGF WT and KO cells were plated (4 x 10^3 cells/well or 8 x 10^3 cells/well) in 96 well plates (Corning) in culture conditions as described above. At 48 hours, media was aspirated and replaced with DNA binding dye solution. Cells were incubated at 37°C for one hour and samples were measured using a Wallac 1420 fluorometer (PerkinElmer, Shelton, CT). Cell number was calculated based on a standard

curve generated for primary cells according the manufacturer's protocol.

Cell Cycle Analysis

CTGF WT and KO cells were plated at 5 x 10^5 cells/plate in 100 mm dishes (Corning) and allowed to adhere for 12 hours. The cells were then serum starved for 24 hours followed by a return to α-MEM/10% FBS for 24 hours. Cells were lifted from the plates by treatment with 0.25% Trypsin, 2.21 mM EDTA, 1X (Mediatech, Manassas, VA), washed once in 1X PBS (Mediatech, Manassas, VA), pelleted at 300g at 4°C, resuspended and fixed in 1% PFA solution (Affymetrix) for one hour at 4°C. Cells were washed in 1X PBS, pelleted, and resuspended in 70% ethanol (Decon Laboratories, Inc, King of Prussia, PA) for at least two hours at 4°C. Cells were washed twice in 1X PBS (Mediatech) and pelleted. Cells were resuspended in 1X PBS containing 180 units of RNase ONE Ribonuclease (Promega, Madison, WI), 0.1% Triton X-100 (Fisher Scientific), and 40 µg/mL propridium iodide (Sigma, St. Louis, MO) and incubated for 30 minutes at 37°C. Flow Cytometry was performed on a BD FACSauto Flow Cytometer Ruo Special Order System (BD Biosciences, San Jose, CA). Data was analyzed using FlowJo software (FlowJo, Ashland, OR) where cell cycle was analyzed utilizing a Dean/Jett/Fox algorithm.

Western Blotting

CTGF WT, KO, and over-expressing (OE) osteoblast culture dishes were washed twice with cold 1X PBS and cells were lysed in 1X RIPA lysis buffer (EMD Millipore) containing 1% protease inhibitor (Sigma) then incubated for one hour at 4°C. Protein concentration of lysates was determined using BCA Protein Assay Kit (Thermo Scientific, Rockford, IL). Membranes were blocked with LI-COR® Blocking Buffer (LiCor Biosciences, Lincoln, NE) for one hour at room temperature and then incubated with a goat polyclonal anti-CTGF antibody (Santa Cruz Biotechnology, Dallas, Texas) diluted to a 1:200 ratio in blocking buffer overnight at 4°C. Membranes were washed with 1X PBS- 0.1% Tween20 (Fisher Scientific) and incubated with anti-goat IRDye® 800 CW (LiCor Biosciences) (1:5000) diluted in blocking buffer. Membrane was scanned using the LI-COR Odyssey Infrared Imaging System.

Adhesion Assay

Ninety six-well non-tissue culture treated plates (Falcon® Becton Dickinson, Franklin Lakes, NJ) were coated with fibronectin (Sigma), rCTGF (ProSpect, Ness Ziona, Israel) or 1% BSA (Fisher Scientific) in PBS (Mediatech) and left to dry in a tissue culture hood. To block nonspecific binding sites in coated wells, 1% BSA was added to the wells and the plate was incubated at 4°C for one hour. BSA was discarded and wells were washed with 1X PBS (Mediatech) prior to adding 3 x 10^4 primary osteoblasts to the wells and incubation at 37°C for 45 minutes. Wells were washed with 1X PBS (Mediatech). CyQuant® NF dye (Invitrogen) was added to each well and the plate was incubated at 37°C for one hour. Fluorescence was measured using a microplate reader with excitation at ~485 nm and emission detection at ~530 nm. Relative fluorescence units (RFUs) were converted to cell number using standard curve made by performing adhesion assay for different cell numbers.

Immunofluorescent Staining and Cell Spreading Assay

Glass chamber slides (Nunc, Rochester, NY) were coated with 2 µg/ml fibronectin (Sigma) in PBS and were left to dry in a tissue culture hood. Primary cells (2 x 10^3) in serum-free media were added to chambers and incubated at 37°C for eight hours. Cells were fixed with 4% paraformaldehyde in 1X PBS (Affymetrix) for 15 minutes, washed three times with washing buffer (1X PBS containing 0.05% Tween20 (Fisher Scientific) and then blocked with blocking solution (2.5% BSA (Fisher Scientific) in PBS (Mediatech)) for 30 minutes at room temperature. After fixation, 1:500 mouse monoclonal anti-vinculin (Millipore) diluted in blocking solution was added to the chambers, which were then incubated overnight at 4°C. After three washes with washing buffer, fluorescence secondary antibodies conjugated to DyLight™ 488 (Jackson Immunoresearch Laboratories, West Grove, PA) and diluted 1:2000 in blocking solution, or TRITC-conjugated phalloidin (Millipore) diluted 1:5000 in blocking solution, were added to the chambers, which were then incubated for one hour at room temperature. After three washes with washing buffer, the chamber slides were cover slipped using Vectashield® mounting medium with Dapi fluorescence (Vector, Burlingame, CA). Fluorescence imaging was performed using a Nikon E1000 (Nikon, Melville, NY). Cell spreading areas were measured using ImageJ.[16]

Rac Activity Assay

The Rac activity assay was performed on primary cells cultured for two hours in tissue culture dishes (Corning) coated with 2 µg/ml fibronectin (Sigma) or uncoated dishes (negative control) in a serum-free medium. A Rac1 Activation Assay Biochem Kit™ (Cytoskeleton, Denver, CO) was used to pull down active Rac1. Then, 300 µg of total cell protein was incubated with 10 µg PAK-PBD beads from the kit, and incubated for one hour at 4°C. Beads were washed once with the kit's washing buffer. After centrifugation, 20 µl of Laemmli sample buffer (Bio-Rad, Hercules, CA) containing 5% β-mercaptoethanol (Fisher Scientific) was added to the beads and samples were boiled for two minutes. Western Blot analysis was performed on the samples using a mouse monoclonal (1:1000) anti-Rac1 primary antibody (Cytoskeleton) and 1:5000 horseradish peroxidase conjugated to a donkey anti-mouse secondary antibody (Jackson Immunoresearch Laboratories). Bands were visualized with using a chemiluminescence detection system (Thermo Scientific).

Statistical Analysis

One-factor analysis of variance (ANOVA) was performed to evaluate the effect of each variable on two or more independent groups. In the event of a significant group effect, a Bonferroni post-hoc test was performed to compare selected pairs of group means. Adjusted probability *(p)* values are reported. A *p* of value less than 0.05 was considered statistically significant.

Results

Based on an incidental finding in the original description of the CTGF knockout phenotype,[11] we examined the development of the palate in newborn (P0) CTGF knockout (KO) mice and their wild-type (WT) littermates. Newborn heads were stained with phosphotungstic acid (PTA) to allow for soft-tissue visualization and three dimensional (3-D) reconstruction of the craniofacial tissues. Micro-CT analysis revealed a cleft palate resulting from failure of secondary palate formation (Fig. 1). Transverse sections through the palate showed that in KO mice the palatal primordium failed to grow, elevate, and fuse. This results in a large open communication at the midline between the oral and nasal cavities (Fig. 1A,B). Interestingly, the nasal septum and lateral nasal wall also exhibited severe malformations including a distorted, curvilinear septum and severely deformed nasal conchae (Fig. 1C,D). Coronal sections of paraffin-embedded heads from P0 WT and KO mice confirmed the failure of formation of the secondary palate in KO mice (Fig. 2). The palatal primordia did not appear to progress beyond the early stage of palate development when they first appear as vertical projections from the medial surface of the developing maxilla (Fig. 2B). There was no evidence of subsequent elevation, horizontal growth, or fusion to form a palate as seen in WT mice (Fig. 2B). As a consequence, the inferior edge of the nasal septum remains unattached, the oral and nasal cavities remain in open communication with one another, and the tongue morphology is markedly different in KO compared to WT mice (Fig. 2B).

The process of palate development involves a complex series of cell-cell and cell-matrix interactions and temporal regulation of cellular functions such as cell migration, adhesion, proliferation and differentiation.[1, 4, 7] In the next series of experiments, we established cultures of mesenchyme-derived pre-osteoblasts (pOBs) derived from KO and WT mice, and used these primary cultures to compare basic cellular functions between KO and WT cells. Cell proliferation was first assessed using the CyQuant assay, demonstrating that proliferation in KO pOBs was significantly decreased compared to WT pOBs (Fig. 3A). Flow cytometric analysis of propidium iodide stained cells allowed us to determine the relative proportion of cells in each phase of the cell cycle. These analyses revealed a significant reduction of KO pOBs in the S phase while significantly more accumulate in the G1/G0 phase compared to WT pOBs (Fig. 3B).

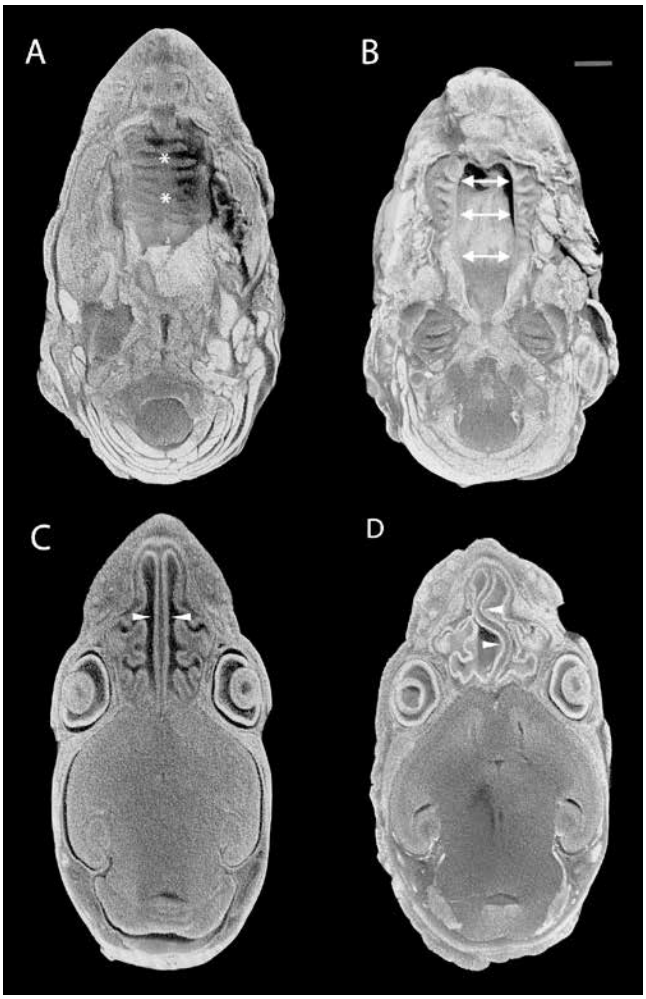

Figure 1. Micro-CT analysis of palate (top, **A** and **B**) and nasal septum/cavity (bottom, **C** and **D**) in postnatal day 0 (P0) heads from wild-type (WT; **A** and **C**) and CTGF knockout (KO; **B** and **D**) mice. Specimens were stained with phosphotungstic acid to allow visualization and volumetric reconstruction of craniofacial tissues. The palate in WT mice (designated by * in **A**) is fully formed and fused, while remaining open in KO mice (designated by arrows in **B**). Nasal septum (arrow heads) and lateral wall of nasal cavity exhibit significant developmental deformities in KO **(D)** compared to WT **(C)** mice. Scale bar = 1 mm.

Next, we evaluated whether the absence or overexpression of CTGF can affect the cell adhesion to various matrix components. For these experiments, we used KO and WT pOBs, as well as WT pOBs that were infected with an adenoviral-CTGF vector to overexpress CTGF (CTGF OE). The lack of endogenous CTGF in KO cells and significantly increased CTGF expression levels in OE pOBs were confirmed by Western blot analysis (Fig. 4A). The adhesion assay demonstrated decreased cell adhesion in KO cells compared to WT cells, while adhesion was significantly increased in the OE cells cultured on fibronectin (Fig. 4B). BSA was used as a negative control substrate. Similar results were obtained when cells were cultured on rCTGF (Fig. 4B), vitronectin (data not shown) or collagen type I (data not shown).

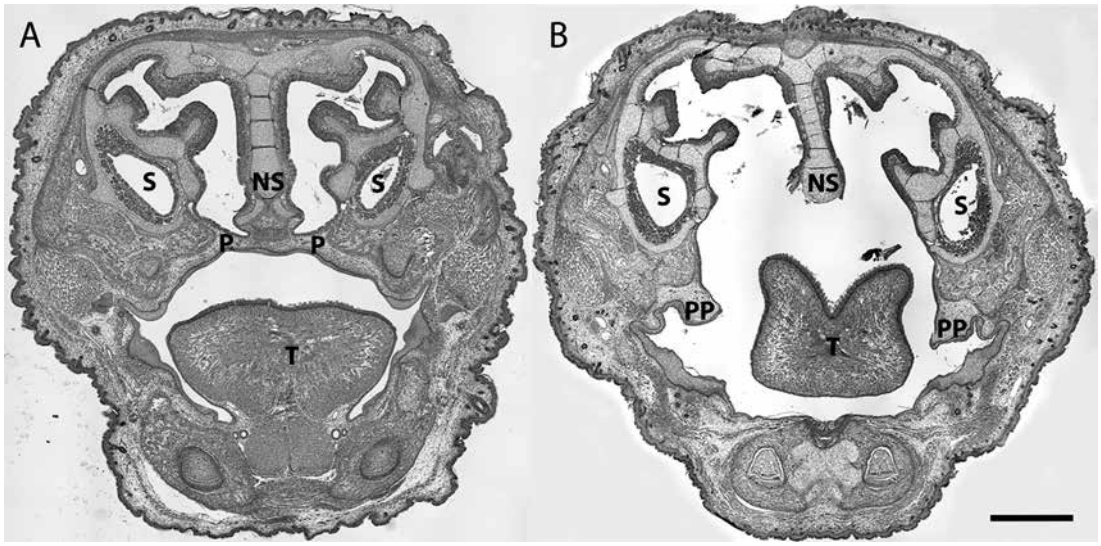

Figure 2. Coronal sections of WT **(A)** and KO **(B)** postnatal day 0 (P0) heads. In the WT section **(A),** the secondary palate (P) is present and is fused with the nasal septum (NS). In the KO section **(B),** the palatine primordia (PP) are located laterally, the horizontal palatal shelf is absent and the nasal septum is suspended with no attachment at its inferior margin. S = sinus, T = tongue. Scale bar = 500 μm.

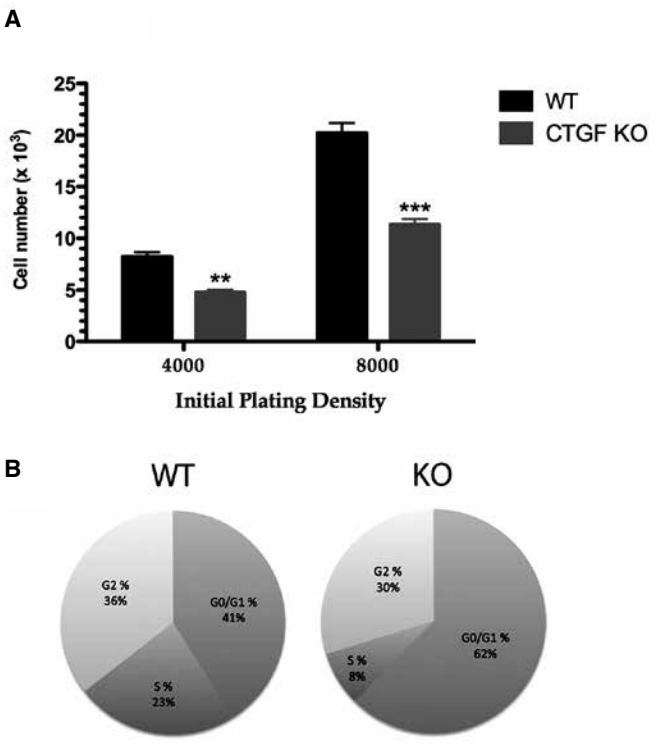

Figure 3. Proliferation **(A)** and cell cycle **(B)** analyses of primary mesenchyme-derived cells from WT and CTGF KO mice. **(A)** Proliferation was assessed using Cyquant proliferation assay at 48 hours. KO cells demonstrated a significant decrease in proliferation compared to WT cells. **(B)** Flow cytometry of propidium iodide-stained cells revealed that CTGF KO cells accumulate in G0/G1 phase. Data were analyzed by FlowJo software utilizing a Dean/Jett/Fox algorithm.

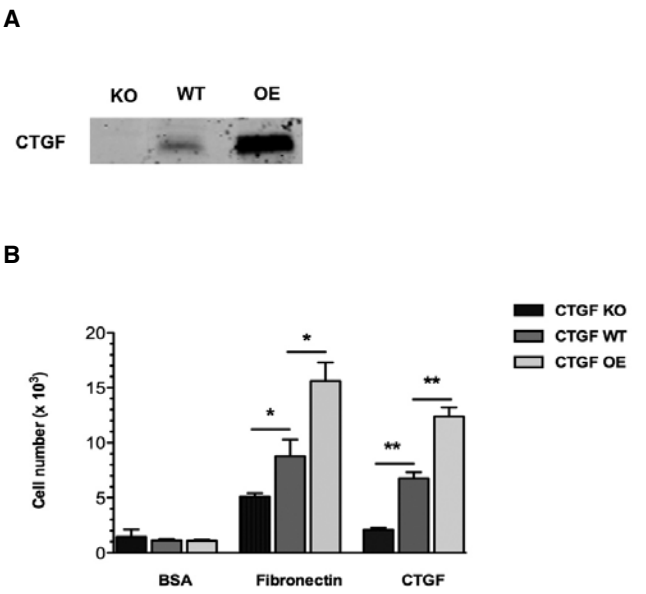

Figure 4. Effects of endogenous CTGF expression on cell adhesion. **(A)** Western blot analyzing CTGF expression in lysates of mesenchyme-derived cells from CTGF KO and WT mice as well as WT cells transfected to overexpress CTGF (OE). **(B)** Adhesion assay for CTGF KO, WT and OE cells cultured on different substrates; BSA (negative control), fibronectin (2 μg/ml) or CTGF 2 μg/ml). Cell adhesion is proportional to endogenous CTGF expression levels. *p < 0.05; p < 0.01.

To further investigate the effect of endogenous CTGF expression on cell spreading, we cultured KO, WT and OE pOBs on fibronectin for 1–8 hours. Immunofluorescent staining for actin and vinculin revealed significant qualitative differences in cell spreading and cytoskeletal organization that were dependent on CTGF expression levels (Fig. 5A). KO cells spread poorly and OE cells demonstrated enhanced spreading compared to WT cells (Fig. 5A). Both WT and OE cells demonstrated focal adhesions visualized by vinculin staining within adhesion complexes (Fig. 5A). The actin cytoskeleton in WT and OE cells was well organized with actin stress fibers converging on focal adhesion

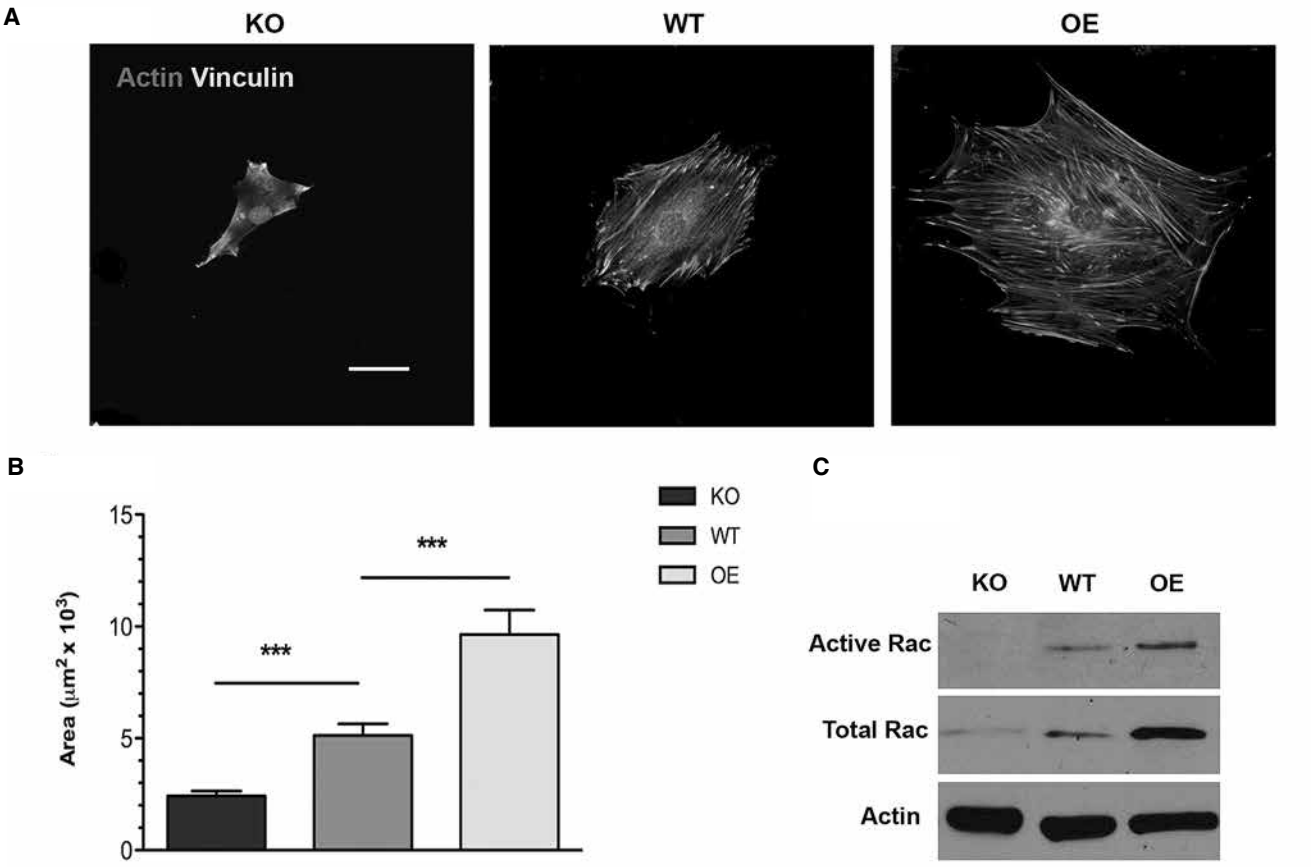

Figure 5. Effects of endogenous CTGF expression on cell spreading and Rac activation. **(A)** Immunofluorescent staining of primary mesenchyme-derived cells (KO, WT and OE) cultured on fibronectin-coated slides. Cells were stained for vinculin and F-actin and stained with DAPI for nucleus. Scale bar = 50 μm. **(B)** Quantification of cell area as measured by ImageJ. N = 50 cells per condition, ***$p < 0.001$. **(C)** Rac activity assay for cells cultured on fibronectin-coated dishes in serum free media. Negative control (cont) for Rac activity represents WT cells cultured on uncoated dishes in serum free media. Cell spreading and Rac (total and activated forms) are proportional to endogenous CTGF expression levels.

complexes. Conversely, in KO cells the focal adhesions were markedly reduced and the actin cytoskeleton was poorly organized. Cell spreading was quantified by measuring cell area and there were consistent and significant differences in cell size that correlated with CTGF expression (Fig. 5B). Furthermore, these differences in cell size were detectable at all times of cell culture ranging from one to eight hours and were also observed in cells that were cultured on a recombinant (rCTGF) substrate (data not shown). To investigate if endogenous CTGF expression affected Rac1 activity, a key player in cell cytoskeletal organization, we conducted a Rac activation assay. This assay demonstrated that OE cells had the highest levels of active Rac while KO cells had little if any active Rac, when compared to WT cells (Fig. 5C). Not only was Rac activation altered in proportion to CTGF expression, but the expression of total Rac also varied depending on CTGF expression with highest levels in the OE cells and lowest levels in the KO cells (Fig. 5C).

Discussion

As demonstrated in this study, the failure of the palatal primordium to grow and elevate in CTGF KO mice indicates that CTGF plays a vital role early in mammalian secondary palatogenesis. The observed nasal septum and lateral nasal wall malformations, along with the cleft secondary palate and previously described skull morphometric abnormalities,[10] suggest a potential common denominator, possibly in mesenchymal derived cranial neural crest cells. Cranial neural crest cells are mesenchyme-derived cells capable of differentiating into osteoblasts and chondrocytes under the influence of local growth factors.[7] This unique characteristic differentiates cranial neural crest cells from neural crest cells destined for other regions of the body,[7] and allows for comparison of changes in cell function and signaling in mesenchyme-derived pre-osteoblasts (pOBs) with the cells forming the mesenchyme of the secondary palate.

CTGF is known to regulate cellular functions and growth factor signaling pathways that have been shown to be necessary for palatogenesis. Palate formation involves the temporal and spatial coordination of cellular events including cell migration, proliferation, differentiation, and apoptosis. Our cell culture experiments utilized mesenchyme-derived pOBs to compare basic aspects of cell function and signaling in cells derived from KO and WT mice. CTGF KO cells exhib-

ited a significant reduction in proliferation owing to a delay in progression from the G1 to S phase. These results are consistent with a previous study which showed that CTGF knock-down resulted in decreased cell cycle progression in mesenchymal stem cells.[17] Since every stage of palatogenesis, fusion aside, relies heavily on cellular proliferation to produce the outgrowth of the maxillary palatal shelves, decreased proliferation may provide a partial explanation for the failure of palatogenesis in the CTGF KO mice. However, cell proliferation is an essential feature of morphogenesis of any structure, and therefore, the fact that the secondary palate is selectively affected suggests that there are additional cellular events requiring CTGF that, when affected, result in failed palatogenesis.

Physical interactions between the extracellular matrix (ECM) scaffolding, underlying mesenchyme, and epithelial cells play a crucial role in guiding palatogenesis.[1] In this study, CTGF KO cells demonstrated a reduced ability to adhere to ECM proteins, and the presence of CTGF within the ECM alone was not sufficient to rescue this decreased adhesion. These results indicate that CTGF plays a separate role in addition to its function as a matricellular protein. CTGF KO cells display a significant reduction in cell spreading, a function that appears to be proportional to the levels of CTGF expression since it was significantly enhanced in cells that overexpress CTGF. CTGF expression levels were also proportional to expression of Rac as CTGF KO cells exhibited marked decreases in total and activated forms of Rac while cells overexpressing CTGF demonstrated significantly increased levels. Rac is crucial for the formation of focal adhesions at the leading edge of migrating cells and its activation results in extension of lamellipodia and cell spreading.[18, 19] Our findings demonstrate that lack of CTGF results in a significant down-regulation of total Rac and that decreased activation of Rac results in reduced spreading of these same cells. The opposite holds true when cells overexpress CTGF. Assessment of CTGF expression levels on cellular migration is currently being pursued.

Among the myriad of factors that have are expressed during development of the palate, transforming growth factor beta (TGF-β) and bone morphogenetic protein (BMP) signaling have been shown to be essential for palate development.[1–4, 20] Previous studies have demonstrated that CTGF expression is induced by members of the TGF-β superfamily, with TGF-β1 being the most potent ligand.[21] In addition, CTGF has been shown to modulate BMP and TGF-β-mediated signaling and functions.[10, 14, 22, 23] Specifically, CTGF potentiates TGF-β signaling while inhibiting signaling induced by BMP-4. We have demonstrated that absence of CTGF in KO mice negatively impacts the expression of TGF-β1 and TGF-β receptor subtypes 1 and 2.[10] We also demonstrated that BMP-2 signaling and differentiation are augmented in the absence of CTGF and inhibited when CTGF is overexpressed in mesenchymal-derived pOBs.[14] We hypothesize that these effects may be due to CTGF sequestration of bioavailable BMP-2 which is unavailable to bind to its receptors and initiate a signaling response when bound to CTGF. Additionally, absence of CTGF negatively impacts expression of hedgehog family proteins.[24] The documented interactions between these crucial factors in palate development and CTGF create an attractive point of interest for future studies. Analysis of the expression of these proteins, their receptors, and specific components of signaling pathways will allow further elucidation of the crucial mechanisms regulating palatal development, thereby providing novel information aimed at developing new therapeutic targets for cleft palate pathologies. We hypothesize that the absence of CTGF alters the temporal and spatial expression of other key factors required for the growth and development of primordial palate tissue.

Taken together our data demonstrate that absence of CTGF results in severe developmental defects in the cranium, specifically focused on the midline structures. It also begins to elucidate potential mechanistic interactions governing palatal development in which CTGF plays a pivotal role in regulating key aspects of cellular function and signaling required for normal palatogenesis. Future studies will focus on the examination of other key proteins known to interact with CTGF and are likely to yield novel information regarding the essential role of CTGF in normal mammalian palatogenesis.

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Original Research

Prolonged Performance of a High Repetition Low Force Task Induces Bone Formation and Improved Microarchitecture in Rats, While Decreasing Tissue Sclerostin

Vicky S. Massicotte;[1, 2] Nicole M. Adams;[3] Paul W. Fisher;[1] Mamta Amin;[1] Mary F. Barbe[1, 2]

[1]*Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA;*
[2]*Musculoskeletal Research Group, Temple University, Philadelphia, PA;*
[3]*Drexel University College of Medicine, Biomedical Sciences and Professional Studies, Philadelphia, PA*

Abstract

Injuries of the hands and wrist are prevalent in many occupations requiring repetitive tasks and may be further aggravated by advancing age; these injuries are termed work related musculoskeletal disorders (WMSDs). Prior studies using an innovative operant rat model of reaching and grasping as a model of WMSDs demonstrated exposure dependent changes in forelimb bones of young adult rats performing repetitive tasks ≤3 months. No one has yet to examine if forelimb bones adapt or degrade further in response to moderate versus high demand repetitive tasks performed for prolonged time periods (up to 24 months). We hypothesized that long-term muscle loading at high repetition low force loads would induce bone adaptation. Therefore, we sought to determine if prolonged performance of a moderate demand upper extremity reaching and grasping task by young adult rats would continue to enhance forelimb bone formation and quality. We hypothesized that continued performance of a high repetition low force (HRLF) task for 24 weeks would lead to increased bone formation. We also hypothesized that RANKL and sclerostin, two proteins that have not been investigated in our rat model of WMSDs, would be reduced in rats performing a HRLF task for 24 weeks, as the bones reach adaptation. We found that 24 week HRLF rats showed several indices of bone formation and adaptation to the task; as well as reduced sclerostin immunoexpression, compared to controls, a reduction that likely contributed to the enhanced bone formation

Introduction

The response of bone to the application of load, whether internal, external, static or dynamic, may include both anabolic and catabolic changes depending on the load magnitude and duration.[1–3] Cyclical low force loading of bone tissue induces osteogenesis.[4–7] Bone quality can be enhanced by exercise and other forms of repeated muscle loading.[8–10] For example, tennis players have increased bone mass density (BMD) at the mid-radius of their dominant forearm and increased grip strength.[11] Voluntary grip strength is a strong determinant of bone architectural parameters, even more so than measurements of muscle cross-sectional area.[12] Studies examining if voluntary grip strength correlates with bone mineral density findings show variable results with findings ranging from forelimb site-specificity to widespread/systemic increases in bone mineral density.[13–15] Direct links between physical activity, increased grip strength and bone changes are site specific and cumulative when osteogenic changes are considered.[13] Most studies examining the impact of muscle loading on bones look at bone mineral density as a determinant of bone strength. In reality, bone microarchitecture restructuring can improve biomechanical properties with minimal changes to bone mineral content or density. An increase in bone strength of 64% has been shown to increase bone mineral density by only 5%.[10] Micro-computed tomography (microCT) has become the new gold standard to determine bone microarchitecture, a major contributor to bone strength and quality.[16] Skeletal integrity is determined by bone quantity and trabecular structure, both of which contribute to bone quality.[17–19] Bones are dynamic dense connective tissues that constantly undergo remodeling and repair through life, adapting to change in activity and force loads.[20, 21] Quantity (bone volume) and organization (microarchitecture) of trabeculae are strongly predictive of the mechanical properties of a bone.[18, 22, 23]

Studies examining the effects of excessive dynamic loads induced by intensive treadmill running, repetitive jumping, or intensive repetitive reaching and grasping at high repetition low force versus high repetition high force loads show that increasing the intensity of weight-bearing or muscle loading exercise/activities can be associated with declines in bone volume density and quality.[2, 24, 25]

A small number of studies have examined changes occurring in upper extremity bones of humans as a consequence of occupational tasks.[26–30] Increased incidence of hand/wrist osteoarthritis and reduced bone mass has been identified in

female dentists and teachers with heavy or one-sided hand workloads.[26–28] There are also bone scan studies of patients with upper extremity musculoskeletal disorders show increased blood flow and pooling (suggestive of inflammation) in affected forearm bones.[31, 32] The latter finding is important since presence of chronic inflammatory processes in bones is known to increase bone resorptive activity.[33, 34] In a large study examining job-related osteoarthritis, a significant association was found between hand osteoarthritis in females and high impact "jolting" of the hand (abrupt movement or shock), but no association in subjects performing lower impact hand-intensive tasks.[35] Jolting of the hands is a novel risk factor to develop occupational musculoskeletal disorder,[35] in addition to already known factors (e.g., vibration, cold, awkward position, repetitive motions).[36–38] There is a need to establish reach rate and load level boundaries for occupational repetitive tasks that lead to anabolic bone changes rather than catabolic tissue damage.

Increased levels of cytokines can also contribute to bone changes. Pro-inflammatory cytokines are known to stimulate osteoclastogenesis and activity, and impair osteoblast differentiation,[39–43] while other cytokines are required for enhanced bone remodeling and repair.[42, 44, 45] RANKL (Receptor activator of nuclear factor kappa-B ligand) is a cytokine linked to osteoclast activation during remodeling and increases in bone after osteocyte apoptosis due to bone microdamage.[46–49] Increased RANKL is a first step necessary for bone adaptation and repair after new strains.[47, 50–52] RANKL is part of the TNF superfamily of ligands (TNFSF11), stimulates differentiation and activation of osteoclasts by binding to receptor RANK (Receptor Activator of Nuclear Factor κ B) located on osteoclast precursor cells. Repetitive mechanical bone loading also decreases osteocyte-produced sclerostin,[53, 54] a potent inhibitor of bone formation that antagonizes Wnt pathway signaling in osteoblasts.[55] Down-regulation of sclerostin is essential for an osteogenic response to mechanical loading.[56] Sclerostin is also believed to have a catabolic effect on bones by promoting osteoclast formation and activity in a RANKL-dependent way.[57]

We have developed an operant rat model of an occupational repetitive task in which rats learn a reaching, grasping and pulling task for a food reward. With this model, we have shown that performance of repetitive tasks for up to 12 weeks leads to either trabecular bone pathological bone changes or adaptation, dependent on the repetition rate, force load, and duration of task.[25, 58–60] An intensive high repetition high force task for 6–12 weeks resulted in decreased trabecular bone volume density and cortical bone thinning in radial bones of young adult rats, concomitant with higher and more sustained increases in bone inflammatory cytokines.[25, 60–62] These increased inflammatory cytokines were the same that can affect bone cell homeostasis and induce net bone loss (e.g., interleukin-1beta and tumor necrosis factor alpha (TNF-α).[41, 42, 63] In contrast, performance of a moderate demand task of high repetition low force (HRLF) for 6–12 weeks lead to increased trabecular bone volume density and other indices of trabecular adaptation in the distal radius of young adult rats, concomitant with moderate and transient increases in bone pro-inflammatory cytokines.[25, 59, 64] A small amount of adaptation was also observed in the 12-week HRLF rats in the mid-diaphyseal cortical bone in the form of increased periosteal perimeter and marrow area.[64] However, we have yet to determine if continued performance of a moderate HRLF task leads to continued bone formation. This is particularly pertinent as we recently reported that rats performing the HRLF task for up to 24 weeks had cyclical increases in pro-inflammatory cytokines in serum and musculotendinous tissues that contributed to increased fibrotic and degradative proteins in these tissues.[65]

Therefore, our goal here was to determine if prolonged performance of an upper extremity reaching and grasping task at high repetition low force (HRLF) levels for 24 weeks continue to increase forelimb bone formation and quality, and the effects on bone inflammatory cytokines versus proteins necessary for bone adaptation and repair, specifically, RANKL and sclerostin. We hypothesized that continued performance of a HRLF task for 24 weeks will continue bone formation and adaptation, with reduced inflammatory processes, biomarkers of bone remodeling, RANKL and sclerostin levels.

Materials and Methods

Animals and Overview

The Temple University Institutional Animal Care and Use Committee approved all experiments in compliance with NIH guidelines for the care and use of laboratory animals. A total of 44 female Sprague-Dawley rats were used. Female rats were used in this study because: 1) Human females have a higher incidence of work-related musculoskeletal disorders (WMSDs) than males;[66] and 2) for comparison to bone data from our past studies on female rats using this model.[25, 58, 59, 61, 67] Adult rats (2.5 months of age at the onset of experiments) were randomly assigned to a food restricted control group (FRC, n = 21) or to a high repetition low force (HRLF) group, a task that they performed for 24 weeks (HRLF 24W, n = 12), for a total of 33 in the study. All rats were housed in a central animal facility in separate cages with a 12 hour light:dark cycle, and free access to water and environment enrichment toys.

Prior to the initiation of the experiments, all rats were handled for 10 minutes/day for one week. All rats were initially food-restricted for seven days to no more than 10–15% less than their naive weight to initiate interest in 45 mg food reward pellets (a 1:1 mix of purified grain and banana flavored pellets; each type purchased from Bioserve, NJ, USA). After that week, all food-restricted rats (FRC and HRLF rats) were given extra rat chow to gain weight quickly back to only 5% less than age-matched normal control rats kept

on hand for this purpose. All rats were provided with equal rations of food reward pellets and Purina rat chow daily. The high repetition low force (HRLF) rats first trained to learn the task in a four-week training period of 10 min/day for five days/week, before performing the task for two hours/day, three days/week for 24 weeks, as described further below. FRC rats rested until euthanasia at age-matched time points as HRLF rats.

All rats were inspected weekly and again post-mortem for presence of illness or tumors in order to reduce confounders for serum cytokine increases (none were observed). To further reduce illness related confounders, additional sentinel rats were examined for presence of viral infections or other illnesses as part of the regular veterinary care (none were detected).

Task Apparatuses

The behavioral apparatuses used were as previously described.[25, 68] Briefly, rats reached through a shoulder height portal and then isometrically pulled on a horizontal 1.5 mm metal bar attached to a load cell (Futek Advanced Sensor Technology, Irvine, CA) positioned 2.5 cm outside of the chamber wall. The load cell output was interfaced with a signal conditioner (Analog Devices, Norwood, MA), which amplified and filtered the signal before it was sampled digitally at 100 Hz with Force Lever software (Med Associates, St. Albans, VT). The metal bar (lever) and its load cell were interfaced with custom written Force-Lever software that allowed a choice of a set force level that the rat had to pull and then hold for at least 50 milliseconds,[69] before a food reward was provided (version 1.03.02, Med Associates, St. Albans, VT). Pulling force was constantly monitored during each session for each rat. A series of auditory indicators (Stimulus Clicker; Med Associates, St. Albans, VT) lasting five seconds cued the animal to attempt a reach. The rats were trained (described further below) to grasp the force lever bar, and pull toward the chamber wall at a force effort of 15% of the maximum grip strength of control rats for at least 50 milliseconds (ms).[69] If reach and force criteria for the task were met within a five second cueing period, a 45 mg food pellet was dispensed into a trough located at floor height for the animal to pick up.

Training Regimen for the HRLF task

HRLF rats were first trained to learn the reaching and handle-pulling task during a four-week period for 10 min/day, five days/wk, in which they ramped upwards towards the HRLF task level force. During this period, the rats moved through several stages of training, as previously described.[25] Briefly, in week 1 of training, they were placed in a plastic box outfitted with Plexiglas portal and plastic trough located at shoulder height, and introduced to the 45 mg food reward pellets. When rats learned to reach (without a specified reach rate) into the trough for the food pellets (typically three days), they were moved to operant chambers, where they learned with the aid of auditory and light cueing to reach through a shoulder-height portal to isometrically pull the force lever attached to a force transducer. In week 1, rats learned to grasp and pull on the force lever bar with a negligible force without any specified repetition rate, for a food reward (cueing was provided). In week 2, rats were required to pull at 11 grams (5% of their maximum pulling force (MPF), as previously described.[25] By the beginning of week 3, they were required to pull at 30 g (15% of their MPF), without any specified repetition rate. At the beginning of week 4, a specific pull cue is introduced. By week 4, rats were able to perform the HRLF task of four reaches/min at 15% of their MPF. Trained rats reached this HRLF level only during the last 3–4 days of their 4th week of training at 10 min/day, five days/week.

HRLF Task Regimen

Trained rats went on to perform the high repetition low force (HRLF) task at a low force at a reach rate of four reaches/minute (every 15 seconds), for two hours/day, four 30-minute sessions/day, three days/week, for a total of 24 weeks. The daily task was divided into four 30-minute sessions separated by 1.5 hour each in order to avoid satiation. The rats had to grasp the force handle and exert an isometric pull for at least 50 ms with a graded force effort of 15% ± 5% (30 ± 1.5 grams, equivalent to 0.23 N) of their naïve maximum voluntary pulling force (MPF). Rats were allowed to use their preferred limb to reach (the ''reach'' limb), as described and depicted previously.[25, 70] For this study, tissues were collected and assayed from the radius of the dominant reach limb.

Determination of Reach Force on the Lever Bar

Force lever data were recorded continuously during each task session for later calculation of voluntary reach force via an automated script (MatLab; Mathworks, Natick, MA). Reach force was the average force (expressed as a percentage of maximum pulling force) applied to the force handle for all reaches on a given day. Reach Force data was obtained from 24 week HRLF rats in week 1 and in week 24. Week 1 was used as the baseline for reach performance variables since that was the first week rats actually performed the task regimens for two hours/day, three days/week.

Tissue collection

At 24 weeks after onset of the HRLF task, animals were deeply anesthetized with 5% isofluorane using oxygen as the carrier, and euthanized by cardiac puncture for blood collection using an 18-gauge needle at 36 hours after their last task session (in order to avoid activity-dependent cytokine changes). FRC rats were euthanized at this same time point so as to serve as age-matched controls. Blood was kept on ice for 30 min, and allowed to clot before being centrifuged. Serum was harvested and frozen at –80°C until use. Thereafter, cohorts of rats were either perfused transcardially with

0.9% saline and then fixed with 4% paraformaldehyde in 0.1 M PO_4 buffer, pH 7.4, for micro-computerized tomography (microCT, n = 7/group) and then histomorphometry (n = 6–8/group), or tissues were flash frozen for protein assays (n = 6–8/group).

Serum Analysis

The blood collected during anesthesia was stored on ice for 30 min, then centrifuged at 1,800 g for 20 min at 4°C, flash-frozen, stored at –80°C until analyzed (n = 7/group). Serum was assayed using commercially available ELISA kits for CTX-1 (Immunodiagnosticsystems, RatLaps EIA, AC-06F1) and osteocalcin (Immunodiagnosticsystems, Rat-MID Osteocalcin EIA, AC-12F1). Serum CTX-1 is a measure of C-telopeptide fragments of collagen type I generated during osteoclastic bone resorption.[71] Osteocalcin is a non-collagenous protein of the bone matrix that is synthesized by osteoblasts, making the measure of serum an indicator of bone formation.[72] Serum was also analyzed for RANKL using a Millipore Milliplex Map Kit Rat RANKL Single Plex Magnetic Bead Kit (RRNKLMAG-31K-01, Millipore Corporation, Billerica, MA, USA), for sclerostin levels using a Quantikine ELISA immunoassay kit (MSST00, R&D Systems, Minneapolis, MN, USA), and for estrogen estradiol using a Calbiotech SKU kit (ES180S-100), following manufacturer protocols. For the RANKL bead assay, each sample was run in duplicate and analyzed using a Bio-Rad Bio-Plex System with a Bioplex manager 4.0 software (Hercules, CA, USA) as recommended and needed for this bead assay method. For all other ELISA assays, duplicate samples were analyzed using a VersaMax microplate reader using a SoftmaxPro Version 5 software (Molecular Devices LLC. Sunnyvale, CA, USA). The individual carrying out these analyses was blinded to treatment.

MicroCT Imaging and Analysis

After fixation, as described above, forelimb bones were collected (n = 7/group), cleaned of soft tissues, and stored in phosphate buffered saline (PBS) with sodium azide until micro-CT analysis of the radius. Skyscan volume rendering software (CTVox) and analysis software (CTAn) was used to render the 3D models and transaxial sections. MicroCT analysis was performed according to recent guidelines,[73] and as previously described.[58] The microCT analysis of the trabecular bone in the distal metaphyseal region of the radius, and the cortical bone in the mid-diaphyseal region of the radius, were the same as described in detail previously.[58]

Histomorphometry

The radial bones used for micro-CT analysis were embedded in paraffin (decalcified in a 14% acid free EDTA solution), using previously published methods,[59, 61] and used for histomorphometry (n = 5–7/group). Bones were sectioned into 5 μm longitudinal sections, placed onto charged and coated slides (Fisher Scientific, Tissue Path Superfrost Plus Gold Slides), dried at 55°C overnight. Mounted serial sections were then stained with Hematoxylin and Eosin (H&E) and TRAP for counting osteoblasts and osteoclasts. For these histomorphometric analysis, sections of the radial bone were measured at the distal metaphysis beginning 100 μm below the chondro-osseous junction of the secondary spongiosa and 100 μm in from the surrounding cortical bone using a 20x objective and image analysis software (BIOQUANT Osteo II, Bioquant Image Analysis Corp., Nashville, TN), using methods described by Parfitt et al.[74] Osteoblast numbers per bone surface (Ob.N./B.S.) on trabecular surfaces was determined in H&E stained sections, and numbers of osteoclasts (TRAP+) per bone surface (N.Oc/BS) were counted in H&E stained sections, on trabecular surfaces in the secondary spongiosa, using a Nikon E800 microscope interfaced with an image analysis program (Bioquant Osteo 2012 v12.1). Only multinucleated osteoclasts on the bone surface with three or more nuclei were counted. A minimum of three adjacent serial sections was used for counting.

Flexor forelimb tissues were collected from the same rats and limbs as above as a flexor mass, postfixed "en bloc" by immersion overnight in 5% paraformaldehyde in phosphate buffer (pH 7.4). A cross-sectional piece of the flexor digitorum muscle, of 1.5 mm in thickness, was removed with a scalpel from the mid-region of the muscle at its widest point. This cross-sectional piece was equilibrated in sucrose for three days, and then cryosectioned into cross-sectional slices of 12 μm thick each. These sections were mounted on slides, dried and stained with H&E. An image analysis program (Bioquant) was used to measure the cross-sectional area (CSA) of the entire muscle belly in mm^2 using a 2X objective.

Immunohistochemistry for Bone Sclerostin and RANKL

Immunohistochemistry for RANKL or sclerostin was performed on paraffin-embedded decalcified bone serial sections (n = 5/gp), after de-paraffinization with xylene and rehydration through a series of alcohol washes, 0.5% pepsin antigen retrieval, and 4% serum/blotto blocking steps. Secondary antibodies tagged with horseradish peroxidase were used (see Table 1 for antibodies and incubation time used). The horseradish peroxidase was visualized using diaminobenzidine (DAB) with a metal enhancer substrate system (SigmaFast D0426, Sigma-Aldrich). Radial bone sections were used to quantify and localize RANKL and sclerostin protein expression in the distal trabecular radial bone in the same region as used for the cell counts above, and in the mid-diaphyseal region of the radius at 100 μm away from the cortical periosteal bone. The area with positive immunostaining (which includes matrix and cell surface) and total trabecular bone matrix area was determined using an image analysis program (Bioquant) and previously described methods.[75] The percent area with immunostaining was determined by then dividing the area with positive immunostain-

ing by the total trabecular bone matrix area, and multiplying by 100. At least three adjacent trabeculae within this area of interest were quantified in sequential tissue sections per rat. Only the dominant task limb was used and quantified. The person carrying out the immunohistochemical analysis and quantification was blinded to treatment.

Analysis of Bone Inflammatory Cytokines

Forelimb bones were collected from separate cohorts of animals (n = 6–8/group) during euthanasia. Soft tissues were removed and bones flash-frozen. The distal portions (radial and ulnar epiphysis and metaphysis, and first row of carpal bones) were separated from the diaphysis of the radius and ulna, then powdered, homogenized, and assessed for interleukin (IL-1β), tumor necrosis factor -alpha (TNF-α), IL-6 and IL-10 using commercially available ELISA kits (BioSourceTM, Invitrogen Life Sciences, CA), as described previously.[67] Each sample was run in duplicate. ELISA assay data (pg cytokine protein) were normalized to μg total protein, which was determined using a bicinchoninic acid (Pierce BCA Protein assay #23225, Thermo Scientific, MA). The person carrying out ELISAs and cell counts was blinded to treatment.

Statistical Analyses

Student's T-test were used for comparison between of FRC to HRLF 24W. A p-value <0.05 was considered significant. Data are expressed as mean ± standard error of the mean (SEM).

Results

Trabecular Bone Shows Adaptation to Prolonged Performance of a HRLF Task

We observed increased bone volume fraction (BV/TV) in HRLF 24W rats, compared to FRC rats (Fig. 1A). Specific bone surface (BS/BV) was at baseline levels in HRLF 24W rats, compared to FRC rats (Fig. 1B). Trabecular thickness (Tb.Th) was significantly increased in HRLF 24W rats (Fig. 1D), although there were only marginal increases in trabecular number (Tb.N.) and separation (Tb.Sp) in HRLF 24W rats, compared to FRC rats (Fig. 1C,E). The degree of anisotropy (DA) was decreased in HRLF 24W rats, compared to FRC rats (Fig. 1F), indicative of increased trabecular organization with task performance. The shape of the trabecular shape changed from rod-like to plate-like in HRLF 24W rats (indicated by a decreased SMI), a change known to increase bone strength[76] (Fig. 1G). Representative reconstructed microCT trans-axial images also show an increase in trabecular volume and thickness in HRLF 24W rats, compared to FRC rats (Fig. 1H and I).

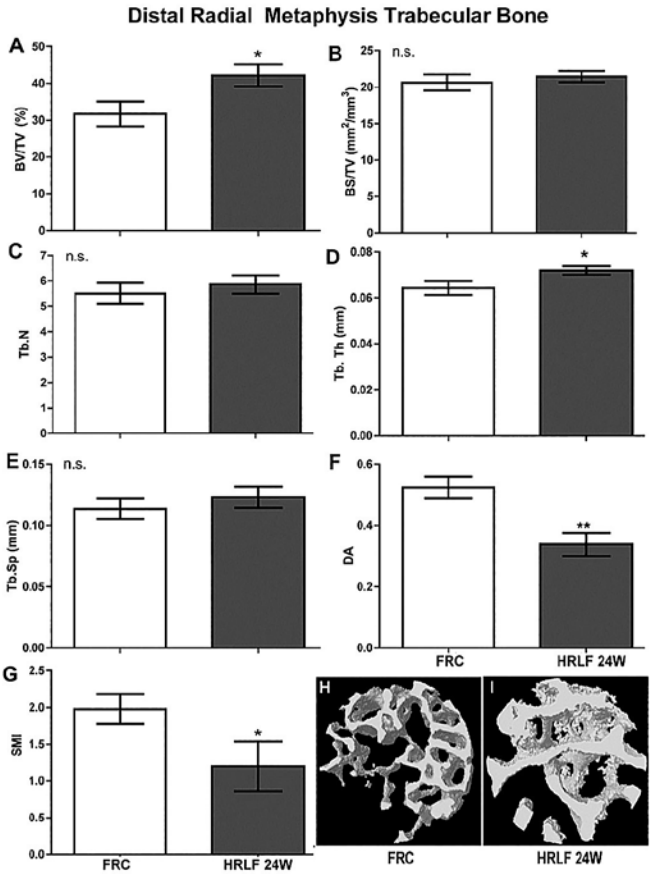

Figure 1. MicroCT analyses of trabeculae in the distal radius of young adult food restricted control (FRC) and high repetition low force (HRLF) rats that had performed the task for 24 weeks (HRLF 24W). **(A)** Bone volume/tissue volume (BV/TV), **(B)** bone surface/tissue volume (BS/TV), **(C)** trabecular number (Tb.N), **(D)** trabecular thickness (Tb.Th), **(E)** trabecular separation (Tb.Sp), **(F)** degree of anisotropy (DA) 0 = isotropic 1 = anisotropic, and **(G)** structure model index (SMI) 1 = plates, 2 = rods, 3 = cylinders. **(H)** Representative transaxial 3D images of the distal radial trabecular bone area analyzed in each group. Mean ± SEM shown. * and **p < 0.05 and p < 0.01, compared to FRC rats. n.s. = not significant.

Table 1. Antibodies Used for Immunohistochemistry

Protein Target	Cat. #	Host	Type	Dilution	Incubation (h)	Temp.	Source
Primary Abs							
RANKL	sc-7628	Goat	Polyclonal	1:400	24 hours	4°C	Santa Cruz Biotechnology, Dallas, TX, USA
Sclerostin	Ab99340	Rabbit	Polyclonal	1:200	24 hours	4°C	Abcam, Caambridge, MA, USA
Secondary Abs							
Donkey anti-goat	705-035-003	Donkey	IgG H+L	1:100	2 hours	RT	Jackson ImmunoResearch, West Grove, PA, USA
Goat anti-rabbit	111-035-144	Goat	IgG H+L	1:100	2 hours	RT	Jackson ImmunoResearch, West Grove, PA, USA

Cortical Bone Only Shows Discrete Changes with Prolonged Performance of a HRLF Task

At the mid-diaphysis of the radius, both total area (Tt.Ar) and cortical bone area (Ct.Ar) increased in HRLF 24W rats, compared to FRC rats (Fig. 2A,B), so that the ratio of Ct.Ar./Tt.Ar was unchanged (Fig. 2C). There was no difference in cortical thickness (Ct.Th) in HRLF 24W rats, compared to FRC rats (Fig. 2D), although the marrow area (Ma.Ar) showed a trend towards an increase ($p = 0.06$) and the periosteal perimeter (Ps.Pm) was increased in HRLF 24W rats, compared to FRC rats (Fig. 2E,F), indicative of both endosteal and periosteal growth so that cortical thickness was maintained. A decrease in closed pore volume (Po.V.(cl)) was observed in the HRLF 24W rats, compared to FRC rats (Fig. 2G). Representative reconstructed microCT trans-axial images show a decrease in cortical porosity in HRLF 24W rats, compared to FRC rats (Fig. 2H and I).

Small Increases in Bone Inflammatory Cytokines in HRLF 24W rats

There was a small but significant increase in levels of three pro-inflammatory cytokines, IL-1β, TNF-α and IL-6, in both distal and proximal forelimb bone regions of HRLF 24W rats, compared to FRC rats (Fig. 3A–C and E–G). In contrast, IL-10 levels decreased in distal forelimb bone regions of HRLF 24W rats, compared to FRC rats (Fig. 3D), but not in proximal forelimb bone regions (Fig. 3H).

Indices Related to Bone Turnover Were Static or Decreased in HRLF 24W Rats

Systemic levels of osteocalcin (indicative of bone formation) and sclerostin levels did not change significantly with prolonged HRLF task performance (Fig. 4A and C). However, the number of osteoblasts per trabecular bone surface (N.Ob/BS) decreased in the distal radius, as did sclerostin

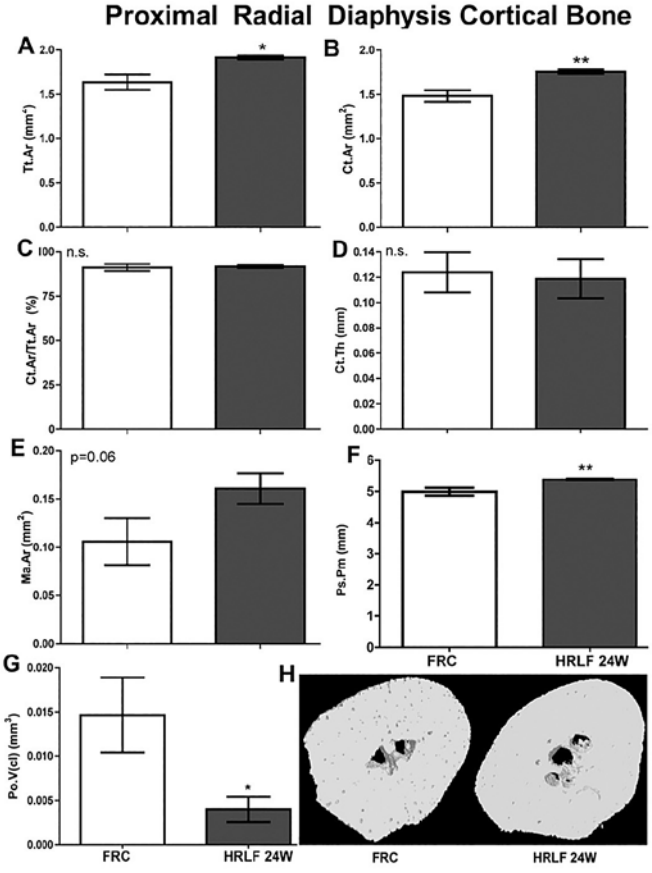

Figure 2. MicroCT analyses of mid-diaphyseal cortical bone in the radius of young adult FRC and 24 week HRLF rats (HRLF 24W). **(A)** Total area of the periosteal envelope (Tt.Ar), **(B)** cortical bone area (Ct.Ar), **(C)** cortical area fraction (Ct.Ar/Tt.Ar), **(D)** cortical thickness (Ct.Th), **(E)** marrow area (Ma.Ar), **(F)** periosteal perimeter (Ps.Pm), and **(G)** closed pore volume (Po.V (cl)) indicative of cortical porosity. **(H)** Representative transaxial 3D images of cortical bone area analyzed in the radius for each group. Mean ± SEM shown. * and **$p < 0.05$ and $p < 0.01$, compared to FRC rats. n.s. = not significant.

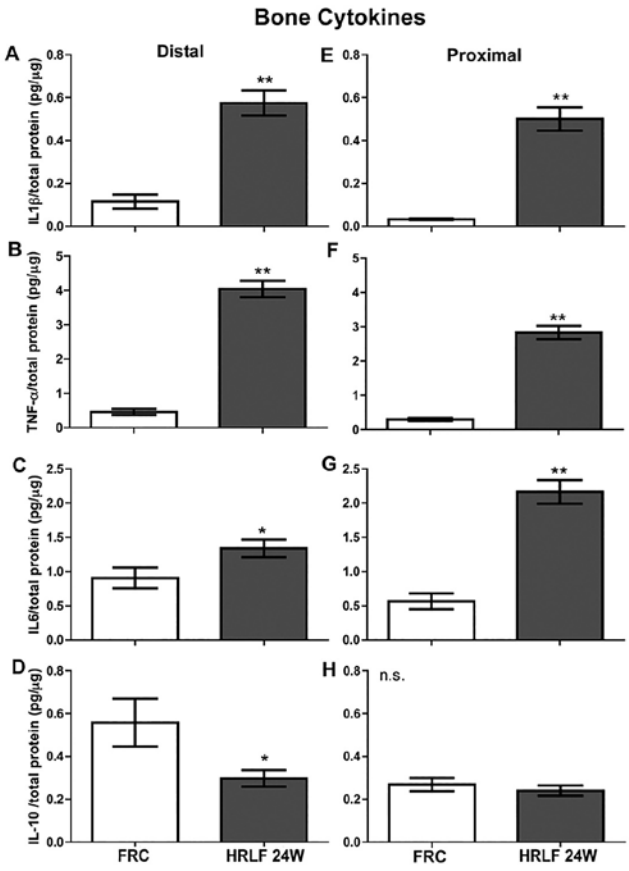

Figure 3. Inflammatory cytokines in distal and proximal forelimb bone regions of young adult FRC and 24 week HRLF rats (HRLF 24W). The distal region included the metaphysis of the radius and ulna and the first row of carpal bones. The proximal region included the diaphysis of the radius and ulna. **(A** and **E)** IL-1beta, **(B** and **F)** TNF-alpha, **(C** and **G)** IL-6, and **(D** and **H)** IL-10. Mean ± SEM shown. * and **$p < 0.05$ and $p < 0.01$, compared to FRC rats. n.s. = not significant.

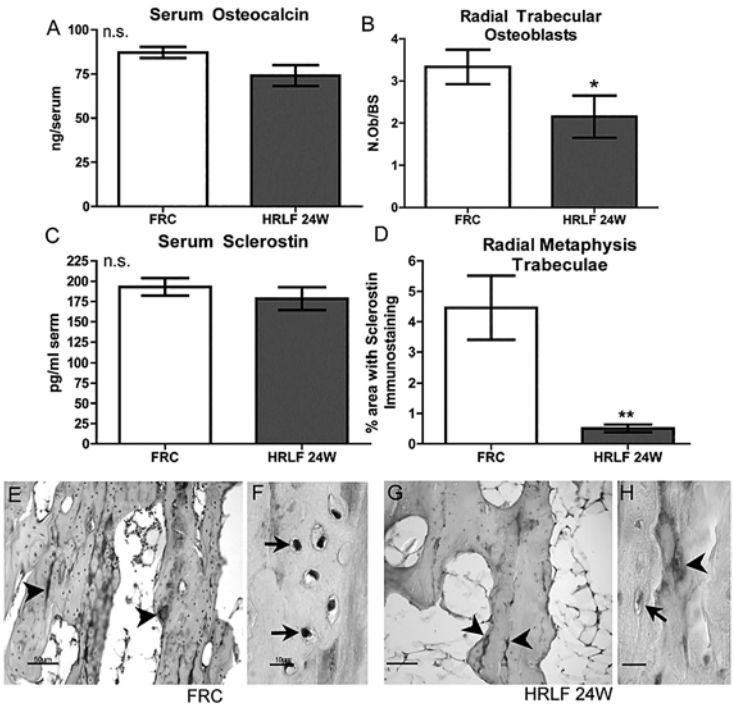

Figure 4. Serum levels of biomarkers of bone formation (osteocalcin) and sclerostin, and osteoblast numbers and sclerostin immunohistochemistry in the distal trabeculae of the radius of young adult FRC and 24 week HRLF rats (HRLF 24W). **(A)** Serum osteocalcin levels. **(B)** Number of osteoblasts per bone surface (N.Ob/BS) in the distal radial trabecular region. **(C)** Serum sclerostin levels. **(D)** Quantification of sclerostin immunohistochemistry in the distal radial trabecular region. **(E** and **F)** Sclerostin immunohistochemistry (brown DAB precipitate) in the distal radial trabecular region of a FRC rat. Arrowheads indicate sclerostin within the bone matrix, while arrows indicate sclerostin immunoexpression in osteocytes. **(G** and **H)** Sclerostin immunohistochemistry in the distal radial trabecular region of a HRLF 24W rat. Mean ± SEM shown. * and **$p < 0.05$ and $p < 0.01$, compared to FRC rats. n.s. = not significant.

immunostaining in HRLF 24W rats, compared to FRC rats (Fig. 4A–D). Sclerostin immunostaining was higher in the matrix (arrows) and in osteocytes (arrowheads) of distal radial trabeculae of FRC rats, than in HRLF 24W rats (compare Fig. 4E,F to G,H).

Systemic levels of CTX1 (an indicator of bone resorption) and RANKL levels did not change significantly with prolonged HRLF task performance (Fig. 5A and C). In contrast, the number of osteoclasts per bone surface (N.Oc/BS) decreased in the distal radial trabeculae of HRLF 24W rats, compared to FRC rats (Fig. 5B). There were also no changes in RANKL immunostaining between the two groups (Fig. 5D). RANKL immunostaining was similar in osteocytes of FRC and HRLF 24W rats (Fig. 5E).

Flexor Digitorum Muscle Cross-sectional Area and Voluntary Reach Force Loads

Prolonged performance of the HRLF task did not increase the cross-sectional area of the flexor digitorum muscle belly of HRLF 24W rats, compared to FRC rats (Fig. 6A). Analysis of voluntary reach force loads on the lever bar showed that the HRLF 24W rats had learned to pull the lever bar at the target of 15% of their maximum pulling force, which is equal to 30 grams (0.23 Newtons) of force on this bar (Fig 6B).

Serum Estrogen Levels Similar in Each Group

Serum estrogen estradiol levels did not differ between the two groups: FRC: 3.23 ± 0.94, and HRLF 24W: 2.56 ± 0.41, mean ± SEM.

Discussion

We previously reported that performance of a moderate demand reaching and pulling task of high repetition low force (HRLF) for 12 weeks triggers trabecular bone formation, despite (or perhaps because of) low grade levels of pro-inflammatory cytokines[25, 59] known to affect osteogenesis and encourage bone resorption.[39, 41–43] The current study is the first study examining the effects of repetitive reaching and grasping for >12 weeks on forelimb bone microarchitecture and bone inflammatory cytokine levels. This is also the first investigation of effects of repetitive reaching and grasping on RANKL, a cytokine essential for osteoclast differentiation during remodeling,[46–49] and sclerostin, a protein responsive to bone mechanical stimuli[77, 78] and a negative regulator of osteoblast differentiation and function.[79, 80] We found that a 24 week HRLF task increased trabecular bone volume, compared to control rats, and increased periosteal and endosteal apposition in the mid-diaphyseal cortical bone, although accommodation to the task was also evident in these bones regions. There was a low-grade increase in bone inflammatory cytokines, and no alteration in RANKL immunoexpression yet decreased sclerostin immunoexpression in distal radial trabeculae of HRLF 24W rats.

The increase of bone volume density (BV/TV) and trabecular thickness (Tb.Th) in the HRLF 24W rats indicates bone adaptation to the task, as does the decreased degree of anisotropy (DA), indicative of evenly distributed trabecular bone associated with improved strength, quality and resistance to mechanical loading.[81] Improved structure in HRLF 24W rats is also supported by the decreased SMI, indicative of a transition to plate-like shaped trabeculae associated with higher mechanical strength.[81–84] However, trabecular number and separation were unchanged between the two groups. In 1998, Turner et al. reported that increased duration of skeletal loading is not proportional to osteogenesis, but that the initial 'abnormal' strain of a new task eventually becomes 'normal,' as does loading frequency and magnitude when maintained at consistent levels, and that bones accommodate to routine demands.[85] Since we observed increased trabecular numbers and decreased trabecular separation in HRLF 12W rats, as well as increased trabecular bone volume density,[25] the absence of other trabecular bone changes suggests that the radius is accommodating to the HRLF task by week 24. This hypothesis of accommodation is further supported by decreased numbers of osteoblasts and osteoclasts on the

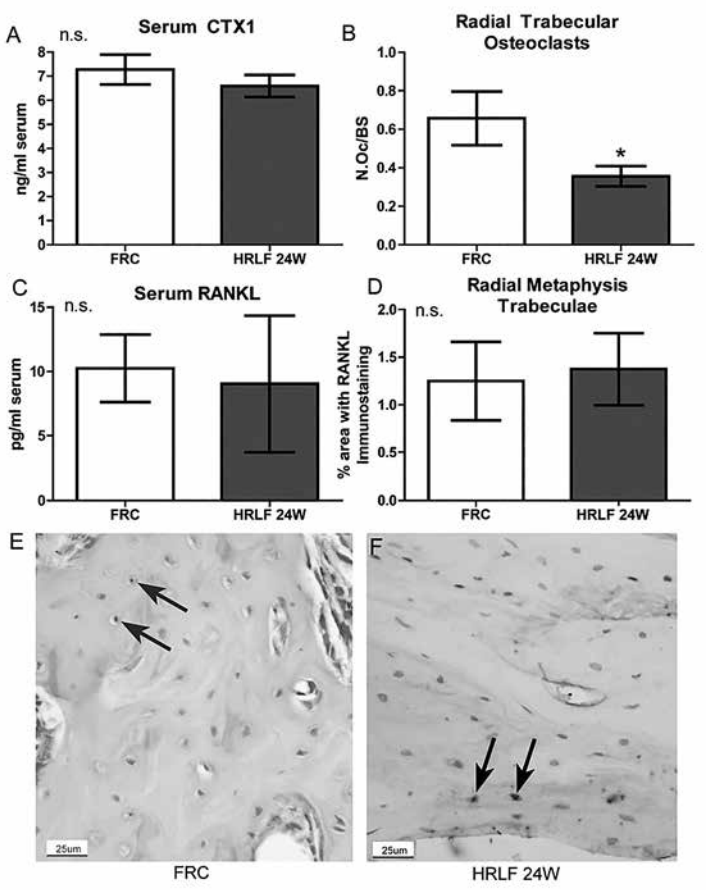

Figure 5. Serum levels of biomarkers of bone resorption (CTX-1) and RANKL, and osteoclast numbers and RANKL immunohistochemistry in the distal trabeculae of the radius of young adult FRC and 24 week HRLF rats (HRLF 24W). **(A)** Serum CTX1 levels. **(B)** Number of osteoclasts per bone surface (N.Oc/BS) in the distal radial trabecular region. **(C)** Serum RANKL levels. **(D)** Quantification of RANKL immunohistochemistry in the distal radial trabecular region. **(E)** RANKL immunohistochemistry in the distal radial trabecular region of a FRC rat. Arrows indicate RANKL immunoexpression in osteocytes. **(F)** RANKL immunohistochemistry in the distal radial trabecular region of a HRLF 24W rat. Mean ± SEM shown. *$p < 0.05$, compared to FRC rats. n.s. = not significant.

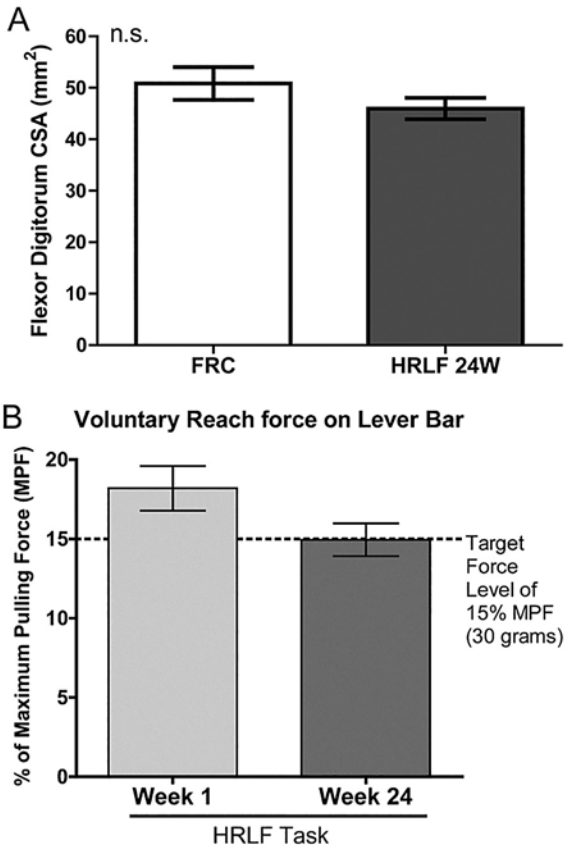

Figure 6. Flexor digitorum muscle size and voluntary reach force on the lever bar. **(A)** Quantification of the total muscle cross-sectional area (CSA), reported as Mean ± SEM for FRC and 24 week HRLF rats (HRLF 24W). **(B)** Voluntary reach force on the lever bar, assayed using force transducer data collected during task performance. HRLF 24W pulled at the target 15% of their maximum pulling force (MPF). n.s. = not significant.

bone surface of radial trabeculae in HRLF 24W rats, compared to control rats.

In the mid-diaphyseal region of HRLF rats, we observed increased total area (Tt.Ar), cortical area (Ct.Ar), marrow area (Ma.Ar, albeit as a trend only of $p = 0.06$), and periosteal perimeter (Ps.Pm) in HRLF 24W rats, compared to control rats. The increase in Ps.Pm is a form of bone adaptation to resist bone fracture.[86, 87] The Ps.Pm increase compensated for the marginal increase in marrow area (Ma.Ar), so that radial bone cortical thickness (Ct.Th) was not altered from control levels in HRLF 24W rats. These findings indicate adaptation in the mid-diaphyseal cortical bone of the radius with continued performance of the HRLF task. We did not evaluate bone mass density (BMD) in this study. BMD correlates with multiple factors such a grip strength, body weight, muscle mass, age, fat content, activity levels, and force of loading.[11–13, 87–90] A recent study indicates that microstructure is more relevant than mineral content when evaluating adaptation and improvements in bone morphometry.[91]

Low-grade inflammatory cytokine increases were present in forelimb bones of HRLF 24W rats, compared to control rats. The levels observed were slightly higher than previously found in young adult HRLF 12W rats,[64] but four fold or more fold lower than in rats performing a high repetition high force task for 12 weeks.[25] TNF-α and IL-1β are produced by osteoclasts and interfere with osteoblast differentiation and proliferation[41, 42] in a dose-dependent manner.[39, 92] Other reports stipulate that low doses of TNF-α or IL-1β stimulate osteoblast proliferation and osteogenic differentiation.[93–95] Thus, some of the observed bone changes are likely due to the continued presence of low levels of bone inflammatory cytokines that activate both osteoclasts and osteoblasts for damage removal and repair.[42, 96]

Sclerostin immunoexpression was reduced the distal radial trabeculae of HRLF 24W rats, compared to FRC rats,

although local radial bone changes in sclerostin were not reflected in the serum. Sclerostin production is responsive to mechanical stimuli.[77, 78] Applied mechanical loads have been shown repress sclerostin production, releasing its antagonism of Wnt/beta-cantenin signaling[78, 97] so that mechanical loading-induced bone formation occurs.[56] Our data of reduced sclerostin in the radial trabeculae of HRLF rats, compared to control rats, combined with indices of bone formation, are consistent with these other loading studies.

RANKL was unchanged in HRLF 24W rats, compared to FRC rats, in both serum and in radial trabeculae. RANKL plays a key role in the modulation of bone remodeling, especially during loading and periods of bone repair.[48, 98–100] Increased osteocyte apoptosis after bone microdamage induces the release of RANKL from neighboring osteocytes.[46, 47, 101] Perhaps we missed an earlier loading induced increase in RANKL since we only assessed the 24 week time point, or perhaps the absence of bone microdamage in this low loading protocol did not lead to increased RANKL production.

The cross-sectional area of the flexor digitorum muscle was not different in HRLF 24W rats compared to FRC rats. This HRLF task is not an exercise training program designed to induce muscle mass or strength gains, but instead requires rats to pull at a consistent low force equivalent to 15% of their maximum pulling force (30 grams) in order to receive a food reward. The voluntary reach force data shown in Figure 6 shows that the HRLF 24W rats met this goal. While many cell types and tissues adapt to new demands,[10, 25, 85, 102] the lack of change in the cross-sectional area of the flexor digitorum muscle suggests that the HRLF task did not stimulate functional gains in this muscle, as previously reported in our model.[25] We have reported the presence of significant muscle fibrosis and reduced reflexive grip strength (tested with a rat grip strength meter) in the same HRLF 24W rats used in this study.[103] The current findings indicate that despite the increase in muscle fibrosis in these HRLF 24W rats, they are able to maintain a voluntary reach force of 15% on a lever bar for a food reward.

In conclusion, both trabecular and mid-diaphyseal regions of radii of young adult female rats showed changes consistent with bone adaptation to prolonged performance of this high repetition low force repetitive task. Bone cytokines were increased in HRLF 24W rats, compared to FRC rats, but at low-grade levels only that were apparently below the level needed to stimulate osteoclast proliferation and activity. The decrease in sclerostin was likely a result of mechanical loading induced repression of this protein, a change that likely contributed to the net bone formation. Thus, repetitive low force occupational tasks by young adult animals appear to benefit forelimb bone structure.

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Case Report

Acute Tetraplegia After Posterior Cervical Laminectomy for Chronic Myelopathy

Justin Iorio, MD;[1] Andre Jakoi, MD;[2] F. Todd Wetzel, MD[1]

[1]*Department of Orthopaedic Surgery, Temple University Hospital, Philadelphia, PA;*
[2]*Department of Orthopaedic Surgery, Drexel University College of Medicine, Philadelphia, PA*

Introduction

Progressive spinal cord dysfunction in people aged 55 years and older is most commonly caused by cervical myelopathy.[1] Surgical options for multilevel cervical myelopathy (MCM) include anterior, posterior, or anterior-posterior (combined) decompression. Patients with persistent symptoms of cord compression despite a previous procedure are indicated for revision surgery. Revision surgery following an anterior approach can be performed through the same approach or an alternative, posterior approach. The posterior approach avoids iatrogenic injury to the trachea, esophagus, and neurovascular structures which are often tethered by scar tissue and at risk due to altered anatomy.[2] Regardless of approach, spinal cord injury (SCI) is an infrequent, but major complication.[3, 4] Paralysis may occur due to iatrogenic or mechanical injury, or may be secondary to cord edema, ischemia, and reperfusion.[1, 4–6] We report a case of a 73-year-old female with persistent MCM despite a previous three-level anterior cervical procedure who developed an incomplete C6 tetraplegia during revision cervical laminectomy and posterior instrumentation. The pathophysiology of MCM is discussed in addition to perioperative imaging, neuromonitoring and use of steroids.

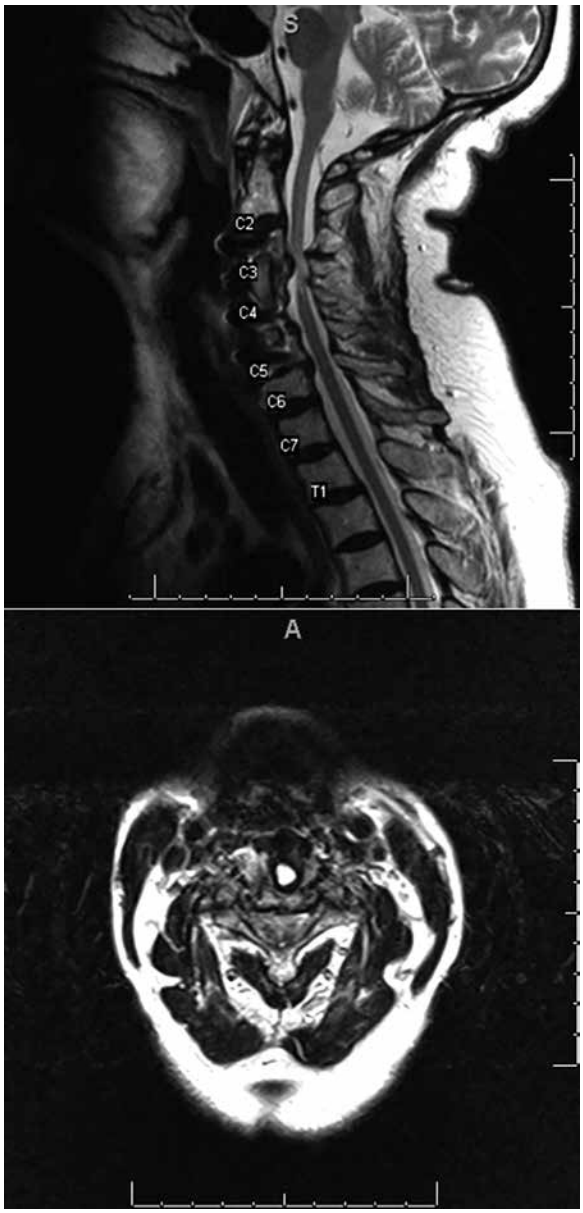
Case Presentation

The 73-year-old patient was referred to the senior author (FTW) for complaints of chronic neck pain with radiation to her bilateral hands, weak intrinsic hand function, and progressive gait dysfunction. At initial physical examination, she had preserved cervical lordosis, bilaterally diminished upper extremity reflexes, bilateral motor deficits affecting C6 to T1, and intact sensation throughout all extremities. Hoffmann and Babinski signs were negative. She required the use of a walker and demonstrated a broad-based gait. She was assessed as a Nurick Grade 4 (unable to walk without assistance) and Ranawat 3A (ambulatory but with long tract signs). A computed tomography (CT) myelography study revealed diffuse cervical spondylosis producing most severe central spinal stenosis at C3 to C4 and myelomalacia from C3 to C5.The patient was indicated for C3 to C6 anterior cervical discectomy and fusion (ACDF), C4 corpectomy, and fibular strut allograft from C3 to C5.

The patient initially did well; however, the patient began to demonstrate progressive upper motor neuron (UMN) signs at four months postoperatively. An MRI revealed posterior soft tissue protrusion at C3 to C4 resulting in effacement of the thecal sac, T1 hypointensity from C3 to C5, and T2 hyperintensity at the same levels, indicating persistent cord compression (Figures 1A-B). The T1 and T2 findings suggested a cord pathologies including intraspinal edema, cell death, gliosis, and demyelination.[2] The patient was indicated for a revision posterior procedure because of persistent cord compression. At six months after her index procedure, the patient underwent a C3 to C6 laminectomy and lateral mass instrumentation from C3 to C6. Intraoperative neuromonitoring was used throughout the procedure and included somatosensory evoked potentials (SSEPs) and transcranial motor evoked potentials (tcMEPs).

A standard posterior cervical exposure was performed. Lateral mass screws were inserted from C3 to C6 using fluoroscopic guidance and anatomic landmarks. There were no changes in neuromonitoring signals. Cervical laminectomy was performed by creating a trough at the lamina-facet junction from C3 to C6. The C4 hemi-lamina was removed lastly because this was the site of major cord compression. The spinal cord was noted to be pulsatile. Immediately following removal of the laminae, however, changes in tcMEPs and SSEPs were reported. Anesthesia was informed to maintain mean arterial pressure (MAP) at or above 90 mmHg, which it had been for the duration of the surgery, and high-dose steroids were initiated (methylprednisolone 250 mg IV). Local autograft was applied to decorticated bone prior to closure. At this point, the tcMEPs and SSEPs improved in the left upper extremity, but not in the other extremities. The patient was extubated and transferred to the neurosurgical intensive care unit for maintenance of MAP, high-dose IV steroids (methylprednisolone 250 mg IV every six hours for 24 hours), and serial exams.

In the acute postoperative period, the patient had bilateral C6 sensation, 4/5 elbow flexion motor strength, 2/5 wrist extension, and 0/5 strength from C7 to T1. Sensation was markedly diminished or absent from C7 to T1. In the bilateral lower extremities, sensation was preserved from L2 to S1 and motor was absent with the exception of 1/5 strength in the left hip muscles and 2/5 strength from the knee dis-



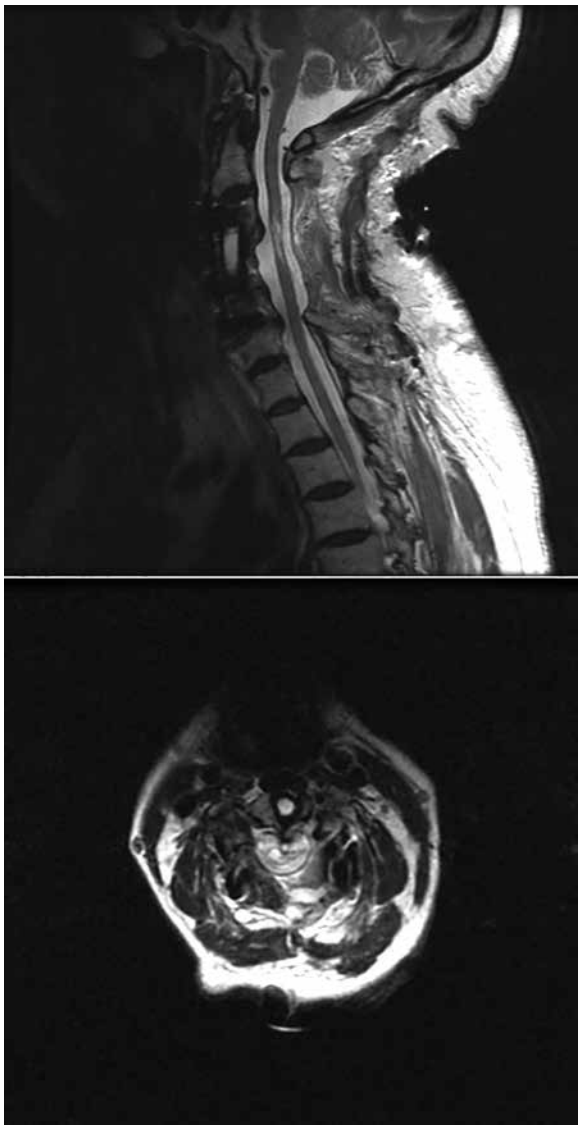
Figures 1A-B

tally. Postoperative MRI of the cervical spine demonstrated increased T2 hyperintensity and cord expansion at C3 and C4 compared to the pre-laminectomy MRI (Figures 2A-B).

Discussion

The incidence of major neurological injury after spinal surgery is very low. In a 10-year study of 4,087 adult patients who underwent cervical spine surgery, only 0.293% suffered a major deficit defined as a motor grade of two or less in two or more extremities.[3] However, understanding the pathophysiology of MCM and techniques of minimizing complications is important in avoiding catastrophic complications such as paralysis. We report a case of acute C6 tetraplegia which occurred during posterior cervical laminectomy for recalcitrant cervical myelopathy.[4, 7, 8] In this patient, the timing of neurological injury (immediately following removal of laminae) and postoperative MRI findings (T2 hyperintensity and cord expansion) supports cord edema and reperfusion injury as plausible explanations.

The pathophysiology of MCM, even prior to surgery, is a risk factor for neurological deterioration due to the development of a "sick cord," which reflects pathological changes in the spinal cord that lower the threshold for injury. May et al.[9] found that preoperative MCM was the strongest risk factor for neurological injury during cervical surgery and Ranawat 3A patients, as in our case, were twice as likely to have neuromonitoring changes than lesser Ranawat scores. Chronic spinal cord compression results in neuronal cell death, limited cord perfusion, and changes in local vasculature.[6, 7] Oligodendrocytes, the myelinating cells of the nervous system and trophic supporters of neurons, undergo apoptosis as a



Figures 2A-B

result of both oxidative and mechanical insults.[7] Cord compression produces ischemia and, ultimately, an acidotic environment that is unsuitable for the highly metabolic oligodendrocytes and clearance of reactive oxygen species produced during cellular processes.[7, 10] Additionally, oligodendrocytes contain large amounts of iron for myelin production; the release of iron from damaged cells contributes to free radical formation and lipid peroxidation.[7, 10] Changes in spinal cord perfusion are also affected by anteroposterior compression of transverse arterioles from the anterior spinal artery, resulting in ischemia of gray and white matter. Further spinal cord injury occurs from mechanical compression by bony and soft tissue structures on the neural elements during cervical motion.[11, 12]

The neurological insult which resulted in paralysis occurred intraoperatively. In this case, we postulate that chronic spinal cord demyelination and altered vascularity rendered the cord vulnerable to the effects of laminectomy and decompression. Cord edema, a consequence of free radicals, is secondary to altered vascular permeability. The post-laminectomy cord expansion from vascular inflow further increased cord edema. Cord ischemia worsened as fluid leaked into the extracellular space against the resistance of the firm pia matter, thereby increasing interstitial pressure.[6] Subsequent neurological injury was detected by monitoring at the time of laminae removal.

Intraoperative neuromonitoring (IONM) is commonly utilized for intraoperative assessment of neurological integrity. The rationale for IONM is to supply feedback with changes in neural function prior to irreversible neural damage.[13] SSEPs monitor and provide direct information concerning dorsally-located, ascending spinal cord sensory tracts and indirect information about ventrally-located motor tracts. tcMEPs, in contrast, evaluate the functional properties of the corticospinal motor tracts, spinal nerve roots, peripheral nerves, and nerve plexuses.[13] The downside of SSEPs is that they do not provide information regarding individual nerve root function nor do they assess the motor tracts. Damage to the spinal cord motor tracts may occur without an associated change in SSEPs.[13, 14] Neural injury is detected more quickly with tcMEPs because SSEPs reflect signal averaged data which lags behind changes in tcMEPs. In a review of cervical spine surgeries, Hilibrand et al.[15] found that tcMEP monitoring was 100% sensitive and specific for identifying motor tract injury compared to SSEP monitoring which was 100% specific but only 25% sensitive. In a study of cervical spine surgery, SSEPs were only 27% specific for detecting neurological deterioration.[9] tcMEPs, however, can be affected by severe myelopathy.[2] Spinal cord compression, such as in MCM, increases the likelihood of false-negative findings because the area of the cord supplied by the anterior spinal artery is susceptible to hypotension-induced vascular injury.[16] In this case, it is possible that an impending SCI went undetected for this reason. At the time of injury, a cascade of changes involving sodium, potassium and calcium channels occurred. The cascade caused an interruption of axonal transmission and produced an uncoupling of oxidative phosphorylation resulting in a loss of cellular function and integrity.

"White cord syndrome" was previously reported after anterior cervical discectomy and fusion.[17] Similarly to our experience, the authors did not determine an identifiable cause of cord injury and the patient also sustained an incomplete C6 tetraplegia. T2 hyperintensity in the cord was visualized on postoperative MRI in the absence of compression from surrounding structures. These findings are similar to our patient in which an increase in cord signal changes from baseline were observed immediately after surgery despite posterior decompression (Figures 2A-B). The resultant neurological level in our case did not correlate with the level of highest intensity on MRI imaging, which suggests that the neural injury above C5 was either subclinical or the area of the C5 to C6 cord is more susceptible to reperfusion injury. Additionally, the area of maximal stenosis on pre-laminectomy imaging was at C3. The dorsal and ventral nerve roots are sensitive to ischemic injury between the proximal and middle third, which represents an area of hypovascularity.[13] This may also explain her postoperative clinical findings.

The use of steroids for spinal cord injury is controversial.[18–20] The National Acute Spinal Cord Injury II (NASCIS II) and NASCIS III trials were unable to find an improvement in neurological function for acute SCI.[21] *Post hoc* analyses reported a subclinical improvement in motor scores. Despite the unclear evidence of steroids for acute SCI, physicians continue to administer methylprednisolone. In a recent survey, 56.4% of respondents from the Cervical Spine Research Society reported that they used steroids for incomplete cervical SCI and 76% believed that the complications were strong enough to limit their use.[22] Institutional protocols, fear of litigation, and belief in positive treatment effects were common reasons for their use. Several complications of high-dose steroids have been reported[23, 24] and the efficacy of steroids is unproven.[21, 25] However, the rationale for the administration of methylprednisolone was that, at the cellular level, glucocorticoids stabilize cell membranes, reduce local edema, and augment blood flow to neuronal tissue.[26] The duration of methylprednisolone was restricted to 24 hours, which is associated with fewer complications than extended treatment.[23] In the face of catastrophic SCI, the benefit of any neurological improvement must be weighed against the risks of complications.

Acute tetraplegia following revision surgery for the management of persistent MCM is an infrequent, but devastating complication. A previous report of tetraplegia following ACDF recommended adequate cervical decompression, such as corpectomy and pharmacological treatment postoperatively.[17] We present a similar outcome; however, this complication occurred in a patient who underwent cervical corpectomy and fusion followed by second-stage laminectomy. We believe that adequate decompression had been

performed and her neurological deterioration was a result of underlying spinal cord disease due to chronic MCM. The patient has not made improvements in her neurological status and is currently in a skilled-nursing facility at 11 months after her revision surgery. The identification and understanding of the risk factors for paralysis must be weighed against the benefits of surgery, followed by a detailed discussion with the patient. In the event of a SCI, the physician must provide support to the patient and family members, and guide the patient through the process of recovery. Despite the medical and psychological problems that are faced by the patient, the majority of acute SCI patients report good or excellent quality of life at long-term follow-up.[27]

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Senior Abstract

Maintenance of Correction in Scoliosis Associated with Cerebral Palsy

Patrick J. Cahill, Joshua M. Pahys, Justin Iorio, Jahangir K. Asghar, Melissa Morrison, Paul D. Sponseller, Amer F. Samdani

Senior Bio Questionnaire

- Full Name: Justin Avery Iorio
- Birthdate: 6/30/1983
- Hometown: Syracuse, NY
- Undergraduate School: Northeastern University
- Undergraduate Degree: BS, Neuroscience
- Medical School: SUNY Upstate Medical University
- Fellowship: Hospital for Special Surgery–Spine Surgery
- Significant Other: Natalya Iorio
- Children: None
- Hobbies: Outdoor athletics

Introduction

The ability to correct spinal and pelvic deformity associated with cerebral palsy (CP) with spinal fusion surgery is well documented. Whether that correction is maintained long-term is less well understood. We report radiographic outcomes of patients with CP immediately postoperatively and at two-year follow-up. We hypothesize that patients who underwent spinal fusion maintained a predictable and lasting improvement in spinal alignment in scoliosis associated with CP.

Methods

We performed a retrospective analysis of a multicenter, prospective, controlled study of patients with CP and severe spinal deformity. Baseline (B), first erect (FE) post-op, and two-year follow-up radiographs were analyzed. All patients had a minimum two-year follow-up.

Results

150 patients met the inclusion criteria. The average age at surgery was 14.1 years. 55% were male. The Cobb angle of the major deformity was corrected 68% from an average of 82° to 27° ($p < 0.001$). Only slight progression of deformity occurred from FE to two-year follow-up: Cobb angle (27° to 29°, $p = 0.001$), pelvic obliquity (7.6° to 9.1°, $p = 0.001$), and thoracic kyphosis (37° to 35°, $p = 0.069$). The postoperative progression, while statistically significant, is not likely clinically significant in magnitude.

Discussion

A two-year follow-up study of radiographic outcomes for patients with CP and severe scoliosis showed that operative intervention provided good radiographic outcomes that are maintained at two years.

	Baseline	First Erect	Two-year Follow-up	Baseline vs. Two-year (p)	First Erect vs. Two-year (p)
Cobb°	82	27	29	<0.001	0.001
Pelvic Obliquity°	27	8	9	<0.001	0.001
% Correction from Baseline	—	68	65	—	—

Senior Abstract

Ulnar Distraction Osteogenesis for Treatment of Ulnar Based Forearm Deformities in Multiple Hereditary Exostoses

Stephen Refsland, MD; Scott Kozin, MD; Dan Zlotolow, MD

Senior Bio Questionnaire

- Full Name: Stephen Andrew Refsland
- Birthdate: 6/15/1978
- Hometown: St. Louis, MO
- Undergraduate School: University of Pennsylvania
- Undergraduate Degree: BA, Philosophy, Politics and Economics
- Medical School: Drexel University College of Medicine
- Fellowship: St. Lukes-Roosevelt CV Starr Hand Fellowship
- Significant Other: Joanna Refsland
- Children: None
- Hobbies: Surfing, snowboarding

Purpose

MHE is a rare genetic disorder that is characterized by multiple osteochondromas. Forearm deformities are found in 30–60% of those affected with the condition. The vast majority of forearm deformities result from a relative shortening of the ulna due to growth disturbance of the distal ulnar physis resulting in a varus bow. At our institution, we retrospectively identified 19 children over the past 10 years with a progressive deformity of one or both of their forearms who had undergone distraction osteogenesis of the ulna to treat an ulnar based forearm deformity. The purpose of this study was to publish outcomes of distraction osteogenesis in a rare deformity for which treatment is not well studied so as to add to the knowledge currently available.

Methods

We identified 18 MHE patients over the past 10 years at our institution that had distraction osteogenesis of the ulna through an external fixator for progressive forearm deformity. We used radiographic parameters to compare preoperative and postoperative radiographs at non-standardized time intervals. We used medical records to collect demographic data, identify range of motion and subjective patient measures preoperatively and then postoperatively.

Results

A total of 22 operations were performed on 18 patients. There was a statistically significant improvement in a number of the radiographic parameters: ulnar and radial radius of curvatures, ulnar variance, carrying angle of the elbow, angle of the radius relative to the shaft, and radiocapitellar congruency postoperatively. There was a trend towards improvement in pronation, supination, and total arc of motion, although not statistically significant. There was one case of premature consolidation, eight cases of minor pin site infection, and one case of a major pin site complication that required admission to the hospital for IV antibiotics.

Conclusions

Ulnar lengthening osteotomy through distraction osteogenesis is an effective surgery for those with MHE and ulnar based forearm deformities. Looking retrospectively at our results, a number of radiographic parameters improved without harming forearm function. These included a trend towards radiocapitellar reduction and restoration of the carpal bones axis to an anatomic normal position. There was only one major pin site infection, the rest of the infections were effectively treated with antibiotics as an outpatient. We believe our results support the use of this treatment.

Significance

The results at our institution further support the efficacy of distraction osteogenesis in the treatment of forearm deformities in patients with MHE.

Senior Abstract

Senior Bio Questionnaire

- Full Name: Craig David Steiner
- Birthdate: 5/4/1983
- Hometown: Brooklyn, NY
- Undergraduate School: Queens College, City University of New York
- Undergraduate Degree: BA, Philosophy
- Medical School: Albert Einstein College of Medicine of Yeshiva University
- Fellowship: Hospital for Special Surgery–Spine Surgery
- Significant Other: Tehilla S. Steiner, MD
- Children: Samantha Morgan Steiner
- Hobbies: Family, ancient history, classical antiquity and literature

The Effect of the First Assistant on Outcomes in Surgery for Adolescent Idiopathic Scoliosis

Patrick J. Cahill, Joshua M. Pahys, Craig Steiner, Kimberly Hayes, Jahangir K. Asghar, Randal R. Betz, Harms Study Group, Amer F. Samdani

Summary: We evaluated the effect of the level of training of the physician-in-training first assistant on outcomes in surgery for adolescent idiopathic scoliosis (AIS). Neither clinical outcomes (estimated blood loss, surgical time) nor radiographic outcomes (% correction, alignment) were different whether a fellow or resident was the first assistant.

Hypothesis: Cases with first assistants in their fellowships will have better radiographic and clinical outcomes than those with residents as the first assistant.

Design: Retrospective review of a multicenter prospectively collected AIS database.

Introduction: Pediatric spinal deformity surgery is technically demanding and involves steep learning curves. With safety as a paramount concern in AIS surgery, it is reasonable to question how the trainee's involvement as first assistant affects patient outcome.

Methods: We compared outcomes of posterior spinal fusion surgeries for AIS with a minimum of two-year follow-up stratified based on the level of training of the first assistant as a resident (R) or fellow (F). Radiographic results, blood loss, operative time, and days of hospitalization were analyzed and compared between the two groups. We included only centers that utilized both levels of physicians as first assistants.

Results: 252 AIS surgeries from eight centers were identified. 185 cases were performed with a fellow as the first assistant and 67 with a resident. Preoperative radiographic and demographic parameters were not different among the groups. The level of the first assistant did not have an association with surgical time (F: 319 min. v. R: 312, p = 0.694), EBL (F: 878 mL v. R: 996, p = 0.298), cell saver transfusion volume (F: 250 mL v. R: 329, p = 0.121), or post-op Cobb angle (F: 17° v. R: 17°, p = 0.398).

Conclusion: Clinical and radiographic outcomes were not affected by the level of training of the first assistant.

		Fellow	Resident	*p* Value
Preoperative characteristics	Lenke Distribution			0.112
	Primary curve Cobb	57°	56°	0.638
	Thoracic Cobb	54°	53°	0.584
	Lumbar Cobb	40°	43°	0.198
	Primary curve flexibility (%)	39	36	0.209
	Thoracic Kyphosis	24°	21°	0.169
	Lumbar Lordosis	59°	60°	0.586
Perioperative outcomes	Surgical time (min.)	319	312	0.694
	EBL (mL)	878	996	0.298
	Cell saver volume (mL)	250	329	0.121
Two-year radiographic outcomes	Correction (%)	71	69	0.217
	Primary curve Cobb	17°	17°	0.398
	Thoracic Cobb	16°	18°	0.301
	Lumbar Cobb	15°	15°	0.824
	Thoracic Kyphosis	22°	20°	0.185
	Lumbar Lordosis	54°	56°	0.12

Senior Abstract

Senior Bio Questionnaire

- Full Name: Richard Jason Tosti
- Birthdate: 7/1/1982
- Hometown: Yardley, PA
- Undergraduate School: Pennsylvania State University
- Undergraduate Degree: BS, General Science
- Medical School: Temple University School of Medicine
- Fellowship: Hand, Wrist, Elbow and Microvascular Surgery; Harvard Medical School, Massachusetts General Hospital
- Significant Other: Alana Tosti
- Children: Alex Tosti
- Hobbies: Acoustic guitar, muay thai boxing, wrestling
- Interesting Fact: Lived in Thailand for a year and competed in muay thai boxing

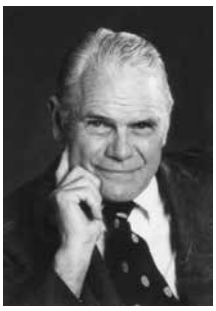
Is Antibiotic Prophylaxis Necessary in an Elective Soft Tissue Hand Surgery?

Rick Tosti, MD; John R. Fowler, MD; Joe Dwyer, MD; Joseph Thoder, MD; Asif M. Ilyas, MD

Antibiotic prophylaxis for clean soft tissue hand surgery is not yet defined. Current literature focuses on overall orthopedic procedures, traumatic hand surgery, and carpal tunnel release. However, a paucity of data exists regarding the role of antibiotic prophylaxis in a broader variety of soft tissue hand procedures. The goal of the current study was to evaluate the rates of surgical site infection following elective soft tissue hand surgery with respect to administration of prophylactic antibiotics. A multicenter, retrospective review was performed on 600 consecutive elective soft tissue hand procedures. Procedures with concomitant implant or incomplete records were excluded. Antibiotic delivery was given at the discretion of the attending surgeon. Patient comorbidities were recorded. Outcomes were measured by the presence of deep or superficial infections within 30 days postoperatively. The four most common procedures were carpal tunnel release, trigger finger release, mass excision, and first dorsal compartment release. The overall infection rate was 0.66%. All infections were considered superficial, and none required surgical management. In patients who received antibiotic prophylaxis (n = 212), the infection rate was 0.47%. In those who did not receive prophylaxis (n = 388), the infection rate was 0.77%. These differences were not statistically significant (P = 1.00).

Special Event

The Howard H. Steel Lecture at the Philadelphia Orthopaedic Society



Presented by:

Dr. Mininder S. Kocher
Associate Director, Division of Sports Medicine, Harvard Medical School and Boston Children's Hospital

"Management of ACL Injuries in Children and Adolescents: Getting to PLUTO"

This year saw another phenomenal speaker at the annual Howard H. Steel Lecture series in Dr. Mininder S. Kocher. Dr. Scott Kozin of Shriner's Hospital for Children graciously provided a rousing introduction to the day's honored speaker and provided some historical and unique insight into Dr. Howard Steel for whom the series is named.

Dr. Kocher is currently an Associate Director in the Division of Sports Medicine at Harvard Medical School and Boston Children's Hospital, and is a leader in his field. He gave a thought-provoking discussion illustrating our approach to ACL management in the skeletally immature and elucidated possible future endeavors and pursuits. He also then participated in a well-attended panel discussion on the same topic, along with Dr. Alfred Atanda (DuPont Pediatric Sports Medicine), Dr. Shannon Safier (St. Christopher's Hospital Pediatric Sports Medicine) and Dr. Lawrence Wells (CHOP Associate Director of Sports Medicine), as pictured below. This year again found great success in honoring Dr. Steel, and was well received by the residents and faculty from all of the Philadelphia Orthopaedic Society programs to which Dr. Steel has been so influential. We are proud to again continue this proud tradition in the name of our own Dr. Howard H. Steel.

Colin Mansfield

Left to right: Dr. Mininder Kocher, Dr. Alfred Atanda, Dr. Shannon Safier, Dr. Lawrence Wells

Special Event

American Academy of Orthopaedic Surgeons Annual Meeting 2014

March 11–15, 2014 — New Orleans, LA

The heat was strong in Louisiana last year, but record temperatures were recorded when Temple University Orthopaedics hit the scene. The convention center in New Orleans was roaring with the latest from orthopaedic surgeons from around the globe, but our department made a strong showing with four presentations including two that were recognized with national awards.

Below is a list of our presented research:

Antibiotic Sensitivities in Hand Infections: Changing MRSA Drug Resistance Profiles
By Rick Tosti, John Fowler, Alyssa Schaffer, and Asif Ilyas
Selected as a "top poster" which will be featured on the "guided poster tour session" by Terry Light MD

Prospective Evaluation of Pronator Quadratus Repair Following Volar Plating of Distal Radius Fractures
By Rick Tosti and Asif Ilyas
Re-presented in a special exhibit as the Julian M. Bruner Award winner for "Best Poster" at the ASSH Meeting in San Francisco. Published as the lead article in the September issue of *JHS.*

Impact of Statins on Postoperative Venous Thromboembolic Events Following Total Knee and Hip Replacements
By Kate Criner and Arianna Trionfo
Winner of the 2013 Temple University Resident Research Day

Vascular Complications in Total Knee Arthroplasty: A Newly Recognized Complication and Lessons from Our Practice
By Andrew Star and Richard Han

Rick Tosti, MD

Special Event

Resident Research Day

April 26, 2014

On April 26, 2014, the Temple University Department of Orthopaedic Surgery held its annual Resident Research Day. This event served as a platform for Temple's current orthopaedic surgery residents to showcase their research initiatives. Frank Liporace, MD, Associate Professor of Orthopaedic Surgery at NYU/Hospital for Joint Diseases, was our keynote speaker guest judge. Dr. Liporace is a leader in the field of Orthopaedic Trauma and he gave a lecture entitled "Pilon Fractures: Bony and Soft Tissue Management." His talk highlighted some of the newest research and shed light on current techniques in management of these often devastating injuries.

Jim Lachman, MD (PGY-2) won first place for his biomechanical study of meniscal repair techniques. His project, which was a collaboration between the Departments of Orthopaedic Surgery and Mechanical Engineering, found no significant difference between failure rates for newer, more costly suture technologies and the currently accepted meniscal repair methods.

Rick Tosti, MD (PGY-4) took second place for his work entitled "Emerging multi drug resistance in hand infections caused by methicillin-resistant Staphylococcus Aureus (MRSA)." His study found that increasing bacterial resistance to widely-used empiric antibiotics may necessitate use of novel antibiotic regimens for treatment of hand infections. Dr. Tosti's work was also published in the *Journal of Bone and Joint Surgery.*

Third place went to Scott Barbash, MD (PGY-5) for his project entitled "Optimal differentiation of tissue types using combined mid- and near-infrared spectroscopy." This investigation, done in collaboration with the Department of Bioengineering, demonstrated a spectroscopy technique that can be used to verify the incorporation of tendon grafts used to repair ACL ruptures.

Arianna Trionfo, MD

Special Event

Alumni Day 2014

The LuLu Country Club served as the location for the Temple-Shriners Alumni meeting of Temple University Hospital's Department of Orthopedics and Sports Medicine. As in years past, this picturesque golf course has been the perfect backdrop for Temple's family of physicians to learn and meet with their colleagues and friends.

The event began with a lecture on current concepts in patellofemoral problems, given by Wayne Sebastianelli, MD, Director of Athletic Medicine at Penn State University. Dr. Milo Sewards then presented "An Open Forum on Cutting-edge Technology in Orthopaedics." These lectures were followed by a panel discussion on "The Team Physician in the Modern Era," where Drs. Sebastianelli and Moyer highlighted several significant changes in sports medicine.

Kate Harper and Arianna Trionfo hit the links in matching activewear

The scientific program concluded with presentations by the recipients of the Resident Research Award. Jim Lachman (1st place), Rick Tosti (2nd place) and Scott Barbash (3rd place) were afforded the opportunity to showcase their academic achievements in the presence of many distinguished alumni.

Residents and alumni then took to the fairway to demonstrate their athletic ability. Several foursomes of golfers proved that their talents reach far beyond the walls of the operating room.

Arianna Trionfo

Special Event

2014 Philadelphia Orthopaedic Trauma Symposium Hosted by Temple Orthopaedics

Dr. Thoder demonstrating periarticular reconstruction of the distal humerus

The 6th annual Philadelphia Orthopaedic Trauma Symposium was held on June 6–7th, 2014 at Temple Hospital's Medical Education and Research Building. The event was organized and led under the direction of Temple's own Dr. Saqib Rehman, MD and Jaimo Ahn, MD (University of Pennsylvania), and featured two distinguished keynote speakers, Dr. Toney Russell, MD (University Rhode Island) and Dr. Christopher Born, MD (University of Tennessee). The course faculty included 25 orthopaedic surgeons from Philadelphia and the surrounding area hospitals, including presentations from Temple faculty members, Dr. Saqib Rehman, Dr. Christopher Haydel, MD, Dr. Joseph Thoder, MD, Dr. Milo Sewards, MD, Dr. William DeLong, MD, and Dr. Alyssa Schaffer, MD. This year's event was very successful, with a large body of participants including attending faculty, residents, physician assistants, nurses, and educators from over 10 different institutions.

The main focus of this year's symposium aimed to highlight modern fracture care, minimally invasive osteosynthesis, and emerging methodologies in orthopaedic traumatology; however, it also succeeded in covering a large sample of additional relevant trauma topics. Presentations provided a current review of techniques and literature, as well as case discussions amongst all members in attendance. Topics included locking and periarticular plate concepts, bone grafting options, advances in pediatric fracture care, tibial nailing methods, and an update on the current concepts of damage control orthopaedics and staging, just to name a few.

William Smith, MD

Poster presentations submitted by area residents and medical students were on display

Special Event

Ponderosa Bowl 2014

Cherry Team Uses Balanced Team Attack to Take the Cup

The fourth edition of the Temple Orthopedics Ponderosa Bowl, sponsored by Dr. Joseph Thoder, Inc., was held in front of a cold, yet rowdy crowd of one on December 7th, 2014. The game featured fierce matchups between returning veterans set on avoiding injury, as predetermined by the bimodal prevalence they so often preach in morning conference, and the young new interns eager to prove their match day results were no mistake.

The Cherry Team was lead by team captain, and former Division I football standout, Jim Lachman, who used his unmatched hatred of even the most appropriate Emergency Room consult as energetic motivation. His teammates included Drs. Christopher Haydel, Dustin Greenhill, Megan Reilly, and Justin Kistler. The White Team was led by intern standout, Peter "Revisedeh, Eyvazzadizzle, Rehmazzadeh, Eyvazzawhat?" Eyvazzadeh. His teammates included Drs. Rick Tosti, Steve Refsland, William Smith, and John Jennings. As in years past, the playing conditions were suboptimal, with rain soaked sod and slick grass, which proved difficult to gain traction upon despite all players outfitted with the finest 10-year-old, almost soleless, running sneakers. The Cherry Team executed a flawless demonstration of an "Andy Reid style" failure of clock management and subsequently allowed time to expire on the goal line, despite having a full compliment of timeouts remaining. The Cherry Team held a seven point lead; however, the White Team looked forward to the start of the second half, riding cheers of "goal line stand!"

The second half was more one sided than the first, led by dominant offensive performances of Justin "Hands" Kistler and Christopher "Megatron" Haydel for the Cherry Team. Despite inspirational and enthusiastic leadership from chiefs Rick Tosti and Steve Refsland, the White Team ultimately fell victim to the balanced attack of the Cherry Team as the quiet, often caught blushing, Megan Reilly provided the game clenching touchdown catch with one minute. Crowned heroine of the game, Reilly was quoted afterwards stating softly, "I was open the whole game; no one could (was) covering me. It wasn't until the last few plays of the game they started sending passes my way. And boy, were they happy they did."

The game was followed by cold refreshments, hot food, and a viewing of real NFL-style football, provided by the home of lead official, Dr. Thoder, whose hospitality and resident support remains unmatched.

William Smith, MD

Departmental News

Faculty

Temple University Department of Orthopaedic Surgery and Sports Medicine

Interim-Chairman

Pekka Mooar, MD

Professors

Joseph Thoder, MD, *The John W. Lachman Professor*
William DeLong, MD
Ray Moyer, MD, *The Howard H. Steel Professor*
Joseph Torg, MD
F. Todd Wetzel, MD, *Vice Chairman*

Associate Professors

Easwaran Balasubramanian, MD
Saqib Rehman, MD
Bruce Vanett, MD
Albert Weiss, MD

Assistant Professors

Joseph Eremus, MD
Christopher Haydel, MD
Cory Keller, DO
Eric Kropf, MD
Matthew Lorei, MD
Michelle Noreski, DO
David Pashman, MD
J. Milo Sewards, MD

Adjunct Faculty — Philadelphia Shriners Hospital

Scott Kozin, MD, *Chief of Staff*
Randal Betz, MD, *Emeritus Chief of Staff*
Philip Alburger, MD
Patrick Cahill, MD
Richard Davidson, MD
Corinna Franklin, MD
Howard Steel, MD, *Emeritus Chief of Staff*
Joshua Pahys, MD
Amer Samdani, MD
William Schrantz, MD
Harold van Bosse, MD
Daniel Zlotolow, MD

Adjunct Faculty — Abington Memorial Hospital

Andrew Star, MD, *Chief of Orthopaedics*
Shyam Brahmabhatt, MD
David Craft, MD
Matthew Craig, MD
Greg Galant, MD
Michael Gratch, MD
Victor Hsu, MD
Moody Kwok, MD
Guy Lee, MD
Thomas Peff, MD
T. Robert Takei, MD
Jeffrey Vakil, MD

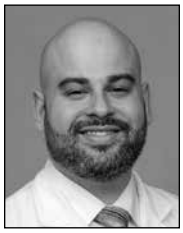
Adjunct Faculty — St. Christopher's Hospital for Children

Peter Pizzutillo, MD, *Chief of Orthopaedics*
Alison Gattuso, DO
Martin Herman, MD
Michael Kwon, MD
Juan Realyvasquez, MD
Joseph Rosenblatt, DO
Shannon Safier, MD
Michael Wolf, MD

Temple University Hospital
Department of Orthopaedic Surgery and Sports Medicine
Faculty 2014–2015

Easwaran Balasubramanian, MD
Joint Reconstruction
General Orthopaedics

Joseph Eremus, MD
Foot and Ankle
General Orthopaedics



Christopher Haydel, MD
Orthopaedic Trauma
General Orthopaedics

Cory Keller, DO
Sports Medicine

Eric Kropf, MD
Sports Medicine
General Orthopaedics

Matthew Lorei, MD
Joint Reconstruction
General Orthopaedics

Pekka Mooar, MD
Sports Medicine
Joint Reconstruction
General Orthopaedics

Ray Moyer, MD
Howard Steel Professor
Sports Medicine

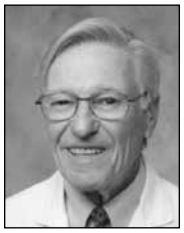
Michelle Noreski, DO
Sports Medicine

David Pashman, MD
General Orthopaedics

Saqib Rehman, MD
Orthopaedic Trauma
General Orthopaedics

J. Milo Sewards, MD
Sports Medicine

Joseph Thoder, MD
John W. Lachman Professor
Hand & Upper Extremity
General Orthopaedics



Joseph Torg, MD
Sports Medicine

Bruce Vanett, MD
General Orthopaedics

Albert Weiss, MD
Hand & Upper Extremity
General Orthopaedics

F. Todd Wetzel, MD
Vice-Chairman
Spine Surgery

Orthopaedic Surgery
& Sports Medicine
Temple University Health System

Temple University Hospital
Department of Orthopaedic Surgery and Sports Medicine
House Staff 2014–2015

Justin Iorio, MD

Hometown: Syracuse, NY

Undergraduate: Northeastern University

Medical School: State University of New York Upstate Medical Center

Fellowship: Spine – Hospital for Special Surgery

Rick Tosti, MD

Hometown: Yardley, PA

Undergraduate: Pennsylvania State University

Medical School: Temple University School of Medicine

Fellowship: Hand, wrist, elbow, microvascular – Harvard/ Massachusetts General Hospital

Craig Steiner, MD

Hometown: Brooklyn, NY

Undergraduate: Queens College, City University of New York

Medical School: Albert Einstein College of Medicine

Fellowship: Spine – Hospital for Special Surgery

Stephen Refsland, MD

Hometown: St. Louis, MO

Undergraduate: University of Pennsylvania

Medical School: Drexel University College of Medicine

Fellowship: Hand – St. Luke's Roosevelt

Colin Mansfield, MD

Hometown: Seattle, WA

Undergraduate: University of Washington

Medical School: Temple University School of Medicine

Interest: Sports

Kasey Komperda, MD

Hometown: Chicago, IL

Undergraduate: University of Illinois

Medical School: University of Pittsburgh School of Medicine

Interest: Sports

Rupam Das, MD

Hometown: Coatesville, PA

Undergraduate: Drexel University

Medical School: Temple University School of Medicine

Interest: Sports

Mark Solarz, MD

Hometown: Malvern, PA

Undergraduate: University of Notre Dame

Medical School: Jefferson Medical College

Interest: Hand

Temple University Hospital
Department of Orthopaedic Surgery and Sports Medicine
House Staff 2014–2015 *(cont.)*

Arianna Trionfo, MD

Hometown: Glassboro, NJ

Undergraduate: Loyola College in Maryland

Medical School: UMDNJ – Robert Wood Johnson

Interest: Pediatrics, sports

James Lachman, MD

Hometown: Bryn Mawr, PA

Undergraduate: Bucknell University

Medical School: Temple University School of Medicine

Interest: Foot and ankle, adult reconstruction

Anastassia Newbury, MD

Hometown: Omaha, NE

Undergraduate: University of Iowa

Medical School: University of Nebraska College of Medicine

Interest: Hand, spine

Dustin Greenhill, MD

Hometown: West Palm Beach, FL

Undergraduate: U.S. Military Academy (West Point)

Medical School: Temple University School of Medicine

Interest: Hand, sports, pediatrics

Katherine Harper, MD

Hometown: London, Ontario, Canada

Undergraduate: McMaster University

Medical School: Royal College of Surgeons in Ireland School of Medicine

Interest: Adult reconstruction, foot and ankle

John Jennings, MD

Hometown: Allentown, PA

Undergraduate: Pennsylvania State University

Medical School: Temple University School of Medicine

Interest: Hand, trauma, sports

James Bennett, MD

Hometown: Charlotte, VT

Undergraduate: Colby College

Medical School: St. George's University School of Medicine

Interest: Pediatric spine

William Smith, MD

Hometown: Havertown, PA

Undergraduate: Pennsylvania State University

Medical School: Jefferson Medical College

Interest: Hand, adult reconstruction

Temple University Hospital
Department of Orthopaedic Surgery and Sports Medicine
House Staff 2014–2015 *(cont.)*

Justin Kistler, MD

Hometown: Horsham, PA

Undergraduate: University of Pittsburgh

Medical School: Temple University School of Medicine

Interest: Hand/upper extremity, adult reconstruction

Courtney Quinn, MD

Hometown: Potomac, MD

Undergraduate: University of Southern California

Medical School: Georgetown University School of Medicine

Interest: Undecided

Megan Reilly, MD

Hometown: Longwood, FL

Undergraduate: University of Florida

Medical School: Georgetown University School of Medicine

Interest: Undecided

Peter Eyvazzadeh, MD

Hometown: Bethlehem, PA

Undergraduate: Bucknell University

Medical School: Penn State University College of Medicine

Interest: Undecided

Temple University Department of Orthopaedic Surgery and Sports Medicine: Research Update 2014–2015

Awards

"Highlighted Poster" for Hand and Wrist Guided Poster Tours at the American Academy of Orthopaedic Surgeons Annual Meeting 2014. Tosti R, Samuelsen B, Bender S, Gaughan J, Schaffer AA, Ilyas AM. Emerging multi-drug resistance of methicillin resistant staphylococcus aureus in hand infections..

Podium Presentations

Kozin S, Refsland S, Zlotolow D. Ulnar Distraction Osteogenesis for Treatment of Ulnar Based Forearm Deformities in Multiple Hereditary Exostoses. Presented at the *American Academy of Orthopaedic Surgeons Annual Meeting,* Las Vegas, NV, March 2015.

Tosti R, Trionfo A, Ilyas AM. Risk Factors Associated with Clindamycin Resistance in Hand Infections Caused by MRSA. Presented at the *American Association for Hand Surgery Annual Meeting,* Paradise Island, Bahamas, January 2015.

Tosti R, Ilyas AM. Prospective evaluation of pronator quadratus repair following volar plate fixation of distal radius fractures. Presented at the *American Association for Hand Surgery Annual Meeting,* Kauai, HI, January 2014.

Mooar PA, Robinson AL. Transforming the Disruptive Physician Investigation Process to Effect Positive Change in an Organization. *National Association of Medical Staff Services,* New Orleans, LA, 2014.

Komperda K, Mansfield C, Ali S, Rehman S. Radiation Reduction in Complex Fracture Patterns: The Distal Tibia Pilon Fracture as a Model. Presented at the *One AO: Common Problems and Common Solutions across Disciplines,* Las Vegas, NV, February 6, 2015.

Poster Presentations

Mansfield C, Komperda K, Ail S, Rehman S. CT Radiation Dosing Can Be Substantially Lowered in Evaluation and Operative Planning of Periarticular Fractures. *American Academy of Orthopaedic Surgeons Annual Meeting,* Las Vegas, NV, March 2015.

Greenhill D, Star A. Minimally Invasive Total Hip Arthroplasty: Can We Reduce the Likelihood of Intraoperative Fracture? *American Academy of Orthopaedic Surgeons Annual Meeting,* Las Vegas, NV, March 2015.

Tosti R, Samuelsen B, Bender S, Gaughan J, Schaffer AA, Ilyas AM. Emerging multi-drug resistance of methicillin resistant staphylococcus aureus in hand infections. Alternate paper presentation at the *American Academy of Orthopaedic Surgeons Annual Meeting,* New Orleans, LA, March 2014.

Tosti R, Samuelsen B, Bender S, Gaughan J, Schaffer AA, Ilyas AM. Emerging multi-drug resistance of methicillin resistant staphylococcus aureus in hand infections. *American Academy of Orthopaedic Surgeons Annual Meeting,* New Orleans, LA, March 2014.

Star A, Han R. Vascular Complications in Total Knee Arthroplasty: A Newly Recognized Complication and Lessons from our Practice. *American Academy of Orthopaedic Surgeons Annual Meeting,* New Orleans, LA, March 2014.

Criner K, Trionfo A. Impact of Statins on Postoperative Venous Thromboembolic Events Following Total Knee and Hip Replacements. *American Academy of Orthopaedic Surgeons Annual Meeting,* New Orleans, LA, March 2014.

Tosti R, Ilyas AM. Prospective evaluation of pronator quadratus repair following volar plate fixation of distal radius fractures. American Society for Surgery of the Hand: Julian M. Bruner Award Exhibit at the *American Academy of Orthopaedic Surgeons Annual Meeting,* New Orleans, LA, March 2014.

Tosti R, Samuelsen B, Bender S, Gaughan J, Schaffer AA, Ilyas AM. Emerging multi-drug resistance of methicillin resistant staphylococcus aureus in hand infections. *American Association for Hand Surgery Annual Meeting,* Kauai, HI, January 2014.

Tosti R, Atiemo E, Jennings J, Baker J, Gaughan J, Mooar P, Schaffer AA, Ilyas AM. Prospective evaluation of vitamin D levels in young adults with and without low energy distal radius fractures. *American Association for Hand Surgery Annual Meeting,* Kauai, HI, January 2014.

Jennings J, Iorio J, Kleiner M, Gaughan J, Star A. Does intraoperative fluoroscopy improve component position during anterior hip arthroplasty? Accepted to *World Arthroplasty Congress,* Paris, France, April 2015.

Publications in Peer-reviewed Journals

Tosti R, Trionfo A, Gaughan J, Ilyas, AM. Risk Factors Associated with Clindamycin Resistance in Methicillin Resistant Staphylococcus Aureus in Hand Abscesses. *J Hand Surgery Am.* Accepted. Awaiting publication April 2015.

Tosti R, Samuelsen B, Bender S, Gaughan J, Schaffer AA, Ilyas AM. Emerging multi-drug resistance patterns of methicillin resistant staphylococcus aureus in hand infections. *J Bone Joint Surg Am.* 2014 Sep 17; 96(18):1535–40. PMID:25232077.

Fowler JR, Munsch BS, Tosti R, Hagberg WC, Imbriglia JE. A comparison of ultrasound and electrodiagnostic testing for the diagnosis of carpal tunnel syndrome using a validated clinical tool as the reference standard. *J Bone Joint Surg Am.* 2014 Sep 3;96(17):e148. PMID:25187592.

Tosti R, Ilyas AM, Mellema J, Guitton TG, Ring D. Interobserver variability in the treatment of small finger metacarpal neck fractures. *J Hand Surg Am.* 2014 Sep;39(9):1722–7. PMID:25034789.

Zlotolow DA, Tosti R, Ashworth S, Kozin SH, Abzug JM. Developing a pollicization outcomes measure. *J Hand Surgery Am.* 2014 Sep;39(9): 1784–91. PMID:25091337.

Tosti R, Foroohar A, Pizzutillo PD, Herman MJ. Smooth wire infections in pediatric orthopaedics: a 17-year experience. *J Pediatr Orthop.* 2014 Apr 29. [Epub ahead of print] PMID: 24787310.

Tosti R, Iorio J, Fowler JR, Gaughan J, Thoder JJ, Schaffer AA. Povidone-iodine soaks for hand abscesses: A prospective randomized trial. *J Hand Surg Am.* 2014 May;39(5):962–5. PMID: 24636027.

Jevsevar DS, Brown GA, Jones DL, Matzkin EG, Manner PA, Mooar P, Schousboe JT, Stovitz S, Sanders JO, Bozic KJ, Goldberg MJ, Martin WR 3rd, Cummins DS, Donnelly P, Woznica A, Gross L. American Academy of Orthopaedic Surgeons. The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition. *J Bone Joint Surg Am.* 2013 Oct 16;95(20):1885–6. PMID:24288804.

Iorio J, Verma K, Samdani AF, Cahill PJ, Betz RR, Singla A. Minimally invasive lateral interbody fusion in the treatment of scoliosis associated with myelomeningocele. 2015. (Accepted to *Surgical Technology International.*)

Jakoi AM, Iorio J, Cahill PJ. Autologous bone graft harvesting: a review of grafts and surgical techniques. 2015. (Accepted to *Musculoskeletal Surgery.*)

Iorio J, Jakoi AM, Rehman S. Percutaneous fixation of the posterior pelvic ring: a review of sacroiliac screws. 2015. (Accepted to *Orthopedic Clinics of North America.*)

Iorio J, Criner K, Rehman S, Meizinger C, Haydel C. Nerve and tendon injury with percutaneous fibular pinning: a cadaveric study. *Injury.* 2014 Dec;45(12):2051–4. PMID 25241722.

Walsh KP, Rehman S, Goldhirsh J. Disparities in internet usage by orthopaedic outpatients. *Orthopedics* 37(2):e133–140 (2014).

Rehman S. Trauma. *Orthop Clin North Am.* 45(1) xv.
Rehman S. Trauma. *Orthop Clin North Am.* 45(2) xv.
Rehman S. Trauma. *Orthop Clin North Am.* 45(3) xvii.
Pipitone PS, Rehman S. Management of traumatic bone loss in the lower extremity. *Orthop Clin North Am.* 45:4(469-82) 2014 Oct.
Rehman S. Trauma. *Orthop Clin North Am.* 45(5) xv.
Cahill P, Steiner CD, Dakwar E, Trobisch PD, Harms Study Group, Lonner BS, Newton PO, Shah SA, Sponseller PD, Shufflebarger HL, Samdani AF. Sagittal Spinopelvic Parameters in Scheuermann's Kyphosis: A Preliminary Study. *Spine Deformity.* (Accepted for publication 2015.)

Textbook Chapters

Quinn C. Tosti R. Infections of the Hand. In Chapman MW, James MA (eds): *Chapman's Comprehensive Orthopaedic Surgery, 4th ed.* New Delhi, India: Jaypee Medical Publishers. Expected publication 2016.

Tosti R, Thoder JJ. Operative treatment of lesser and greater arc injuries. In Hunt TR, Wiesel SW (eds): *Operative Techniques in Orthopaedic Surgery, 2nd ed.* Philadelphia, PA: Lippincott Williams, and Wilkins. Expected publication 2015.
Jennings J, Tosti R, Sewards JM. Arthroscopic treatment of lateral epicondylitis. In Young-Park J (ed): *Sports Injuries to the Shoulder and Elbow, 1st ed.* New York, NY: Springer. Expected publication 2015.
Iorio J, Pahys JM, Samdani AF, Betz RR, Cahill PJ. Vertebral Body Stapling for AIS. In *The Growing Spine: Management of Spinal Disorders in Young Children, 2nd ed.,* edited by Akbarnia B. 2015. (accepted)

Joseph J. Thoder
Orthopaedic Excellence Award

"In recognition of Dr. Thoder's steadfast dedication to the Temple Orthopaedic Surgery Residency. Through his mentorship, we pursue academic and clinical excellence, while learning the importance of heritage, teamwork, and family. This award, presented by the chief residents, honors the orthopaedic resident who best exemplifies the standards of scholarly achievement and personal excellence set forth by Dr. Thoder."

Given as a graduation gift by the class of 2010, Drs. Abi Foroohar, Allan Tham, Ifran Ahmed, and John Parron fund a yearly award given to the resident that demonstrates qualities commensurate with Dr. Thoder's vision of a Temple Orthopaedic Surgeon. Selected from the graduating chief resident class, the recipient is presented with a cash prize and a plaque.

This year, **Arianna Trionfo** (Class of 2017) was selected by Scott Barbash, Rich Han, Emeka Nwodim, and Sam Popinchalk (Class of 2014).

Previous Winners:
2013 — Rupam Das, MD
2012 — Matthew Kleiner, MD
2011 — Richard Han, MD
2010 — John Fowler, MD

Arianna Trionfo, MD

Faculty Award for Excellence in Orthopaedic Education

"Give a man a fish and you feed him for a day.
Teach a man to fish and you feed him for a lifetime."

The graduating chief resident class recognizes a faculty member who was particularly influential in their development as surgeons. The recipient is presented with a plaque and a lifetime of appreciation.

This year, **Dr. Joseph Thoder** was selected by Scott Barbash, Rich Han, Emeka Nwodim, and Sam Popinchalk (Class of 2014).

Previous Winners:
2013 — Saqib Rehman, MD
2012 — Joseph Thoder, MD
2011 — Eric Kropf, MD
2010 — Saqib Rehman, MD
2009 — Joseph Thoder, MD
2008 — Michael Clancy, MD
2007 — Easwaran Balasubramanian, MD
2006 — Joseph Thoder, MD
2005 — Christopher Born, MD

Joseph Thoder, MD

Snapshots from 2014–2015

Ugly Christmas Sweater Day for Joints Silo Rounds: Kate Harper, Will Smith, Colin Mansfield, and Dr. Bala

James Bennett after tanning in Hawaii (the contrast was NOT enhanced in this photo)

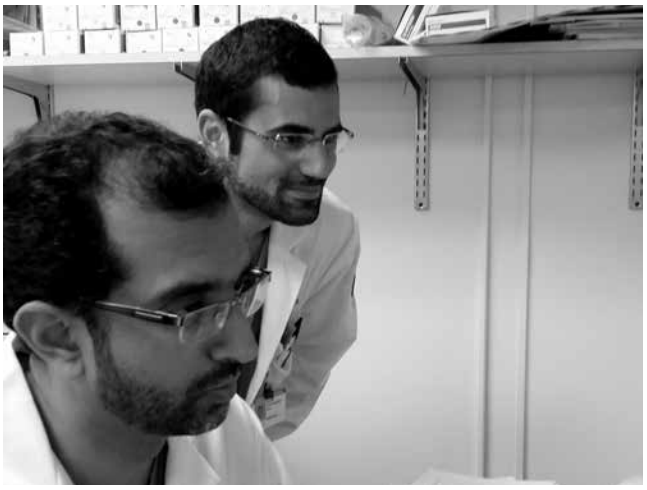
AO North America President Mike Baumgaertner and Temple's Colin Mansfield at the One AO Multi Specialty Meeting in Las Vegas, NV

Steve Refsland demonstrating the compartment pressure monitoring technique on the PGY1 specimen

The Trauma Barbies in full force (Courtney Quinn, Kate Harper, and Arianna Trionfo)

Will Smith photo bombing Dr. Rehman and James Bennett in a bunny suit

Snapshots from 2014–2015



"Rehmazzadeh"

Pizza Fridays: a weekly tradition

Rick Tosti and Dr. Sewards holding down the sideline at the Liacouras Center

Dressed to impress: John Jennings, Kate Harper, Megan Reilly, and Will Smith at Dr. Thoder's " How to be a Gentleman" party

Ortho ladies showing their fashion sense at the "Gentlemen's and Ladies' Social"

Dr. Thoder in traditional Scottish formal wear and Rick Tosti in a corduroy suit at the Gentlemen's Party

Snapshots from 2014–2015

Last Christmas Party as residents for our chiefs: Justin Iorio, Steve Refsland, and Rick Tosti

PGY4 Class at the Christmas Party hosted by the Merion Cricket Club (Rupam Das, Kasey Komperda, Mark Solarz, and Colin Mansfield)

Alex and Rick Tosti supporting Temple Basketball!

What happened to Dr. Clancy's portrait!?!?

Temple Ortho Spartans! Six-mile obstacle course completed by Colin Mansfield, Dustin Greenhill, Rick Tosti, Chris Haydel, Mark Solarz, and Rupam Das

Dr. Eremus and Rick Tosti at the Preview Night for the Philadelphia Horticultural Society

Snapshots from 2014–2015

Justin Iorio showing pin placement for pelvic external fixation

Kasey Komperda eagerly waiting to ask a question at Journal Club

The "Harper Diet"

Jim Lachman and Dustin Greenhill at the arthroscopy course in Rosemont, Illinois

Another successful hip reduction!! (*L-R:* Justin Iorio, Steve Refsland, Arianna Trionfo, Kate Harper, Scott Barbash, and Dr. Bala)

PGY3 Class in order of height (Jim Lachman, Anastassia Newberry, Arianna Trionfo, Dustin Greenhill)

Snapshots from 2014–2015

Congratulations to Craig and Tehilla Steiner on the birth of Samantha Morgan on 12/14/2014!

Congratulations to Jim and Michelle Lachman on the birth of Nora Lynn on 2/20/2015!

Instructions to Authors

Editorial Philosophy

The purpose of the *Temple University Journal of Orthopaedic Surgery & Sports Medicine (TUJOSM)* is to publish clinical and basic science research performed by all departments of Temple University that relate to orthopaedic surgery and sports medicine. As such, *TUJOSM* will consider for publication any original clinical or basic science research, review article, case report, and technical or clinical tips. All clinical studies, including retrospective reviews, require IRB approval.

Editorial Review Process

All submissions will be sent to select members of our peer review board for formal review.

Manuscript Requirements

Manuscripts are not to exceed 15 double spaced type-written pages and/or 5,000 words (minus figures/tables/pictures). The manuscript should contain the following elements: Title page, Abstract, Body, References, and Tables/Legends. Pages should be numbered consecutively starting from the title page.

(1) Title Page — The first page, should contain the article's title, authors and degrees, institutional affiliations, conflict of interest statement, and contact information of the corresponding author (name, address, fax, and email address).

(2) Abstract — The second page, should be a one-paragraph abstract less than 200 words concisely stating the objective, methods, results, and conclusion of the article.

(3) Body — Should be divided into, if applicable, Introduction, Materials & Methods, Results, Discussion, and Acknowledgements. Tables and figures (in JPEG format) with their headings/captions should be listed consecutively on separate pages at the end of the body, not continuous within the text.

(4) References — Should be listed following the format utilized by *JBJS.* For example: Smith, JH, Doe, JD. Fixation of unstable intertrochanteric femur fractures. *J Bone Joint Surg Am.* 2002;84:3553–58.

Submissions

All submissions are now digital. Please submit the manuscript in a Microsoft Word document to templejournal@gmail.com.

Disclaimer: **This journal contains manuscripts that are considered interpersonal communications and extended abstracts and not formalized papers unless otherwise noted.**

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Montgomery / Bucks County
Cell: 610-393-1645
Fax: 267-347-4368
brandebieber@reboundmedical.com

Eric Miller
Harrisburg / Central PA
Cell: 267-252-9750
Fax: 717-657-1245
ericmiller@reboundmedical.com

Brandon Fetherolf
Reading / Allentown / Northeast PA
Cell: 610-301-8296
Fax: 484-660-3299
brandonfetherolf@reboundmedical.com

EJ Gilbert
Western Suburbs of Philadelphia
Cell: 732-690-3854
Fax: 888-618-2818
ejgilbert@reboundmedical.com

Ann Stewart
Philadelphia
Cell: 610-454-8527
Fax: 610-687-2418
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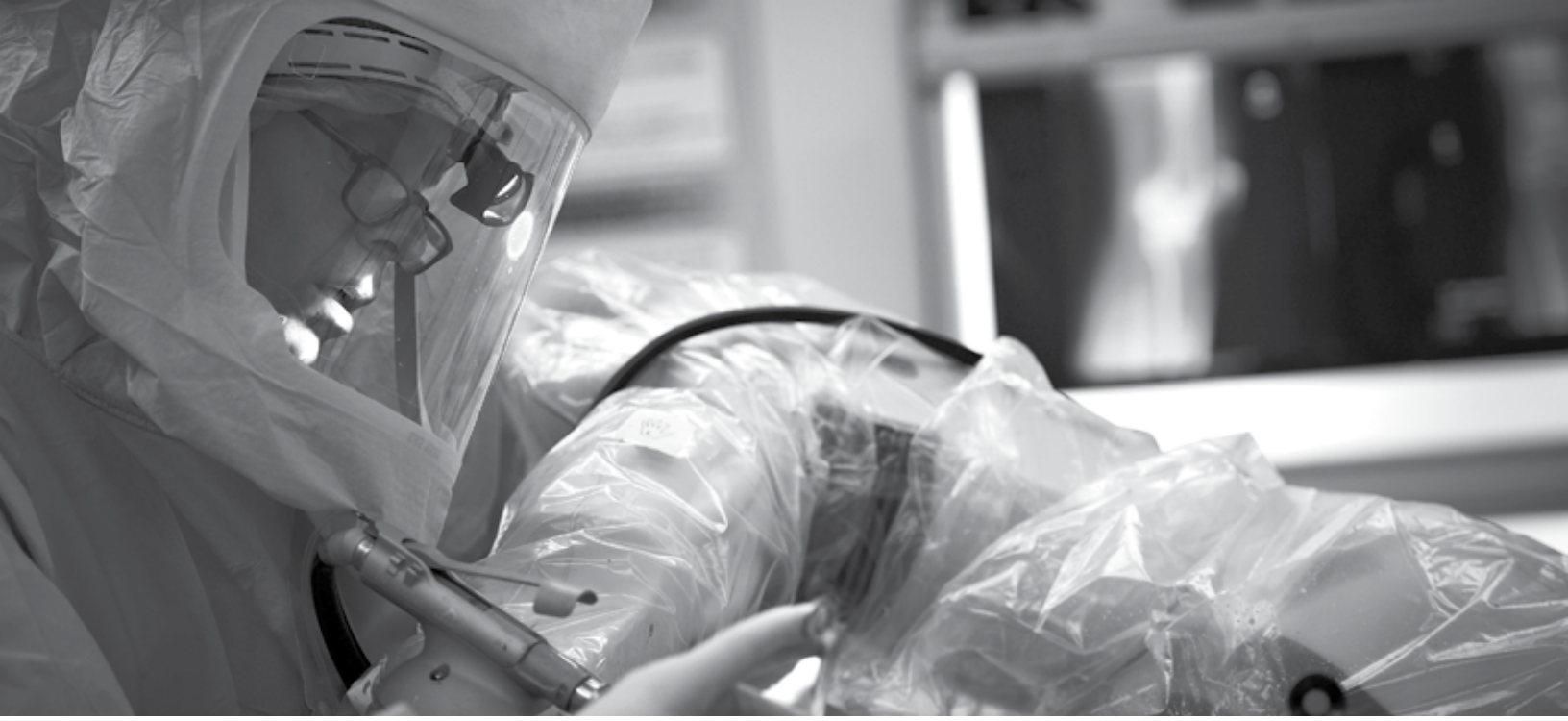

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1. Bhimji S, Alipit V. The Effect of Fixation Design on Micromotion of Cementless Tibial Baseplates. *Orthopaedic Research Society Annual Meeting*; 2012. Poster #1977. 2. Harwin S, et al. Excellent fixation achieved with cementless posteriorly stabilized total knee arthroplasty. *J Arthroplasty*; 2013;28(1):7–13. 3. Alipit V, Bhimji S, Meneghini M. A Flexible Baseplate with a Partially Porous Keel can Withstand Clinically Relevant Loading. *Orthopaedic Research Society Annual Meeting*; 2013. Poster #0939. 4. Stryker Test Report RD-12-044 5. Stryker Test Protocol 92911; D02521-1 v1.

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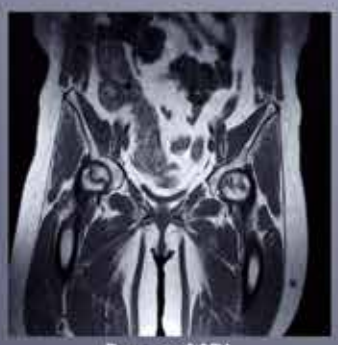

Pre-op MRI
Bilateral Osteonecrosis

Post-op: Right

Post-op: Left

1 Yr. Post-op: Right

1 Yr. Post-op: Left

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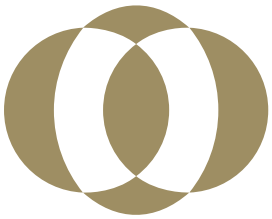

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