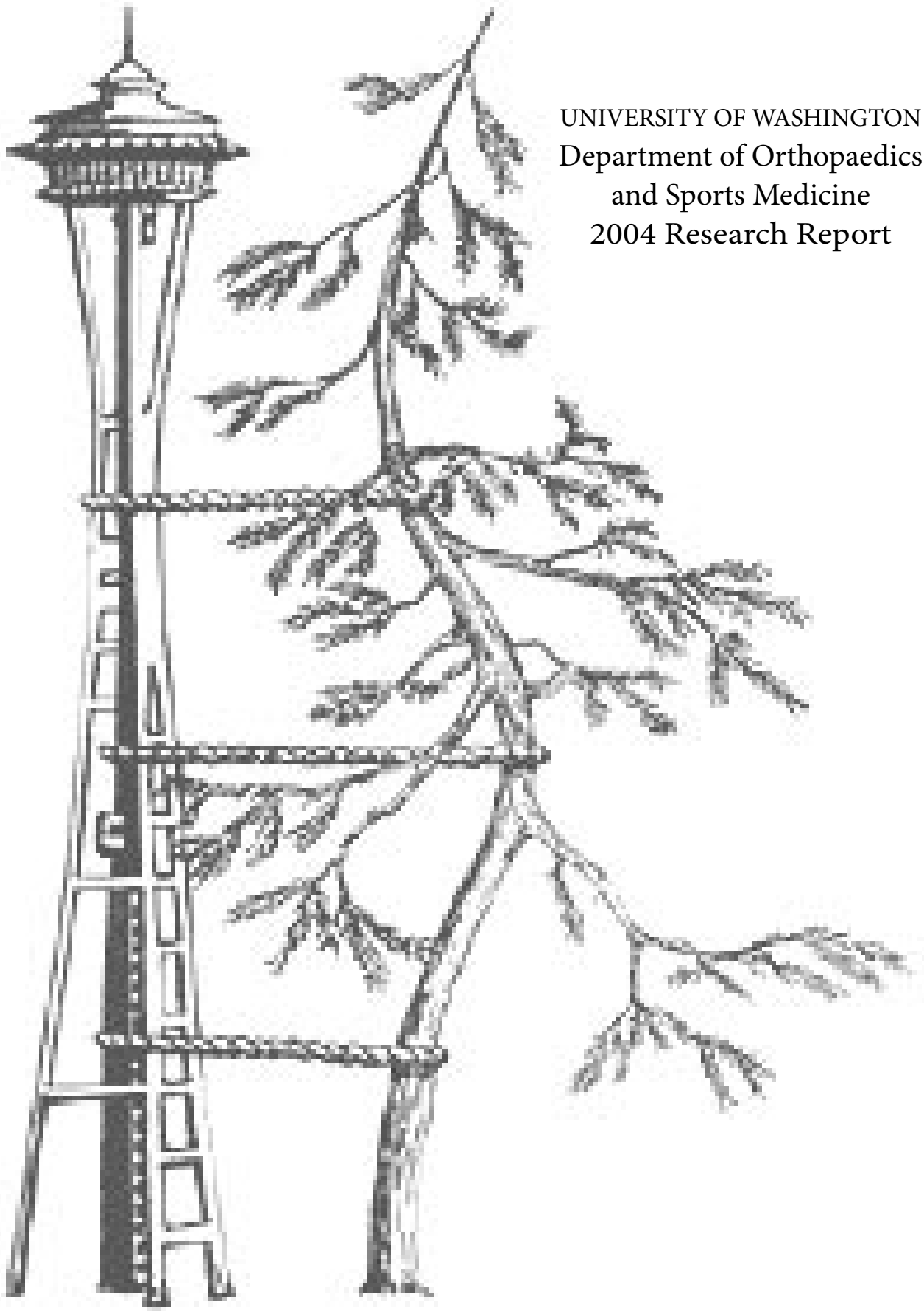
University of Washington

Department of Orthopaedics and Sports Medicine

2004 Research Report



UNIVERSITY OF WASHINGTON

Department of Orthopaedics and Sports Medicine 2004 Research Report

UW Medicine
SCHOOL OF MEDICINE

Department of Orthopaedics and Sports Medicine
University of Washington
Seattle, WA 98195

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Cover Illustration: "The Circus" by Georges Seurat
1891. Oil on canvas.
Photograph: Herve Lewandowski
Musee d'Orsay, Paris
Photo Credit: Reunion des Musees Nationaux / Art Resource, NY

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Foreword

The Orthopaedics and Sports Medicine Research Report for 2004 is dedicated to our great and growing program in spine. After having spent some time thinking about what cover art would best emblemize spine, I chose Georges Seurat's "The Circus", painted in 1891 and currently on display at the Musee d'Orsay in Paris. At once the painting shows the wonderful versatility of the human spine obviously awing the clown at lower center. The spectators at upper left sit comfortably while they observe the action in the ring. The ringmaster stands erect while the acrobat shows extreme flexibility as he hyperextends his spine in a mid air flip. Finally, the lady bareback rider demonstrates the ultimate in spinal grace and freedom as she balances with one foot on the back of the galloping white horse. To achieve this wide range of functions the spine comes together as a composite of many elements, including a myriad of small joints, ligaments, muscles, tendons and nerves in a manner similar to the pointillism technique in which Seurat painted the Circus; rather than blending colors on his palate, he juxtaposed dots of different colors to create the whole. Seurat died of an infectious disease, diphtheria, at the age of 31 before he could complete "The Circus", reminding us that one of the most prevalent spinal conditions in the world remains infection, particularly tuberculosis. While, like "The Circus", our understanding of spine is incomplete, we can be quite proud of the strides the UW spine team is making to lessen the impact of the spinal disorders that will impact 80% of our population sometime during their life.

The Orthopaedic and Sports Medicine spine team is led by Jens Chapman who has recently been honored as the first holder of the Hansjoerg Wyss Endowed Chair. He is joined by Sohail Mirza, Carlo Bellabarba, Dheera Ananthakrishnan, Rick Bransford, and Kit Song. This summer Ted Wagner, who had had a distinguished career in private practice, will return to his academic home in the Department. UW Spine is completed by Rick Deyo from Medicine, who has been an international leader in spine outcomes, and by faculty from neurological surgery, rehabilitation medicine, and radiology. The spine program is establishing a major presence at each of our major medical centers: Harborview, University of Washington Medical Center, the Veterans Hospital and Children's Hospital and Regional Medical Center. Our goal is to provide the best in spine research, education and patient care. The critical partnerships of UW Spine make this happen.

In this year's research report you will meet new members of the Orthopaedics and Sports Medicine family, help us wish farewell to our graduating chiefs, recognize the generosity of our donors. You will also be treated to a sampling of the breadth and depth of the research programs in action in our Department. We lead off with a series of articles by the spine outcomes team, led by Sohail Mirza. These articles show the importance and complexity of applying Codman's End Result Idea: "to follow each patient long enough to find out if they benefited from the treatment and if not, why not?" In advocating a cautious approach to adoption new spinal technologies, Dr. Deyo and Dr. Mirza remind us to carefully consider benefits and risks in identifying those patients best suited for the new procedures. Basic science breakthroughs, such as identification of genetic predispositions for some spinal disorders as shown in the article by Matsui and Fernandes (first authors of fourth and fifth papers), hold great promise for leading to truly innovative advances in the diagnosis and treatment of these conditions. Growing evidence suggests that certain medications can enhance the rate of spine fusion as shown by Bransford et al. Closely related to our spine focus is our research to better understand and regenerate cartilage, including the new work in helping the body grow a new joint surface in the shoulder.

In addition to the articles related to spine, it is a pleasure to share with you a wide range of work on topics ranging from ski/snowboard helmets, to toxic shock in children, to crash testing, to pelvic fractures and to education and the internet. You can see that this is a very creative group of residents, fellows and faculty. They are dedicated to the discovery, application and sharing of the best of knowledge directed at the bone and joint health of the population.

Speaking of our residents, I would like to take this opportunity to acknowledge the true excellence of the women and men who come to the UW Department of Orthopaedics and Sports Medicine to spend five years as our colleagues. The competition for our residency positions is fierce and we have the privilege of working with the brightest and the best, as they become the orthopaedic leaders of the future. Take some time to look at the residency pages in this report and meet our incoming and our graduating residents. The quality of our program has been recognized by the national Accreditation Council on Graduate Medical Education: they have granted the UW with an unprecedented increase in the size of our program to eight positions per year, making it one of the largest residency programs in the country. Our graduates are in high demand for post residency fellowships, for academic positions and for partnership in the private practice of orthopaedics.

Because of the heightened interest in our faculty, our residency, our research and our clinical programs, we are pleased to offer a web site packed with information of interest to patients, residency candidates, potential contributors, and the general public. This site is visited over 3000 times per day by individuals from all over the world. Take a look at www.orthop.washington.edu.

The excellence of this department is, like the paintings of Seurat, the result of hundreds of individual points of color and light created by the individuals who constitute Team Orthopaedics: our staff, our residents, our fellows, our faculty, our partners, our alumni, and our friends who generously contribute to the support of our mission.

Best wishes,

Frederick A. Matsen III, M.D.
UW Orthopaedic Resident 1971-1975

Visiting Lecturers

Vernon T. Tolo, M.D.

This year at our annual LeCocq Lecture on January 22 and 23rd, we were honored to have Dr. Vernon T. Tolo as our 2004 LeCocq Lecturer. Dr. Tolo is currently the Director of the Childrens Orthopaedic Center at Childrens Hospital Los Angeles. He has been chief of orthopaedics at CHLA since 1987. He also is the John C. Wilson, Jr., Professor of Orthopaedics at the Keck School of Medicine at USC. He has been active in many of the major orthopaedic associations. He has been president of the Pediatric Orthopaedic Society of North America, the Scoliosis Research Society, and the Orthopaedic Section of the American Academy of Pediatrics. He is past-president of the American Academy of Orthopaedic Surgeons, with a membership of over 25,000 orthopaedic surgeons.

Dr. Tolo's primary clinical interest in pediatric orthopaedics are spinal deformity, orthopaedic problems associated with skeletal dysplasias and with cerebral palsy, and orthopaedic injuries in children and adolescents. His publications, awards, and grants in these areas are numerous. The faculty, residents, and community physicians were treated to 4 innovating lectures from Dr. Tolo during the 2 days: "Complications of Pediatric Spine Surgery," "Skeletal Dysplasia and the Orthopaedist," "The Evolution of Pediatric Fracture Care," and "Health Care Disparities in Orthopaedics."

Michael G. Ehrlich, M.D.

This year at our annual Residents' Research Days on May 20 and 21st, we were honored to have Dr. Michael G. Ehrlich as our OREF Hark Lecturer. Dr. Ehrlich is the Vincent Zecchino Professor and Chairman in the Department of Orthopaedic Surgery at Rhode Island Hospital, Providence, RI. He has served as the President of the Academic Orthopaedic Society, the Orthopaedic Research Society, and most recently, the Chair of the Committee on Research of the American Academy of Orthopaedic Surgery. He has received the M.A. ad eundem award at Brown, the Excellence in Research Award from the American Orthopaedic Society for Sports Medicine, the Kappa Delta Award from the AAOS for the best orthopaedic research in the United States, and in 1998, he received the Arthur H. Huene Memorial Award, Lifetime Contribution to Pediatric Orthopaedics, from the Pediatric Orthopaedics Society of North America.

Dr. Ehrlich's research interests include limb-lengthening physiology, neuromuscular disorders in children and growth plate transplantation. He works clinically with limb-lengthening, and paralytic disorders. During the 2 days of lectures, the faculty, residents, and community physicians were treated to 3 lectures from Dr. Ehrlich: "Physiology of leg Lengthening," "Management of Cavus Foot Deformity," and "Is There a Role for Club Foot Surgery?" In addition to Dr. Ehrlich's lectures, the R3's and the R4's presented the progress of their research, while the R5's presented the completion of their research projects.

Hansjoerg Wyss Endowed Chair
Jens R. Chapman, M.D.

The Board of Regents of the University of Washington approved the appointment of Dr. Jens R. Chapman as the first holder of the Hansjoerg Wyss Endowed Chair, effective January 1, 2004.

Dr. Chapman's extensive background and outstanding achievements make him an excellent choice for the Wyss Chair. Educated in Germany, he received his medical postgraduate training at the University of Texas Health Science Center and the University of Washington. Dr. Chapman has been a member of the UW faculty since 1990 and has held the title of professor since 2002. In addition to his faculty positions in orthopaedics and neurological surgery, he is a member of the Trauma Council at Harborview Medical Center. Dr. Chapman is nationally and internationally recognized as a leader in spine surgery, and his clinically related research has significantly advanced understanding and care of patients suffering from orthopaedic and spine trauma. Dr. Chapman is active in teaching, serving as a mentor to medical students, residents, and spine fellows in the Department of Orthopaedics and Sports Medicine.

We are delighted to recognize Dr. Chapman's expertise, dedication, and contributions with the appointment to the Wyss Chair. This is precisely the kind of long-term investment that enhances our ability to retain faculty of international reputation and sustain the high quality of our clinical, teaching and research programs.

The Center for Women's Sports Medicine and Lifetime Fitness An Initiative of the University of Washington and its Department of Orthopaedics and Sports Medicine

The Center for Women's Sports Medicine and Lifetime Fitness seeks to become the first permanently endowed program in the United States dedicated to the unique opportunities and challenges of active women — helping women be fit for life. The Center will optimize women's health, focusing on new strategies for identifying risk factors, preventing injury, and accelerating recovery for women of all ages.

By bringing together an interdisciplinary team of physicians and scientists, the Center will lead innovative research and speed the clinical application of its discoveries. The Center will serve as a national resource and leading advocate for women's health and fitness — advancing research, providing state-of-the-art care, disseminating knowledge, and educating the public.

Structure

The Center comprises four essential elements.

1. Advancing Research

The Center's research will focus on creating new strategies for identifying factors predisposing women to injuries to their bones, ligaments, tendons, cartilage, and discs, coupled with the development of minimally invasive methods for reducing the risk of bone and tissue failure.

The Center will leverage the University of Washington's established excellence in genome sciences, cell and molecular biology, collagen biology, radiology and imaging sciences, and outcomes research, bringing together distinguished faculty to focus on lifetime fitness for women. This interdisciplinary team will work collaboratively to spur innovation and speed the process of translating advances from the laboratory to life.

2. Setting the Standard

The Center will participate actively in the real world of sports medicine and lifetime fitness efforts through the nationally recognized UW Sports Medicine Clinic. The Clinic provides care for nearly 1,000 UW varsity athletes and active individuals from the community. Our goal is to apply the knowledge gained about the challenges faced by active women, providing the highest quality health care and setting the standard for achieving lifetime fitness.

3. Educating the Public

The Center will educate the public about new findings, clinical advances, and other information that can help women optimize the lifetime durability of their bones, ligaments, cartilage, and disc structure. The Center will serve as a national resource for those concerned about women's lifetime fitness, including parents, teachers, coaches, physicians, physical therapists, and trainers.

4. Building the Program

We are committed to securing a $10 million endowment, which will ensure an annual operating budget of $500,000 for the Center. These funds will enable us to attract and retain an internationally renowned director for the Center with the skill, experience, and stature to lead this unique and comprehensive program. Thanks to the generosity of The Bill and Melinda Gates Foundation and a group of visionary supporters, we have already reached 20 percent of this goal.

UW Medicine

Research and Clinical Excellence

The Department of Orthopaedics and Sports Medicine at the University of Washington School of Medicine is recognized by U.S. News and World Report as the only orthopaedic program in the United States to have two of its medical centers (University of Washington Medical Center and Harborview Medical Center) among the top 10. The department has 40 full-time faculty members, making it one of the nation's largest. It is also among the top orthopaedic recipients of federal research grants from the National Institutes of Health, National Science Foundation, Centers for Disease Control, Defense Advanced Research Projects Agency, and Veterans Administration.

The Center for Women's Sports Medicine and Lifetime Fitness provides a unique opportunity for a significant strategic investment that will contribute to the health of women of all ages worldwide.

Spinal Fusion Surgery: The Case for Restraint

Richard A. Deyo, M.D., M.P.H. and Sohail K. Mirza, M.D.

Spinal fusion surgery rates in the U.S. are rapidly increasing. Data from the Agency for Heathcare Research and Quality (AHRQ), indicate that the annual number of spinal fusion operations rose 77% between 1996 and 2001. In contrast, hip replacement and knee arthroplasty increased by 13-14% in the same time period (Figure 1).

Spinal surgery is among the most frequent procedures performed in this country, with spinal fusion increasing at a rate much higher than the other common procedures (Table 1). Spinal surgery, taken together, is second only to coronary bypass surgery in terms of total hospital charges (Table 2). The average hospital bill for spinal fusions is over $34,000, excluding professional fees.

Wide variations in the rates of spinal fusion in different parts of the country suggest there may be a limited professional consensus on the indications. Several factors may contribute to the rapid increase in spinal fusion surgery. Much of the rise has occurred in older adults, in association with laminectomies for spinal stenosis. The advent of axial spine imaging around 1979 may have facilitated this rapid increase. Another factor contributing to the rapid increase may be new technology for performing spinal fusions. There has been a succession of new surgical implants for fusion surgery, so that over 150 systems are now marketed. A rapid rise in fusion rates beginning in 1996 coincided with FDA approval of intervertebral "fusion cages", a new generation of surgical implants. The past decade has also witnessed a rapid increase in use of commercially available allograft bone for spinal fusions. Most recently, bone morphogenetic proteins have been discovered, purified, and tested in clinical trials to improve the success of bony fusions.

Discogenic pain may be the most controversial indication for performing spinal fusion. Advocates cite recent results from a Swedish randomized trial comparing spinal fusion with non-surgical care for patients with one or two level disk degeneration. The non-surgical group received a broad range of treatments including physical therapy, electrical nerve stimulation, acupuncture, injections, cognitive training and others, based on individual physician preferences. Surgical patients showed greater improvements than non-surgical patients in pain relief, function, depressive symptoms and return to work. Nonetheless, only 63% in the surgical group considered themselves "much better" or "better". A more recent randomized trial suggested no advantage of fusion over a carefully designed rehabilitation program for such patients, so the evidence is conflicting, at best.

In comparison to simple discectomy or laminectomy, spinal fusion requires more extensive dissection, decortication of bone, longer operative time, and often placement of implants. Thus, it is not surprising that fusion is associated with more complications than other types of spinal surgery. Among Medicare patients, compared to any operation without fusion, surgery that included fusion was associated with more complications, more blood transfusions, and higher, six week post-operative mortality.

Spinal fusion surgery is undoubtedly effective for some conditions in some patients. However, wide geographic variations in use of the procedure, rapidly rising surgical rates, high re-operation rates, and high complication

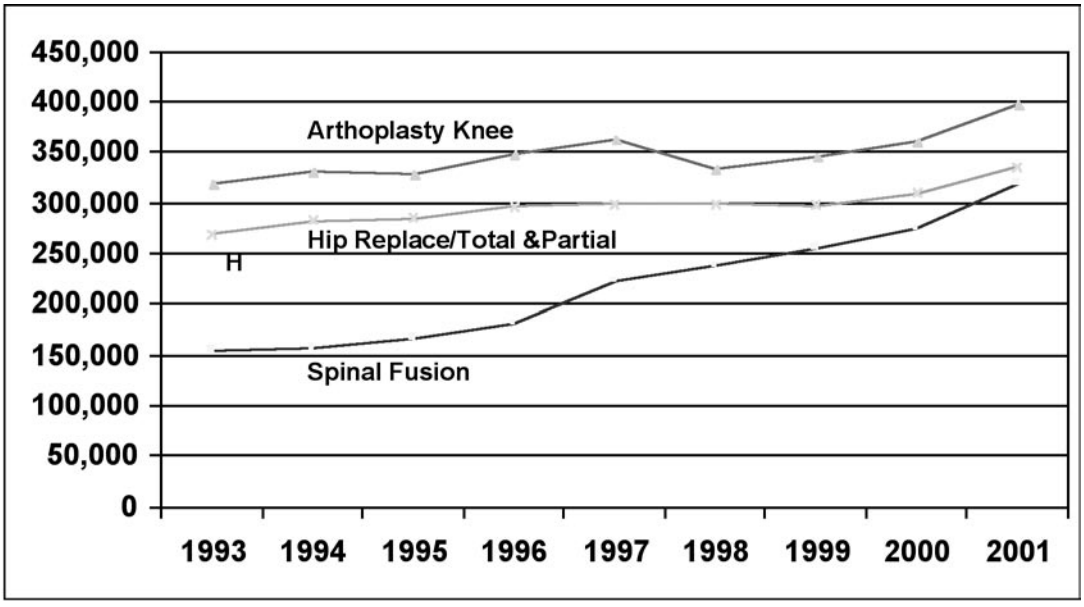

Figure 1: Number of operations per year in the U.S.

Procedure Type	Total Number	Hospital Charge (ave)	% Change (1997 to 2000)
Hysterectomy	597,000	$11,100	3.4%
Cholecystectomy	401,000	$18,300	1.6%
CABG	350,000	$58,000	-8.8%
Knee Arthroplasty	328,000	$23,300	1.1%
Hip replacement	305,000	$25,800	3.9%
Lumbar Discectomy	294,000	$14,700	-1.3%
Appendectomy	277,000	$12,800	1.8%
Colorectal Resection	262,000	$34,400	1.9%
Vascular, not head and neck	221,000	$35,900	6.7%
Spine Fusion	211,000	$31,300	55.4%

Table 1: Frequency of inpatient surgical procedures in the year 2000.

rates raise concerns that the procedure may be overused. Its efficacy for the most common indications, such as degenerative disc disease, remains unclear.

Evidence-based practice for degenerative spine disorders would might limit spinal fusions to spondylolisthesis and only rare cases of disk herniation or spinal stenosis without spondylolisthesis. More clinical trial evidence is required for degenerative disk disease. Because of more frequent complications, more re-operations, and higher costs, the growing use of surgical implants is difficult to justify in the absence of evidence for improved clinical outcomes.

New implant technology such as artificial discs should be approached with caution. The evidence for efficacy and safety of these devices is limited at best. If ongoing trials suggest results equivalent to spinal fusion, it may be faint praise, given the paucity of evidence for the efficacy and safety of spinal fusion in conditions such as discogenic pain. Similar concerns can be raised about other new technologies for back pain, including electro-thermal therapy, analgesic pumps, and implanted spinal stimulators.

The Food and Drug Administration (FDA) should require rigorous evidence prior to approval of spinal implants for degenerative conditions. For all spinal implants, randomized trials should probably be required prior to FDA approval. Thorough post-marketing surveillance for complications should become mandatory.

Finally, the emphasis of research might profitably shift from examining "how to fuse" to examining "who to fuse". The indications for this invasive and expensive procedure remain unclear despite rapidly increasing use. European randomized trials of spinal surgery versus non-surgical treatments suggest that controlled trials are feasible. Although the use of sham surgery remains controversial for ethical reasons, we believe randomized trials incorporating a sham operation may be justifiable for this procedure, because it is not for a life threatening condition; the primary clinical outcomes are subjective; and patients are subjected to a high rate of complications. Only with more and better clinical studies will the indications and optimal technique for spinal fusion become clear.

Procedure Type	Total Charges	% Change (1997 to 2000)
CABG	$20.3 billion	-8.8
Spine surgery	$10.9 billion	7.0
Colorectal resection	$ 9.0 billion	1.9
Vascular, not head and neck	$ 7.9 billion	6.7
Hip Replacement	$ 7.9 billion	3.9
Knee Arthroplasty	$ 7.6 billion	1.1
Cholecystectomy	$ 7.3 billion	1.6
Hysterectomy	$ 6.7 billion	3.4

Table 2: Total hospital charges of inpatient surgical procedures in the year 2000.

Supported in part by Grant #P60 AR48093 and Grant # K23AR48979-01 from the National Institute of Arthritis, Musculoskeletal and Skin Diseases.

Recommended Reading

Fritzell P, Hagg O, Wessberg P, Nordwall A. 2001 Volvo Award Winner in Clinical Studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine 2001;26: 2521-32.

Ivar Brox J, Sorensen R, Friis A, et al. Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. Spine 2003; 28:1913-21.

Deyo RA, Ciol MA, Cherkin DC, Loeser JD, Bigos SJ. Lumbar spinal fusion. A cohort study of complications, reoperations, and resource use in the Medicare population. Spine 1993; 18:1463-70.

Classifying Adverse Occurrences in Spine Surgery

Sohail K. Mirza, M.D., Lorri A. Lee, M.D., Andrew T. Dailey, M.D., Robert Goodkin, M.D., Patrick J. Heagerty, Ph.D., Judith A. Turner, Ph.D., and Richard A. Deyo, M.D., M.P.H.

An early warning system is needed to identify surgical devices and techniques that perform poorly when introduced into general practice. Reliable safety information is particularly needed for surgical procedures where efficacy is not clear but risks are potentially very serious. Though surgery can be life saving for spinal fractures and tumors, most spinal operations are elective, where patients must compare anticipated benefits in improved pain, function, and quality of life against the real risks of a variety of surgical options. Despite controversy surrounding efficacy, the rate of spinal fusion procedures is rapidly increasing in this country. With an estimated annual growth rate of 20%, the spinal device industry continues to proliferate spinal fusion materials and fixation devices. Expensive technological innovations in minimally-invasive surgical approaches, biologic fusion materials, and complex spinal fixation devices frequently gain widespread use based on limited comparative data and minimal systematic surveillance after implantation. On the other hand, awareness of adverse effects associated with these innovations accumulates haphazardly and disseminates slowly. Lack of understandable, universal outcome measures that meaningfully adjust for patient, disease, and treatment factors is frequently cited by the private sector as a primary impediment to routinely gathering safety information on implanted surgical devices.

Heightened awareness of surgical errors is a wake-up call for surgeons to establish leadership in regaining the confidence of their patients. Patients demand credible assurance of a safe system of medical care. Tackling the problem of adverse events associated with surgery demands a direct and open approach, first in identifying and acknowledging these events, and second, in discussing them in a learning environment that creates a deeper understanding of how to prevent future adverse outcomes.

Our goal is to encourage systematic evaluation of adverse events associated with spine surgery. Monitoring adverse event rates may more rapidly identify problems with new surgical techniques than measurement of long-term pain and function outcomes. High rates of preventable adverse occurrences may signal an early warning for poor quality surgical care. Assessing quality of surgical care by measuring adverse occurrences has been the basis of surgical morbidity and mortality conferences for over a hundred years. Standardizing and quantifying that process has direct meaning for surgeons and patients. We believe systematically describing adverse occurrences associated with spine surgery will better inform patients considering surgery, protect spine surgeons from undue blame when things go wrong, and

Code	Type of Error	Description
1	Diagnostic	Error in diagnosis or delay in diagnosis
2	Diagnostic	Failure to employ an indicated test
3	Diagnostic	Use of outmoded tests or therapy
4	Diagnostic	Failure to act on the results of monitoring or testing
5	Treatment	Technical error in performance of an operation, procedure, or test
6	Treatment	Error in administering the treatment (including preparation for operation or treatment)
7	Treatment	Error in dose of drug or in the method of use of a drug
8	Treatment	Avoidable delay in treatment or in responding to an abnormal test
9	Treatment	Inapproriate (not indicated) care. Considering the patient's disease, its severity, and comorbidity, the anticipated benefit from the treatment did not significantly exceed the known risk, or a superior alternative was available
10	Preventive	Failure to provide indicated prophylactic treatment
11	Preventive`	Inadequate monitoring or follow-up of treatment
12	System	Failure in communication
13	System	Equipment failure
14	System	Other systems failure
15	Other	Unclassified
*(16	Patient	Patient disease, expected risk)
*(17	Patient	Patient non-compliance)
*(18	Patient	Patient disease, unrelated to spinal surgery)

*Items not included in the Brennan scale.

Table 1: Categories for classifying adverse occurrence etiology (Brennan 1991).

Code	Description
0	No quality of care concerns evident
1	Did not and unlikely to have had an adverse effect
2	Did not but had the potential to have had an adverse effect
3	Had an adverse effect but not life threatening
4	Resulted in loss of major physical function or potentially life threatening
5	Demonstrated a life threatening situation or resulted in death

Table 2: Categories of the JCAHO six-point scale for adverse occurrence severity classification scale.

Category	Summary	Description
0	No effect, no risk	Adverse occurrence required no intervention, resulted in no adverse consequences, and had no risk of adverse consequences.
1	No effect, minor risk	Adverse occurrence required no intervention, resulted in no adverse consequences, but had the potential to result in minor consequences.
2	No effect, major risk	Adverse occurrence required no intervention, resulted in no adverse consequences, but had the potential to result in major but not life threatening adverse consequences.
3	No effect, risk of death	Adverse occurrence required no intervention, but had the potential to result in a life-threatening situation or death.
4	Minor effect, minor risk	Adverse occurrence required a minor intervention or resulted in minor loss of function, and had the potential to result in only minor adverse consequences.
5	Minor effect, major risk	Adverse occurrence required a minor intervention or resulted in minor loss of function, but had the potential to result in major loss of function, though not life-threatening.
6	Minor effect, risk of death	Adverse occurrence required a minor intervention or resulted in minor loss of function, but had the potential to result in a life-threatening situation or death.
7	Major effect, major risk	Adverse occurrence required extensive intervention such as unexpected re-operation or re-admission, or resulted in major loss of function, but was not life-threatening.
8	Major effect, risk of death	Adverse occurrence required extensive intervention such as unexpected re-operation or re-admission, or resulted in major loss of function, and had the potential to result in a life-threatening situation or death.
9	Life-threatening effect	Adverse occurrence resulted in a life-threatening situation.
10	Death	Adverse occurrence resulted in death.

Table 3: Classification scale for rating the severity of the effect and magnitude of risk associated with adverse occurrences.

disseminate lessons which may improve outcomes for future patients.

Systematic safety monitoring of surgical procedures has three important prerequisites: (1) practical definitions of adverse occurrences so that they can be identified consistently; (2) an infrastructure to report the events; and (3) a reliable method of classification to describe the results. We developed definitions and explicit criteria for 175 specific adverse occurrences, trained personnel to identify and report these occurrences prospectively, and provided information systems to record and report them efficiently. Using a subset of the events reported in 2003, we studied the reliability of classifying them reproducibly. In this report we describe the within-observer and between-observer reliability for coding etiology, preventability, and severity of adverse occurrences.

To classify the causes and contributory factors, we selected the etiology scale reported in the Harvard Medical Practice Study (Table 1). We also used the descriptions of preventability reported in the Harvard Medical Practice study, coding events as unpreventable, potentially preventable, and preventable. We required a scale that allowed risk assessment for potentially dangerous events that resulted in no actual consequence, sometimes designated as "near miss" events. We selected the adverse event severity scoring scheme advocated by the Joint Commission on Accreditation of Healthcare Organizations (Table 2). In our training phase for adverse event coding, the reviewers identified problems differentiating real effects from potential effects using this scale. We therefore developed an 11-point scale to assess separately the effects and risk associated with adverse occurrences (Table 3).

To test the reliability of adverse event coding, we selected all adverse events recorded in enrolled subjects from July 2, 2003 to September 30, 2003. We selected 141 adverse events recorded during this window. Using information

	R1-R2	R1-R3	R1-R4	R2-R3	R2-R4	R3-R4	Mean
Etiology, kappa	0.33	0.33	0.33	0.43	0.45	0.28	0.36
Preventability, kappa	0.17	0.36	0.35	0.13	0.34	0.29	0.27
Preventability, weighted kappa	0.33	0.60	0.56	0.24	0.43	0.49	0.44
JCAHO Severity, kappa	0.23	0.35	0.29	0.16	0.23	0.25	0.25
JCAHO Severity, weighted kappa	0.25	0.57	0.34	0.26	0.21	0.31	0.33
Nominal Severity, kappa	0.24	0.17	0.18	0.17	0.31	0.23	0.22
Nominal Severity, weighted kappa	0.27	0.60	0.37	0.34	0.51	0.33	0.40

Table 4: Agreement between pairs of observers for etiology, preventability, and two severity ratings of adverse events.

recorded in the medical records and notes from discussions of these events in clinical care conferences, we developed a brief narrative describing each adverse event. Four reviewers coded each event for etiology, preventability, and severity. Reviewers were selected from different backgrounds to create broad clinical expertise among reviewers. Reviewer 1 was an orthopedic surgeon with fellowship training in spinal surgery and 7 years of experience. Reviewer 2 was an anesthesiologist with 4 years of experience. Reviewer 3 was a neurosurgeon with 7 years experience. Reviewer 4 was a neurosurgeon with 30 years of experience. The reviewers attended three one-hour training conferences and coded approximately 10 adverse events during each conference. After this training period, the reviewers were asked to code the set of 141 adverse events independently.

The reviewers requested additional information on 24 of the 141 adverse events (17%). The reviewers were allowed to select multiple categories for etiology but asked to identify the factor they considered to be the primary or main causative factor. Each reviewer selected only one item for the other three ratings: Preventability, JCAHO Severity, and Numerical Severity. Agreement between each pair of observers is shown in Table 4. Our preliminary analyses have revealed that interrater agreement is generally poor, indicating that further work is needed to improve reliability before the scales can be used in clinical practice.

Future Work

We plan to conduct analyses to determine if agreement is better for certain subsets of adverse occurrences.

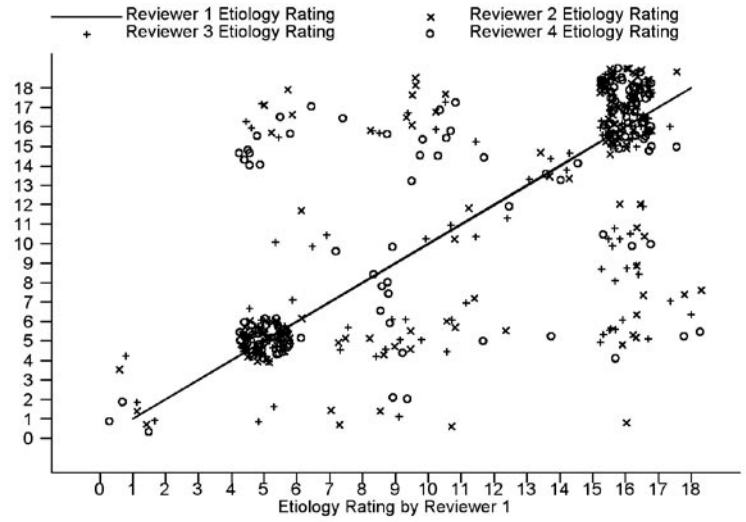

Figure 1: Etiology rating by Reviewer 2, Reviewer 3, and Reviewer 4 compared to the rating by Reviewer 1 (small random error has been added to different ratings with the same value).

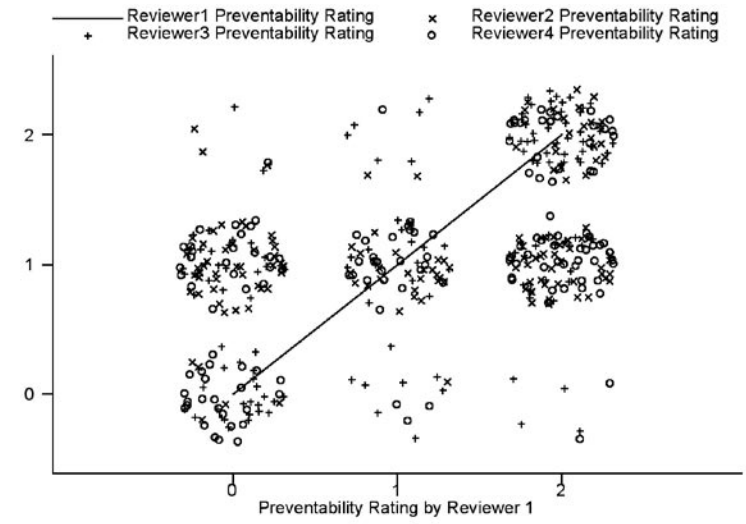

Figure 2: Preventability rating by Reviewer 2, Reviewer 3, and Reviewer 4 compared to the rating by Reviewer1 (small random error has been added to different ratings with the same value).

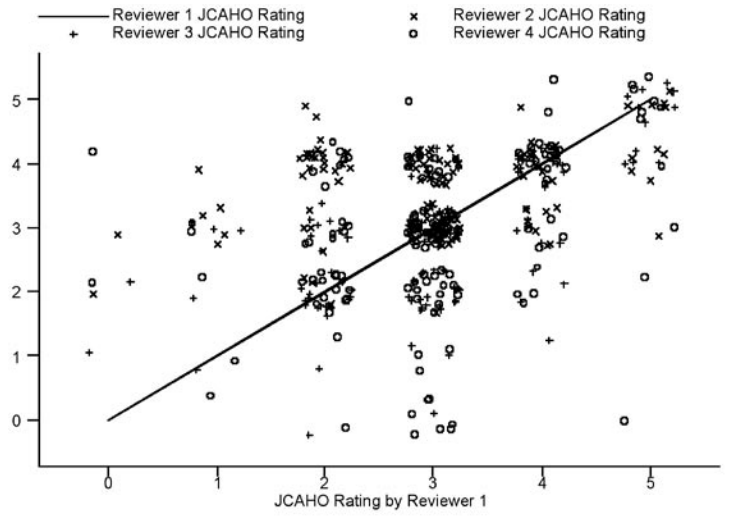

Figure 3: JCAHO Severity rating by Reviewer 2, Reviewer 3, and Reviewer 4 compared to the rating by Reviewer1 (small random error has been added to different ratings with the same value).

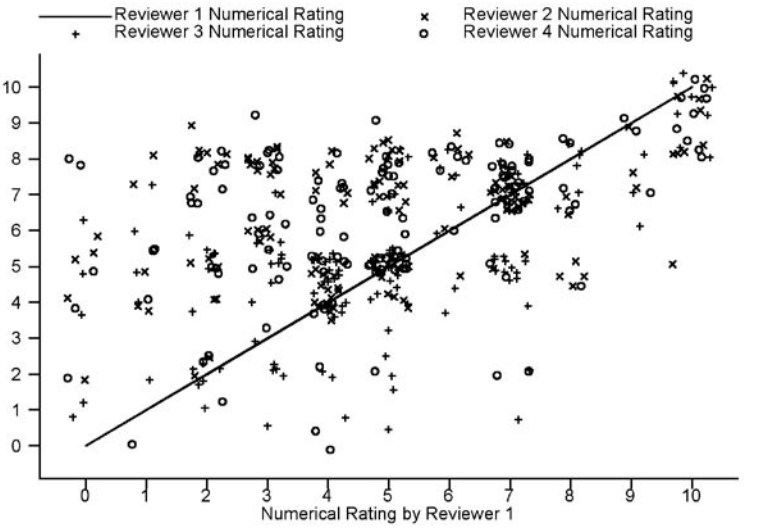

Figure 4: Numerical rating by Reviewer 2, Reviewer 3, and Reviewer 4 compared to the rating by Reviewer1 (small random error has been added to different ratings with the same value).

For example, we found better agreement on etiology for technical complications than for most other categories. We will identify additional information items for the problematic adverse event types and refine their definitions to improve judgments regarding their severity. We will modify the scale descriptions to be more explicit, and then retest reliability of the classification schemes.

Supported in part by Grant #P60 AR48093 and Grant # K23AR48979-01 from the National Institute of Arthritis, Musculoskeletal and Skin Diseases.

Recommended Reading

Deyo RA, Nachemson A, Mirza SK. Spinal-fusion surgery - the case for restraint. N Engl J Med 2004; 350:722-6.

Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. N Engl J Med 1991; 324:370-6.

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Surveillance of Adverse Occurrences in Spine Surgery: Evaluation of Data Quality in the First Year of Implementation

Sohail K. Mirza, M.D., Jens R. Chapman, M.D., Dheera Ananthakrishnan, M.D., Carlo Bellabarba, M.D., Janet O. Bower, R.N., M.H.A., Richard J. Bransford, M.D., Andrew T. Dailey, M.D., Richard A. Deyo, M.D., Robert Goodkin, M.D., Patrick J. Heagerty, Ph.D., Todd S. Jarosz, M.D., Mark A. Konodi, M.S., Lorri A. Lee, M.D., and Judith A. Turner, Ph.D.

Measuring outcomes and safety of spinal surgery is important because this information is lacking for many spinal procedures. Spine surgery procedures are common, expensive, and high-risk. Regional variation shows marked uncertainty regarding indications for surgery. Efficacy of common procedures, such as fusion for back pain, remains unknown. Furthermore, adverse occurrences associated with highly invasive procedures may be under-reported in the literature. When deciding on procedure and surgeon choice, patients ask for specific safety information on their potential surgeon and hospital. However, such quality-related performance information is not readily available for specific surgeons in local settings. Spine surgeons at the University of Washington established a new program to provide this information. The ultimate goal of this program is to improve the outcomes of spinal surgery. In the process, the program will also provide site-specific information on risks and benefits associated with spine surgery procedures (Figure 1).

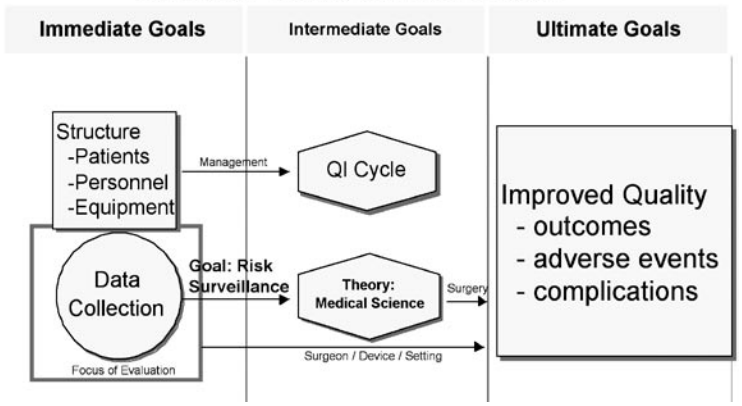

Figure 1: Goals of the UW Spine Quality of Care Surveillance Program and the focus of this evaluation.

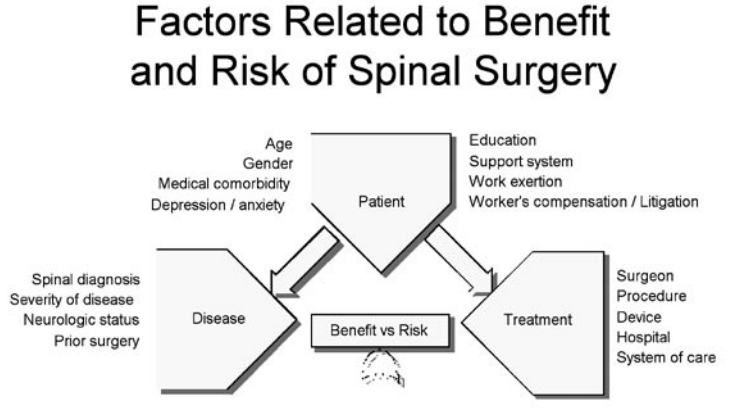

Figure 2: Multivariate model for measuring risk and benefit of spinal surgery.

The Spine Quality of Care Surveillance Program seeks to create a system and culture of routinely and rigorously measuring the outcomes of treatment in all patients undergoing spinal surgery within the UW Medicine healthcare system. The program emphasizes gathering information on the safety of surgical procedures and aims to establish an early warning system for preventable adverse events. Because many different factors can play a role in patient outcomes after surgery, the program collects information on such factors as patient characteristics, spinal disease, and treatment (Figure 2). The program is developing methods for standardized measurement of the severity of spinal disease, the intensity of spinal surgical intervention, and the collection of safety information. The information can then be combined to inform individual patients of the risks and outcomes associated with specific treatments.

With institutional review board approval, participating surgeons routinely enroll patients with spinal disorders in a Spine End-Results Registry (SERR). Enrolled subjects grant permission to track pain, function, type and severity of spinal disease, coexisting medical conditions, type and intensity of treatment, and frequency adverse occurrences. The program was implemented at two institutions, Harborview Medical Center and University of Washington Medical Center, on January 1, 2003. The SERR enrolled 1541 patients in 2003.

Spine surgeons provided surgery information on forms filed in each patient's medical record. We established a weekly closed and confidential conference to review all scheduled spine operations and all adverse occurrences. The inpatient care teams were encouraged to be attentive to adverse

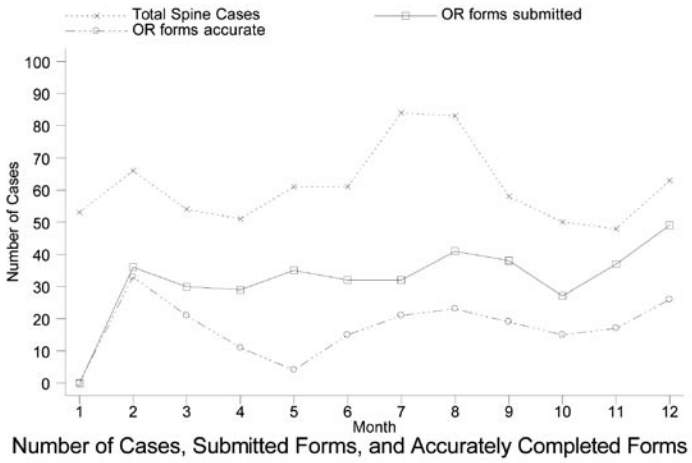

Figure 3: Total volume of spine surgery and overall submission and accuracy rates of information submitted by surgeons during the first twelve months of the program.

occurrences during rounds and other clinical care activities and to report the events and associated circumstances. To design the surveillance methods, we reviewed the literature, and also examined the local UW experience over the past 7 years, to develop a list and definitions for 175 specific adverse events for prospective surveillance. Several secure and confidential mechanisms were established to allow surgeons, residents, and fellows to report adverse occurrences, including making available forms in the operating rooms, inpatient areas, and outpatient clinics, establishing dedicated telephone hotlines, and providing personnel to record information from verbal reports during clinics and conferences. Designated members of our team also reviewed medical records to confirm information on the reported adverse events and to also identify any otherwise unreported events.

Evaluation

To assess resource utilization and eliminate possible redundancy in data collection efforts, we conducted an evaluation of the quality and source for critical data required for surveillance of surgical procedures and associated adverse events. The evaluation examined all spinal surgery procedure performed at one hospital during the first year after implementation of the Spine Quality of Care Surveillance Program. Twelve surgeons performed spinal operations at Harborview Medical Center in 2003. This evaluation assessed the completeness and accuracy of surgical data submitted by these twelve surgeons and the source of reported adverse events.

As part of their surgical procedure documentation in the medical record, the surgeons were asked to complete an operative summary form after each case. We rated the completeness and accuracy of this form with a simple scale: form not submitted; form submitted but incomplete or inaccurate; and form submitted complete and accurate. A complete form contained the following five domains of information:

1. All grafts used.
2. All types of fixation and instrumentation used.
3. The surgical approach.
4. The diseased spinal levels.
5. The treated spinal levels.

Each form submitted by each surgeon was checked for accuracy by comparing the data on the form to the surgeon's operative report in the medical record. We rated the form as accurate if information on all five domains agreed with the dictated with the dictated operative report in the medical record. To assess completeness of adverse event reporting, we identified the primary source for each adverse event identified during prospective surveillance in 2003.

Results

Surgeons are able to provide surgery information on majority of the cases, but often the completed form is inaccurate when evaluated by a strict definition of accuracy (Figure 3). With training, feedback, and intermittent reminders, the response rates and data quality both showed improvement near the end of the first year.

All three sources, surgeons, the spine inpatient team, and the medical record, are important in identifying adverse occurrences. Surgeons report approximately one-third of all the adverse occurrences we identified (Table 2). If we relied only on self-reported adverse occurrences by surgeons, we would severely underestimate the frequency of these events. The inpatient team frequently identifies the events reported by surgeons, and additionally identifies one-third of the total number of adverse events we record. Many of the events reported by surgeons and the inpatient team are not readily identifiable from the medical record. However, twenty percent of the adverse events we identified were only apparent from the chart. The spine surgeons and the spine team frequently function in a consulting capacity; the primary care teams report some adverse events that are not directly reported by the spine service.

Conclusion

It is difficult to integrate clinical research into clinical practice. The documentation requirements of clinical care do not immediately translate into research data. Even with a cohesive and highly motivated clinical team, supported by appropriate training, processes and information systems, gathering reliable data requires additional resources. Surgeons and other members of the inpatient care teams are frequently too busy to consistently provide accurate information suitable for analysis. Clinical research requires dedicated personnel to collect the data essential for meaningful interpretation of results.

Future Work

We are working on identifying a standardized common core set of measures for simplifying the quality-of-care measurement process and make it sustainable for long-term results. We plan to develop a generalizable toolkit for measuring the safety profile of different spinal surgical techniques and devices. Standardized methodology for reporting safety information may

Resource	Task	Time (h/wk) (% effort)		Source of Funding
Research Coordinator	Obtain consent Complete baseline questionnaires	40	(100%)	Orthopedics department
Project Director	Collate and monitor surgery data Collate and monitor anesthetic data Monitor adverse occurrence data	40	(100%)	Research endowment
Data Entry	Data entry	40	(100%)	NIH research grant
Research Nurse	Collect surgery, anesthetic, and intra-operative adverse occurrence data	16	(2 persons at 20% effort each)	Medical centers
Research Nurse	Collect inpatient adverse occurrence data	12	(3 persons at 10% effort each)	Medical centers
Physician reviewers	Review and code adverse occurrences	2	(3 persons at 5% effort each)	Neurosurgery and Anesthesia departments
Principal investigator	Design, coordinate, and supervise study	20	(50%)	NIH research grant
Research Methodology	Design methods and analyze data	3	(3 persons at 2.5% effort each)	NIH research grant

[1]*This list does not include the time provided by surgeons, residents, and fellows for filling out reporting forms or discussing adverse occurrences in weekly conferences.*

Table 1: Personnel involved the UW Spine Quality of Care Surveillance Program and the source of each individual's funding.1

facilitate efforts by organizations such as the Food and Drug Administration to develop guidance documents with benchmarks for approval of new surgical devices and agents. Specifically, we are conducting projects that involve the development and validation of standardized methods to:

(1) identify and classify adverse events associated with spinal surgery;

(2) measure the severity of lumbar degenerative disease so as to allow risk-adjustment for variation in different components of this condition: nerve root compression, joint and disc degeneration, deformity, and multiple spinal segment involvement;

(3) measure characteristics of the surgical procedure so as to enable comparison of procedures performed through different surgical approaches and on different spinal levels;

(4) use these new methods to capture adverse events, disease severity, surgical intensity, and combine them with established methods for medical co-morbidity adjustment, in developing predictive models of early and late outcomes of spinal surgery.

Acknowledgments

We would like to thank Harborview Medical Center and the University of Washington Medical Center for their partnership in establishing the program described in this report. We also would like to thank the following individuals for helping design, establish, and refine the program: Virginia Arvold, Scott Barnhart, Mike Binette, John Culver, Patrick D'Alessio, Jana Day, Rick Goss, Michelle Kelley, Eric Larson, Tim McHenry, Alex Mohit, Chris Shaffrey, Tom Staiger, Louise Suhr, Diana Wiseman.

Supported in part by Grant #P60 AR48093 and Grant # K23AR48979-01 from the National Institute of Arthritis, Musculoskeletal and Skin Diseases.

Source of Report	Number	Percent of All Reports
Surgeon	120	38 %
Inpatient team, nurse or PA	113	36
Inpatient team, fellow	10	3
Inpatient team, resident	1	0
Medical record	68	21
Total	***312***	***100***

Table 2: Source of Reported Adverse Occurrences.

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Deyo RA, Nachemson A, Mirza SK. Spinal-fusion surgery - the case for restraint. N Engl J Med 2004; 350:722-6.

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Measuring the Severity of Lumbar Degenerative Disease

Sohail K. Mirza, M.D., Todd S. Jarosz, M.D., Jens R. Chapman, M.D., Mark A. Konodi, M.S., Patrick J. Heagerty, Ph.D., Judith A. Turner, Ph.D., and Richard A. Deyo, M.D., M.P.H.

Patients with lumbar degeneration present with specific pain symptoms and functional limitations, and they seek the treatment that will provide the most improvement in these areas. The treatment choices offered to symptomatic patients, however, are based not just on symptoms and physical findings but also on imaging findings. When only one disease process is dominant in a particular patient, choice of surgical treatment is relatively straightforward. Disc degeneration is typically treated with fusion procedures. Nerve root compression is treated with decompression surgery. Deformity is treated with realignment through major reconstructive surgery. Because patients with advanced lumbar degeneration frequently have all three degenerative processes occurring concurrently at multiple spinal levels, the surgical treatment offered to a given patient may vary considerably, ranging from laminectomy alone to laminectomy plus anterior and posterior fusion.

Complicating these generalizations is the fact that structural integrity is not tightly linked to pain or functional disability in individuals with degenerative disorders of the spine. Advances in imaging technology over the last two decades have greatly improved our ability to detect more and more subtle variations in anatomic structures of the spinal column. Although imaging studies of patients with pain or nerve root dysfunction commonly show degenerative changes, researchers have identified many similar structural aberrations on imaging studies of asymptomatic individuals. This overlap in imaging findings between symptomatic and asymptomatic patients complicates treatment options for symptomatic patients. Comparing medical and functional outcomes across different treatment options in patients with lumbar degenerative disease requires that we first be able to classify these patients into reproducible disease severity categories. Our goal is to develop such a disease severity scoring system for lumbar degenerative disease.

We are working to develop and validate scales to measure the severity of lumbar spine degenerative disease by characterizing structural changes due to degeneration, deformity, and nerve root compression using subsets of patients

Degeneration: circle a value 0 to 3 at each level	
None	0
Dark disc on T2 MRI	1
End plate edema on T2 MRI	2
End plate sclerosis	3
Height loss: circle a value 0 to 3 at each level	
None	0
Yes, < 50%	1
Yes, > 50%, but not ankylosis	2
Yes, ankylosis	3
Osteophytes: circle a value 0 to 3 at each level	
None	0
Yes, < 2mm	1
Yes, > 2mm but not bridging	2
Yes, bridging	3
Herniation: circle a value 0 to 4 at each level	
None	0
Bulge	1
Protrusion	2
Extrusion	3
Sequestered	4
Stenosis: circle the total score 0 to 6 for each level	
Right foramen	0 or 1
Left foramen	0 or 1
Right lateral recess	0 or 1
Left lateral recess	0 or 1
Central stenosis	0 or 1
Complete block	0 or 6
Total	0 to 6
Listhesis: circle a value 0 to 5 for each level	
None, <10%	0
Grade 1, 10 to 25%	1
Grade 2, 26 to 50%	2
Grade 3, 51 to 75%	3
Grade 4, 76 to 100%	4
Grade 5, > 100%	5
Instability: circle an instability score 0 to 3 for each level	
No instability	0
Mild instability	1
Moderate instability	2
Severe instability	3
Scoliosis and Kyphosis: circle 1 at each involved level and specify total magnitude 0 to 6 for each patient	
<10 degrees	0
11 to 19 degrees	1
20 to 29 degrees	2
30 to 39 degrees	3
40 to 49 degrees	4
50 to 59 degrees	5
> 60 degrees	6

Table 1: Imaging Severity Scales.

Dimension	Rev1 – Rev2	Rev1- Rev1 Rep	Rev2 – Rev2 Rep
Degeneration	0.70	0.72	0.85
Height Loss	0.44	0.49	0.63
Osteophytes	0.47	0.53	0.67
Herniation	0.28	0.61	0.41
Stenosis	0.44	0.37	0.56
Listhesis	0.54	0.64	0.83
Instability	0.38	-0.02	1.00
Scoliosis	0.30	0.71	0.35
Kyphosis	0.41	0.69	0.81
Scol Magnitude	0.51	1.00	0.58
Kyph Magnitude	0.42	0.62	0.62
Average	**0.45**	**0.58**	**0.67**

Table 2: Agreement for each imaging dimension for two reviewers and 10 cases. Both raters rated the cases twice.

enrolled in two ongoing projects: a cohort study of discogenic back pain and a study assessing the safety of lumbar fusion surgery for chronic back pain. We will first develop scales that reliably measure imaging findings related to degeneration, deformity, and nerve root compression. We will then examine the association between these imaging findings and pre-treatment patient functional status, as measured by patient-completed validated measures of back pain-and general health status. This will enable us to determine which structural changes are most strongly associated with pain and function. For example, we will determine whether more severe degeneration is associated with more pain or worse function.

We selected lumbar imaging studies on 10 patients and assembled important images into composite display panels (Figure 1). The selected images included radiographs, Magnetic Resonance, and Computed Tomography-myelography images of the lumbar spine. To show the neural tissue space at each lumbar spinal segment, we showed an axial image of the spinal canal and a sagittal view of neural foramen on each side.

For each spinal segment on each patient, two reviewers (both orthopedic surgeons) assigned a severity score for nine imaging characteristics: disc degeneration, height loss, osteophyte formation, disc herniation, spinal stenosis, spondylolisthesis, instability, scoliosis, and kyphosis (Table 1). We developed consensus-based definitions for the severity scale for each characteristic. The reviewers also assigned two overall magnitude scores to each patient: a magnitude severity score for scoliosis and a magnitude severity of score for kyphosis. Each observer rated the 10 cases at two different times, approximately 3 weeks apart. The inter- and intra-observer kappa values are listed in Table 2. Agreement was in general good to excellent (Maclure 1987).

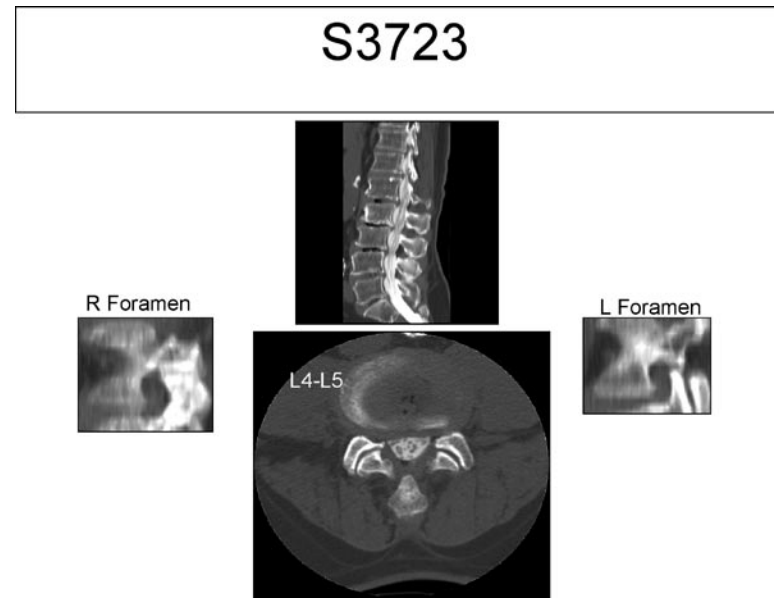

Figure 1: Panel of images CT-myelography for each lumbar segment presented to reviewers. Similar panels were also presented for MR images.

We also calculated a total severity score for each patient based on the sum of the score by the observer across all 11 dimensions. The severity scores by the two raters were highly correlated (correlation coefficient 0.96, Figure 2), suggesting excellent interrater agreement. There was a wide range of severity across patients.

Future Work

We will further evaluate the imaging severity score across more observers and for more cases to determine its reliability for a broad range of patterns of lumbar degenerative disease. We will determine if some of the scales are redundant and can be eliminated. We will then determine the associations of the score for different imaging dimensions with patient pretreatment pain and function, using a sample of approximately 100 patients with lumbar degenerative disease. We will also assess whether imaging characteristics or demographic characteristics are more closely associated with pain and

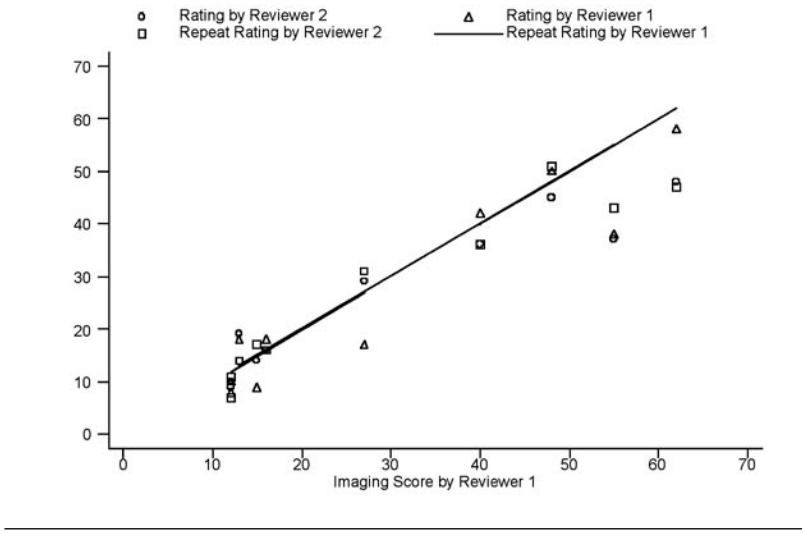

Figure 2: Total Degenerative Disease Severity Score for 10 cases. Score by Reviewer 1 highly correlates with the score given by Reviewer 2 (correlation coefficient 0.96).

function.

Supported in part by Grant #P60 AR48093 and Grant # K23AR48979-01 from the National Institute of Arthritis, Musculoskeletal and Skin Diseases.

Recommended Reading

Maclure M, Willet WC. Misinterpretation and misuse of the kappa statistic. J Epidemiology 1987; 126(2):161-169.

Genetic Association of Lumbar Spondylolisthesis With Type IX Collagen Allelic Variants

Yoshito Matsui, M.D., Ph.D., Sohail K. Mirza, M.D., Jiann-Jiu Wu, Ph.D., Bryan Carter, B.S., Carlo Bellabarba, M.D., Christopher I. Shaffrey, M.D., Jens R. Chapman, M.D., and David R. Eyre, Ph.D.

Disorders of the lumbar spine are the most common musculoskeletal complaints with a lifetime incidence of low back pain in the range 49% to 70%. Occupational risk factors such as lifting heavy loads and driving a motor vehicle are well known, and recent studies reveal significant genetic risks.

Type IX collagen, a quantitatively minor component of cartilages, forms covalent cross-links with type II collagen fibrils, the main structural component of cartilage. Analysis of type IX collagen genes in a Finnish population linked allelic variants that encode tryptophan at position 326 of the α2(IX) chain (Trp2) or at position 103 of the α3(IX) chain (Trp3) to an increased risk of lumbar disc disease (based on MRI) and chronic sciatica (Annunen et al., 1999, and Paassilta, et al., 2001). Since lumbar spine degeneration is not one entity but can be differentiated into several related clinical phenotypes, we performed a case-control study of 108 subjects who underwent lumbar spine fusion surgery to determine whether a certain subset of lumbar spine disease is specifically associated with the tryptophan polymorphisms.

Materials and Methods

Study Design

We designed a prospective case-control study to investigate the association between the presence of a genetic risk factor (a tryptophan allele polymorphism for collagen type IX) and severity-ranked clinical subtypes of lumbar spine degenerative disease requiring surgical treatment. One hundred and eight patients were enrolled in the IRB-approved study. Based on clinical records and imaging studies each patient was assigned by a consensus opinion to one of five categories reflecting progressively severe degenerative changes.

1. No lumbar degeneration (to include patients with a lumbar vertebral fracture treated by fusion); 2. Lumbar degeneration treated with fusion for chronic discogenic pain; 3. Lumbar disc herniation treated by open micro-discectomy for symptoms refractory to non-surgical treatment; 4. Lumbar degenerative spinal stenosis without spondylolisthesis treated by decompression and fusion; 5. Degenerative stenosis with spondylolisthesis treated by decompression and fusion.

Analysis

Genomic DNA was extracted from peripheral blood. Tryptophan polymorphisms of the α2 chain (Trp2) or α3 chain (Trp3) of type IX collagen were detected by polymerase chain reaction (PCR) followed by direct sequencing of the PCR products.

The patients were divided into two groups according to collagen IX genotype: 1) positive for one of the two tryptophan codons (Trp(+) group; Trp2 or Trp3), and 2) no tryptophan codon (Trp(–) group). Unadjusted odds ratios were calculated for presence of tryptophan allele and race, gender, age, and disease classification. Logistic regression was used to adjust for the independent effect of Trp(+) allele, race, gender, and age in predicting the diagnostic classification.

Results

In total, 107 patients were included in the study population. Gender distribution was 50 males and 57 females, with a mean age of 48.3 years (16 to 87). The racial profile was 7 African-American, 3 Asian, 94 Caucasian, and 3 other (1 Middle Eastern, 1 Native American, and 1 Pacific Islander). All patients in the disc degeneration, spinal stenosis without spondylolisthesis, and spinal stenosis with spondylolisthesis, had symptoms for more than a year, with 28 of 35 (80%) of patients in the spondylolisthesis category reporting symptoms for more than five years. Most patients with disc herniation had a shorter duration of symptoms, with 30 of 34 (90%) reporting symptoms for less than a year.

Eleven patients had one or the other tryptophan-encoding allele for collagen type IX. All eleven Trp(+) patients were heterozygotic for one Trp codon; 4 for Trp2+ and 7 for Trp3+. The genotype was independent of age, race, gender, and spinal level of most severe disease. Presence of the Trp-allele, however, was not equally distributed across the diagnostic classification categories (p-value of 0.034 for Chi-square test with more than 2 categories, alpha =0.05). In particular, Trp(+) alleles clustered in the patients classified as spinal

Risk Factor	*Odds Ratio*	*95% Confidence Interval*	*p-value*
Trp(+)	**6.81**	**1.68 to 27.6**	**0.007**
Race (African American or Asian)	0.20	0.024 to 1.61	0.130
Gender (female)	3.19	1.37 to 7.44	0.007
Age 50 years or more	3.18	1.37 to 7.37	0.007

Table 1: Unadjusted Odds Ratios for the association between the diagnostic category "spinal stenosis with spondylolisthesis" and risk factors trp-allele, race, gender, and age. Odds ratios calculated for a 2X2 table for each risk factor (exposure) versus diagnosis of spondylolisthesis (disease), alpha = 0.05

Risk Factor	Odds Ratio	95% Confidence Interval	p-value
Trp(+)	**18.9**	**2.14 to 167.30**	**0.008**
Race (African American or Asian)	0. 06	0.003 to 1.29	0.073
Gender (female)	2.79	1.09 to 7.15	0.033
Age 50 years or more	2.90	1.13 to 7.44	0.027

Table 2: Adjusted Odds Ratios for the association between the diagnostic category "spinal stenosis with spondylolisthesis" and risk factors trp-allele, race, gender, and age, adjusted for the independent effect of each risk factor. Odds Logistic regression for model: Diagnosis(spondylolisthesis) = β1 *trp(w2 or w3 positive) + β2 *Race(African American or Asian) + β3 *Gender(female) + β4 *Age (>50) + error.

stenosis with spondylolisthesis: 8 of 35 patients with spondylolisthesis (23%) were Trp(+) compared to 3 of 34 (9%) for disc herniation, and none in the other three diagnostic groups (fracture, disc degeneration, and spinal stenosis without spondylolisthesis). All eleven patients with Trp(+) allele had nerve root symptoms, with four patients additionally reporting back pain.

A Trp(+) allele was associated with race designation of African-American or Asian (odds ratio 4.61 with Caucasian as the referent group, p-value 0.357) and diagnosis of spondylolisthesis (odds ratio 6.81, p-value 0.0028).

Radiographs of one Trp(+) patient with spinal stenosis and degenerative spondylolisthesis are shown in Figure 1 and MRI images of a second Trp(+) patient with degeneration and isthmic spondylolisthesis are shown in Figure 2, as examples.

We assessed the contribution of four risk factors on the diagnostic classification category of "spinal stenosis with spondylolisthesis". The unadjusted and adjusted odds ratios are listed in Tables 1 and 2, respectively. Three risk factors (Trp(+) allele, female gender, and age greater than or equal to 50 years) are independently associated with the diagnosis of spondylolisthesis. Although race designation of African American or Asian is associated with Trp(+) allele, this race category is not associated with the diagnosis of spondylolisthesis.

Discussion

Our results indicate that the tryptophan polymorphisms are linked to the development of symptomatic spondylolisthesis requiring surgery. All the patients with spondylolisthesis in this study had decompression and fusion surgery to treat symptoms of back pain and nerve root compression. The combination of degenerative changes causing nerve root symptoms and spondylolisthesis indicates that tryptophan polymorphisms may be associated with more severe degeneration resulting in stenosis of the spinal canal or neuro-foramina and slipping of the adjacent vertebrae. Another possible explanation for the association of tryptophan polymorphisms and symptomatic spondylolisthesis is chronic inflammatory irritation of the nerve roots at the site of the lumbar stenosis, and degradation products of tryptophan-containing type IX collagen may cause an inflammatory response and local nerve root irritation.

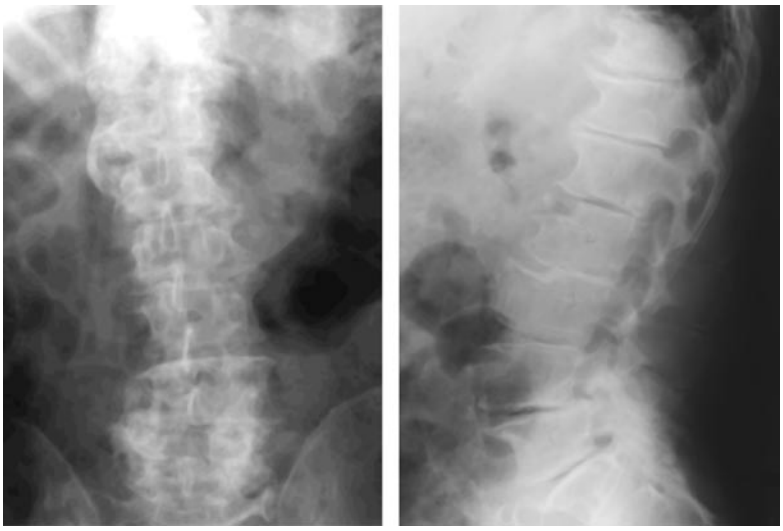

Figure 1: Anteroposterior (left) and lateral (right) radiographs of the lumbar spine of one Trp3+ patient showing extensive disc degeneration and osteophytes throughout and grade 1 degenerative spondylolisthesis at L4/5.

The nucleus pulposus is gel-like and has a similar collagen phenotype to that of hyaline cartilage in which the developing fibrillar network is a cross-linked copolymer of collagens II, IX and XI. The type IX collagen molecule consists of three triple-helical domains, COL1, COL2 and COL3 and four non-helical domains, NC1-NC4. Tryptophan residues do not normally occur in triple-helical domains of collagenous proteins since they tend to disrupt the triple-helix. Trp2 is in the middle of α2(IX)COL2 and Trp3 is in the middle of α3(IX)COL3. The long-term effects of Trp incorporation are unknown, but could include structural changes to the collagen fabric, susceptibility to degradative proteases and/or production of inflammatory metabolites, for example through Trp oxidation products.

Lumbar degenerative disease describes a broad disease group. Our study suggests that a better means of stratifying clinical subtypes of lumbar degenerative disease would help in identifying biological mechanisms of disease phenotypes within this broad classification. We do not have an adequate database on the frequency of the Trp2 and Trp3 alleles in the Pacific Northwest population from which the patients were drawn. So, we cannot assess whether a Trp(+) allele is associated with increased risk of lumbar disc disease in general. It is

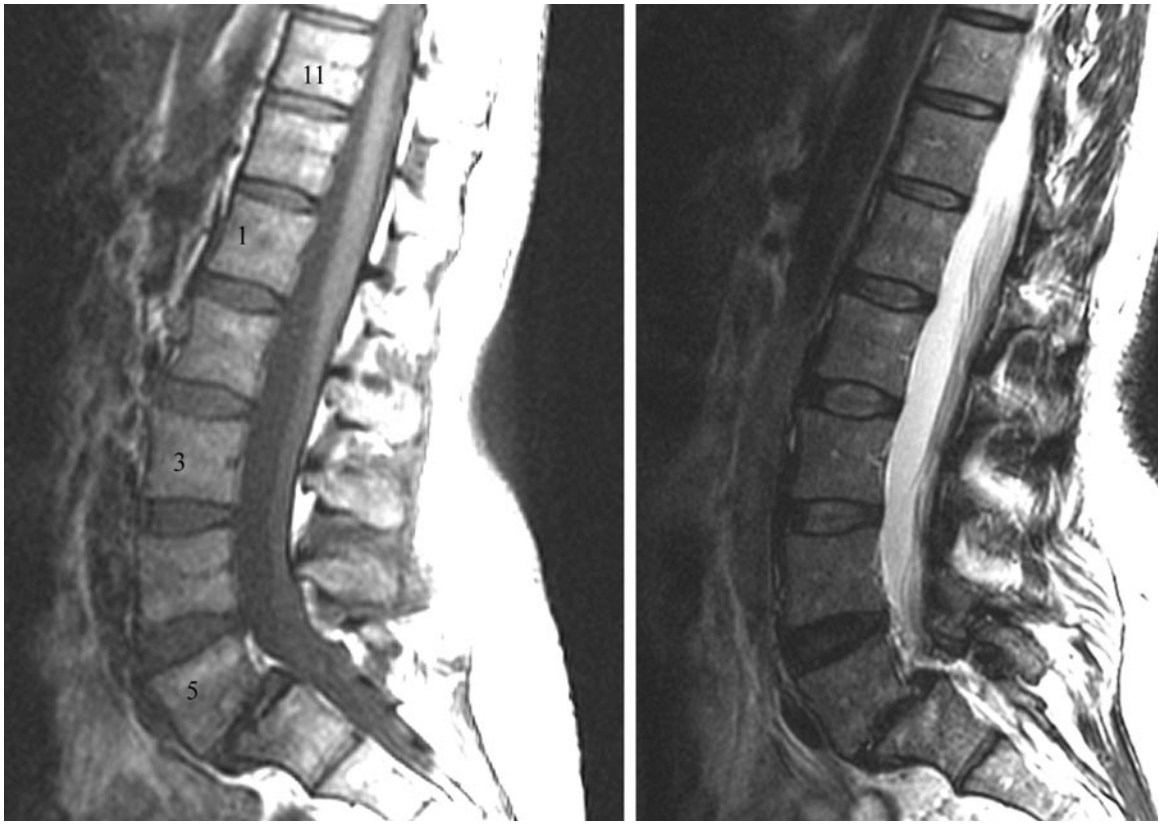

Figure 2: Sagittal T1 (left) and T2 (right) weighted MRI images of a Trp3+ patient with spondylolisthesis. This 50-year-old woman showed grade 2 isthmic spondylolisthesis of L5/S1 with 30% anterior translation of L5 on S1. A bilateral pars defect was evident at L5. The patient showed a 5-year history of progressive back pain prior to surgery.

possible that the risk of any degenerative changes leading to spinal stenosis and spondylolisthesis is much higher in Trp(+) than in Trp(-) individuals, or that Trp(+) patients are more likely to develop symptoms that lead to surgical treatment.

Conclusion

Our findings indicate that the tryptophan polymorphisms predispose carriers to the development of symptomatic spinal degeneration and stenosis associated with spondylolisthesis that needs surgical intervention. Biochemical studies on disc tissue obtained from the subjects with the tryptophan allele may provide clues as to the molecular basis of the linkage.

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Protein Consequences of a C-propeptide Mutation in Col2a1 in the Chondrodysplastic Dmm Mouse

Russell J. Fernandes, Ph.D., Robert E. Seegmiller, Ph.D., Whitney Nelson, B.S., and David R. Eyre, Ph.D.

Type II collagen, the major structural protein of cartilage, is essential for normal embryonic skeletal development and the mechanical properties of articular cartilage. Mutations in the type II collagen gene (*Col2a1*) cause chondrodysplasia and osteoarthritis in mice and humans. The type II collagen monomer, a homotrimer, is synthesized by chondrocytes as procollagen molecules with extension peptides at the N- and C-terminal ends. The process by which the newly synthesized chains associate and fold in the rough endoplasmic reticulum is not well characterized for type II procollagen.

The Disproportionate micromelia (Dmm) mouse carries a three nucleotide deletion in *Col2a1* in the region encoding the C-propeptide resulting in the substitution of one amino acid, Asn (N), for two amino acids, Lys-Thr (KT), in the wild-type gene. Homozygotes (D/D) are disproprotionately short and die at birth (Figure 1A). Heterozygotes (D/+) appear normal at birth but dwarfism is apparent at a week and increases during growth (Figure 1B). This mutation presumably causes a structural alteration in a domain that is highly conserved within type I, II and III collagens. In humans, five dominant mutations within the COL2A1 C-propeptide domain have been reported; all cause forms of spondyloepiphyseal dysplasia.

We have used the Dmm mouse to investigate the role of the C-propeptide in the assembly of stable triple helical type II collagen. Here we report findings of this mutation on type II collagen protein expression in the chondrocytes and cartilage matrix of homozygous and heterozygous Dmm mice.

Materials and Methods

Tissue acquisition and genotype determination

Day-18 fetuses were obtained from matings of heterozygous mice. The genotype of the fetuses was determined by PCR amplification of a region of the *Col2a1* gene followed by restriction enzyme analysis.

Collagen extraction

Rib plates from wild type (+/+) mice and from mice homozygous and heterozygous for the Dmm mutation were minced and extracted with 4 M GuHCl. Collagen in the residue was solubilized by pepsin digestion.

Electrophoresis and Western blotting

Pepsin and neutral salt solubilized collagen chains were resolved by SDS-PAGE, transferred to PVDF membrane and probed with monoclonal antibody (mAb) 1C10 which recognizes CB9,7 in the triple helical region of type II collagen chains. Pepsin solubilized type II collagen from Swarm rat chondrosarcoma cell line RCS-LTC or native type II collagen from human fetal cartilage were used as standards.

Immunohistochemistry

Ten-micron thick frozen sections of fetal ribs, acetone-fixed and hyaluronidase-treated, were exposed to mAb 1C10 and developed using horseradish peroxidase. The staining pattern of the tissue was documented by photomicroscopy.

Results

Biochemical analysis

Figure 2A shows a Western blot of pepsin-extracted type II collagen from wild-type (+/+), homozygous (D/D) and heterozygous (D/+) mouse rib cartilage. Pepsin solubilizes type II collagen from cross-linked fibrils

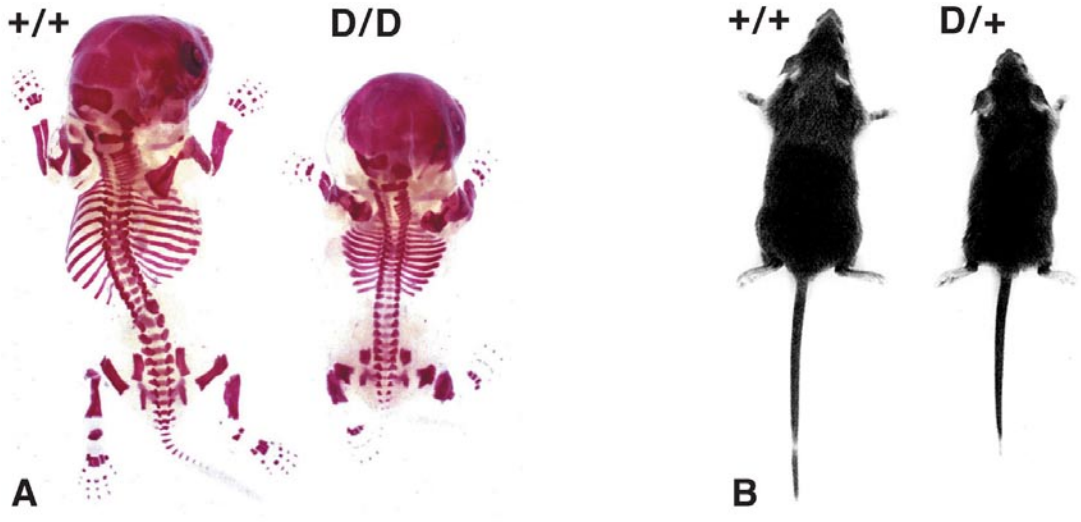

Figure 1: (A) Neonatal skeletons of wild type (+/+) and Dmm (D/D) mice. Note the small ribcage with shortened endochondral bones and spine in D/D. (Pace et al., Dev Dynamics 1997, 208: 25-33). (B) Wild type (+/+) and dwarf heterozygote (D/+) mice at week 4. (Brown et al., J. Embryol. Exp. Morph. 1981, 62: 165-182).

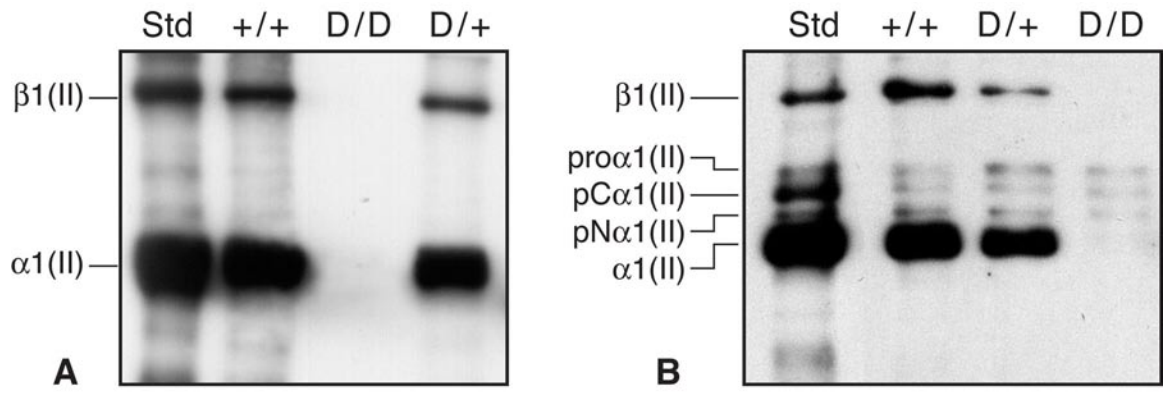

Figure 2: Western Blot analysis of (A) pepsin-extracted and (B) 4M guanidine-HCl extracted type II collagen from wild type (+/+), heterozygous (D/+) and homozygous (D/D) mouse rib cartilage samples. Std = pepsin solubilized type II collagen from the RCS-LTC cell line in (A). Std = 4M GuHCl extract of human fetal cartilage in (B). proα1(II), pCα1(II), pNα1(II) are processing intermediates of type II collagen.

by cleaving telopeptides but leaving the triple-helical domains intact. α1(II) chains are present in wild-type and heterozygous tissue but not in homozygous mouse cartilage samples. Stable type II collagen appears, therefore, to be completely absent from the D/D fetal cartilage matrix. To examine newly synthesized collagen, a 4M guanidine-HCl extract was run similarly (Figure 2B). Fully processed (mature) α1(II) collagen chains and β1(II) dimers were recovered from +/+ and D/+ cartilages. No processed α1(II) chains were detected in the extract from D/D cartilage.

Immunohistochemical analysis

The extracellular matrix of +/+ rib cartilage stained uniformly with mAb 1C10 (Figure 3). Relative to wild type, the staining in homozygote cartilage matrix (D/D) was virtually absent (asterisks). The staining pattern in the cartilage matrix of the heterozygote was heterogeneous but still positive compared to the homozygote tissue. The type II collagen stain was concentrated as

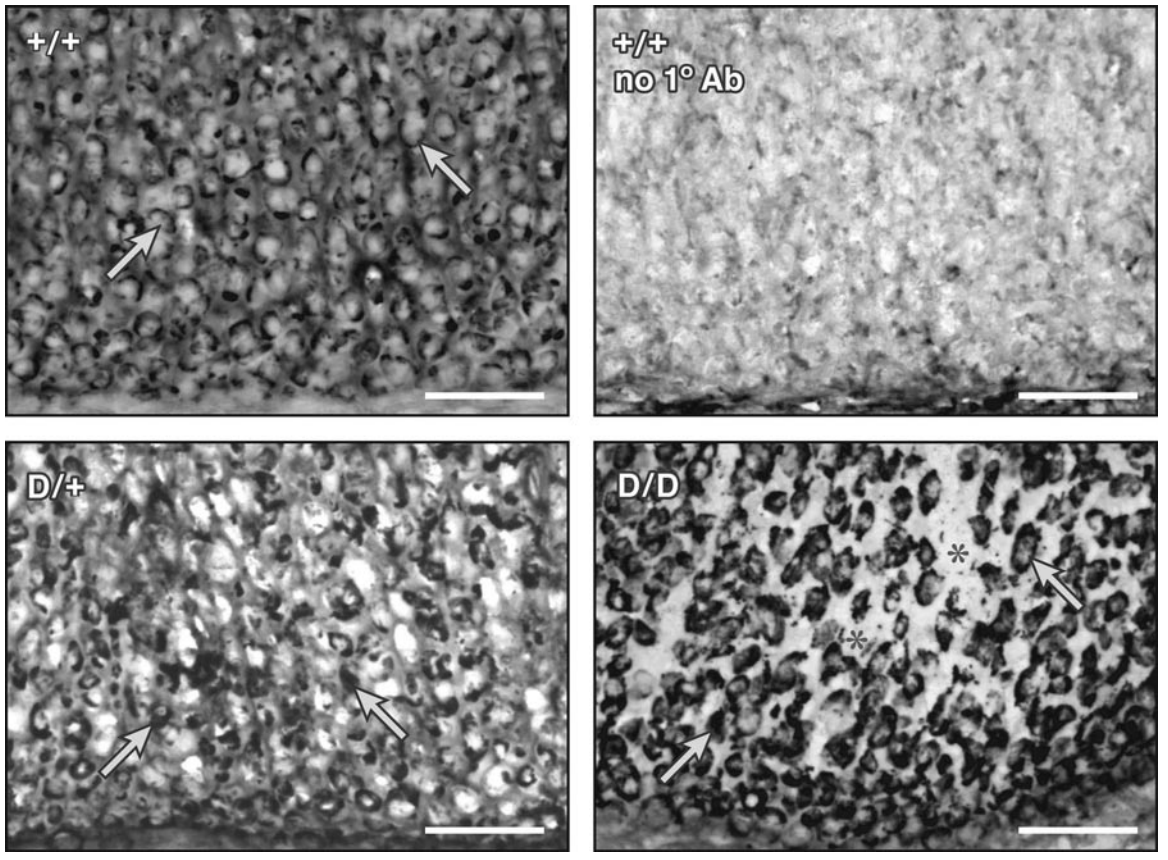

Figure 3: Immunohistochemistry of Dmm mouse rib cartilage revealing the staining pattern of type II collagen.Bar = 0.1 mm.

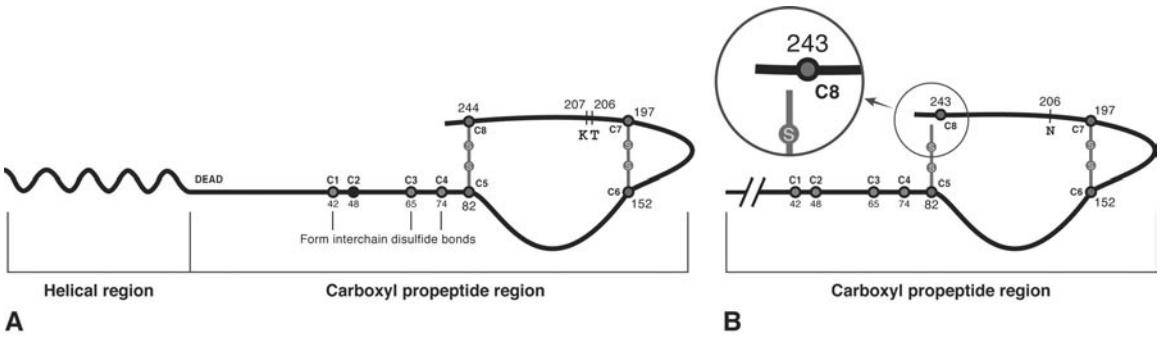

Figure 4: Map of the C-propeptide region of mouse type II procollagen. (A) shows the position of KT206-207 relative to the intrachain disulfide bonds (C82-244 and C152-197). (B) the KT206-207 –> N206 mutation shortens the C-propeptide and alters the net charge in a conserved domain. An intrachain disulfide bond may not form. Residues numbered from the first amino acid [D] of the C-propeptide.

dark punctate deposits in chondrocytes of D/+ and D/D (arrows).

Discussion

Immuno-localization of type II collagen in rib cartilage (Figure 3) clearly shows that cartilage from the homozygous mutant mouse lacks type II collagen staining in the extracellular matrix (compare D/D with +/+). Cartilage from the heterozygous mouse showed less intense matrix staining for type II collagen than the cartilage of wild-type mice (compare D/+ and +/+) but clearly more than in the cartilage from the homozygous mouse (compare D/+ and D/D). These results support the biochemical data (Figure 2) showing that mature stable type II collagen molecules are present in the cartilage matrix of wild-type and heterozygous mice but absent from that of homozygous mice.

Type II collagen was detected as patchy deposits only in the cell lacunae of cartilage from homozygous mice. Some cells in the cartilage of the heterozygous mouse showed similar staining but this was not evident in the cartilage of the wild-type mouse. It seems likely that the cell-associated stain represents deposits of improperly folded intracellular type II procollagen. This observation is consistent with the presence of a distended rough endoplasmic reticulum reported in chondrocytes of the homozygote cartilage and heterozygote cartilage (unpublished data) by electron microscopy.

The lack of any type II collagen in the matrix of the homozygotes explains the severity of the matrix pathology which results in neonatal death of the Dmm mouse. The heterozygous mouse, however, is viable and shows a normal phenotype at birth. Our finding that mature stable type II collagen is present in the heterozygote matrix, albeit at reduced levels, suggests that the normal allele is capable of rescuing the phenotypic effects of the Dmm allele. However, the heterozygote does develop mild chondrodysplasia 1-4 weeks postnatally and joint pathology resembling osteoarthritis later. Our findings are consistent with an insufficiency of type II collagen in cartilage extracellular matrix of heterozygotes during growth.

The data establish that the C-propeptide is important for proper assembly of type II procollagen molecules. The one-for-two substitution, KT206-207N, in the C-propeptide of the α1(II) collagen chain in the Dmm mouse shortens and alters the net charge in a conserved domain. We speculate that this is sufficient to change the secondary structure and interfere with one of the two intrachain disulfide bonds in the C-propeptide from forming (Figure 4). This in turn may disrupt proper chain association so that stable triple-helical molecules cannot assemble from mutant chains alone in the homozygotes with a total failure to be secreted into the extracellular matrix. Analysis of procollagen extracts of cartilage (Figure 2B) supports this conclusion.

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Zoledronic Acid Results in Increased Total Bone Volume in a Rabbit Spine Fusion Model

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Rachael Bugler, and Julie Briody

Lumbar spine fusion is a common surgical procedure, the classic method being an intertransverse process fusion with iliac crest bone graft. Current reported fusion rates are around 75% to 90%, i.e. up to one quarter of operations fail to produce spinal fusion. This is even more of a concern in some pediatric conditions such as neurofibromatosis, where spinal deformity occurs commonly and attempts at fusion are frequently unsuccessful. We have performed trials with nitrogen containing bisphosphonates in distraction osteogenesis which showed significant increases in callus volume, mineral content and strength in treated animals, even in the presence of stress-shielding. In this experiment, we study the effects of single-dose zoledronic acid (ZA) in spinal fusion.

We hypothesise that single dose zoledronic acid will increase fusion mass, mineral content, density and strength. Further, these increases may lead to an increase in fusion rates.

Methods

48 New Zealand white rabbits underwent bilateral posterior intertransverse fusion at L6-L7. A subcutaneous dissection was carried out exposing the lumbar musculature and the iliac crests. Two paramedian fascial incisions were then developed between the multifidus and longisimus bilaterally exposing the transverse processes of L6 and L7. The posterior iliac crests were exposed bilaterally allowing one gram from each side to be harvested for morselized bone graft. The L6 and L7 transverse processes were decorticated prior to the addition of bone graft. Closure of the fascia and skin were then performed.

Excluded animals were replaced such that there were 24 rabbits at each time point.

Local ZA was applied mixed with the iliac crest at a dose of 20 µg. Systemic ZA was administered as a single IV infusion over 20 minutes at surgery at 100 µg/kg.

At the six and twelve week marks, the rabbits were culled and the spines were denuded of soft tissues from L5 to the sacrum. The individual spines then underwent manual palpation to determine whether they were fused or not. XR was performed and remodeling of the fusion mass graded. Grade 3 was remodeling near complete-very few bone graft chips visible, Grade 2 was moderate remodeling - bone chips visible in some areas, Grade 1 was minimal remodeling - multiple bone chips seen in multiple areas. Quantitative CT analysis with of the fusion mass was then performed and analysis software. Thirteen 2mm cuts were made through each spine, and the fusion mass isolated as the region of interest for analysis.

Results

Clinical Evaluation

Fusion by manual palpation at the time was determined as no motion. There was an increase rate of fusion to from 25% to 63% for the Systemic ZA group. This did not reach statistical significance.

Radiology

Radiographic assessment of remodeling is given in Table 1.

At 12 weeks there was a significant difference in remodeling scores ($p<0.05$). Saline group had significantly better scores than Local ZA, but there was no statistically significant difference between Systemic ZA and Saline.

CT

Both vBMD and BMC of the fusion mass was increased in the ZA treated groups at 6 weeks (Figures 3 and 4). These values were maintained over time in the ZA groups, whereas the vBMD fell over time in the saline control groups. At 12 weeks, BMC was 69-87% higher in the treated groups ($p<0.01$). Fusion mass volume was not significantly larger at 6 weeks. Maintenance of a fusion mass volume in treated groups compared to a reduction in size in saline controls led to a 29% increase in Local ZA ($p<0.05$) and 41% increase in Systemic ZA ($p<0.01$) over saline by 12 weeks (Figure 5).

	6 Weeks	12 Weeks
Saline	8	8
Local ZA	8	8
Systemic ZA	8	8
	24	24

Table A: Rabbits at 6 weeks and 12 weeks.

Discussion

In prior studies done at L5/L6 the fusion rates with autologous graft alone have varied from 33-73%. This relatively high fusion rate makes it very difficult to power a study to show a significant difference based on fusion rates. As an example an increase from 73% to 100% would require 27 animals in each group (Sample Power, SPSS Inc). We chose L6/L7 as a model predicting it would have a lower baseline fusion rate as it is closer to the sacrum and the transverse process of L7 is smaller than the more caudal levels. The fusion rate was indeed low at 12.5% at 6 weeks and 25% at 12 weeks.

We chose to use ZA, a third generation bisphosphonate with a nitrogen bearing side-chain, to reverse osteoclastic activity and decrease bone turnover, as it can be given as a single dose. The effect is almost immediate as ZA is given parenterally. Bone turnover reduced within days; the duration of remodeling delay could be theoretically altered by altering the dose of ZA, or by prolonging ZA therapy. Bisphosphonates do not interfere with osteoclast recruitment or attachment, but they do inhibit osteoclast activity.

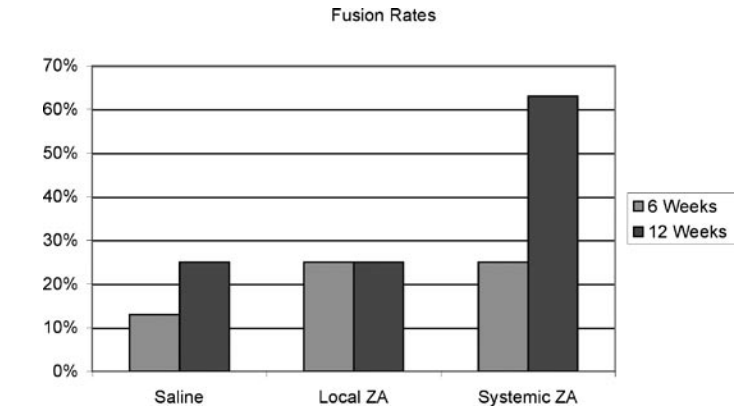

Figure 1: Fusion rates at 6 and 12 weeks for the treatment groups.

6 weeks Totals	3	2	1
Saline	2	4	2
Local	0	4	4
Systemic	0	3	5

12 weeks Totals	3	2	1
Saline	5	3	0
Local	0	3	5
Systemic	2	5	1

Table 1: Radiographic Grading of Remodelling at 6 and 12 Weeks.

The study confirmed our hypothesis that ZA administration would increase fusion mass mineral content, density, and size, and that this increase would be maintained for a longer period of time. We had further hypothesized that by maintaining a high fusion mass density and size, the spine would be more likely to fuse. We indeed achieved an increased fusion rate at 12 weeks from 25% to 63% in the Systemic ZA group, but no change in the local ZA group. Because this study did not have sufficient power this was not significantly different. A post-hoc power analysis reveals that for a baseline fusion rate of 25%, an increase in fusion rate to 50% requires 60 animals in each group, an increase to 75% requires 15 in each treatment group. This analysis can be used for further studies.

We can state that our hypothesis can be rejected for the local dose group. Despite maintaining an increase in fusion mass volume, there was no trend toward increased fusion in the Local ZA group. Of relevance in explanation is the qualitative data we collected on radiological remodeling. Despite using a lower dose in the Local ZA group, the bisphosphonate was directly applied to the bone graft, and at the dose chosen in this study this inhibited remodeling to such an extent that fusion did not occur. In a previous study, Bae et al examined two doses of alendronate in an L5/6 rabbit spine fusion model. They used only a small amount of graft with the hypothesis that alendronate would increase fusion mass size by inhibiting osteoclast activity. Callus size was increased, but at high doses continued throughout the experimental period, fusion rates actually decreased in the high dose group. Our approach is to give a single parenteral dose, which allows remodeling over time as the effect of the drug wears off. The continual dosing given by Bae, and perhaps simulated in our Local ZA group, increased callus size without increasing fusion. These studies confirm fusion mass size can be increased with bisphosphonate use, but further work on dosing, timing and route of administration is required to confirm that this can lead to increased fusion rates, at least in these models.

It is of note that in the saline control group, fusion mass reduced over time even though fusion had not occurred in the majority of cases. Remodeling scores were the most advanced, yet this did not result in fusion. It is this problem that we were trying to address. We believe that substantial remodeling and resorption of bone prior to bony union is inappropriate.

This problem can occur because of a combination of local biological and mechanical factors. One of these factors

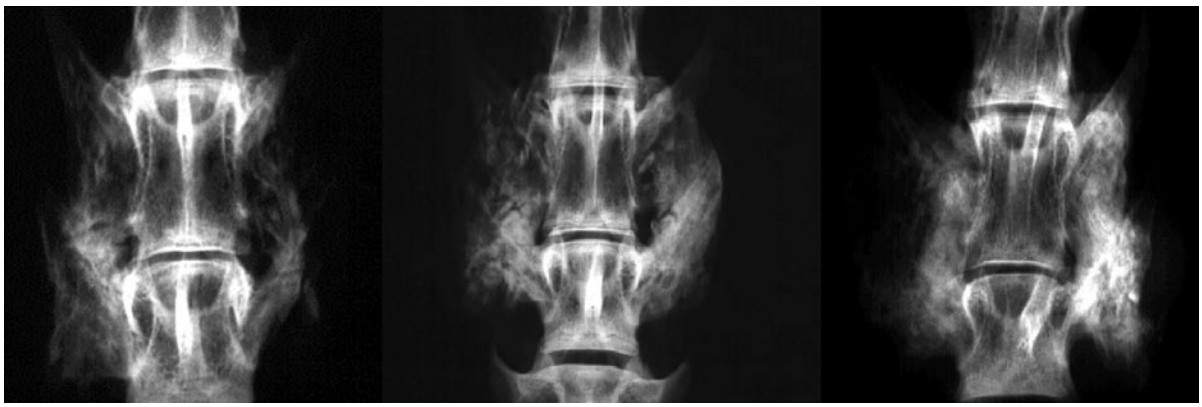

Figure 2: Radiographs. Saline (A), Local ZA (B) and Systemic ZA (C) at 12 weeks. Note the increased apparent density of the bone in the ZA groups. The Local ZA (B) group displays significant remodelling delay – distinct chips of bone graft are still visible at 12 weeks.

may be stress-shielding given the fact that the vertebral bodies are still intact and there is minimal stress between the TPs to induce further bone formation. We have recently performed trials with ZA in distraction osteogenesis in a NZ rabbit model that showed improvement in the volume and mineralization of new bone and reduced stress-shielding osteoporosis. Bone mineral accrual was significantly faster in the treated groups in the first two weeks after distraction. The cross sectional area of new bone formed in the regenerate was increased by 49% in the ZA group, and by 59% in another group given a second ZA dose at 2 weeks. The bone mineral content (BMC) of the regenerate was increased by 93% in the ZA group versus controls and by 111% in the re-dosed ZA group. Mechanical testing of the tibia in four-point bending showed increases in peak load of 29% for the single dose group and 89% for the re-dosed group. Further study revealed that complete remodeling occurs over 44 weeks after the single dose intervention. A similar effect would be expected in our rabbit spine fusion model in which stress shielding is also present. With systemic ZA administration we were able to delay remodeling and allow a majority of the cases to fuse by 12 weeks.

The approach of concomitant bisphosphonate use in fusions could be problematic if osteoclasts were necessary for removal of all chondral elements in endochondral ossification. However, in another experiment, we noted no difference in the disappearance of chondrocytes from a fracture callus, nor do nitrogen containing bisphosphonates inhibit the mineralisation of the cartilagenous septae after hypertrophy of the chondrocytes. In simple terms, bisphosphonates do not seem to interfere with the endochondral ossification front. They do interfere with resorption of the calcified cartilaginous matrix scaffold on which new bone forms – the latter is the desired effect of the intervention in this scenario, we wish to retain this scaffold for bone formation for a longer time.

It has recently been shown that vascularization and removal of non-calcified cartilage matrix in the growth plate is the role of endothelial cells and chondrocytes themselves, as evidenced by no interference with this process at the growth plate with high doses of Clodronate or in mice completely lacking osteoclasts. While this has not been proven in endochondral ossification in fracture callus or fusions, our preliminary data is consistent with this.

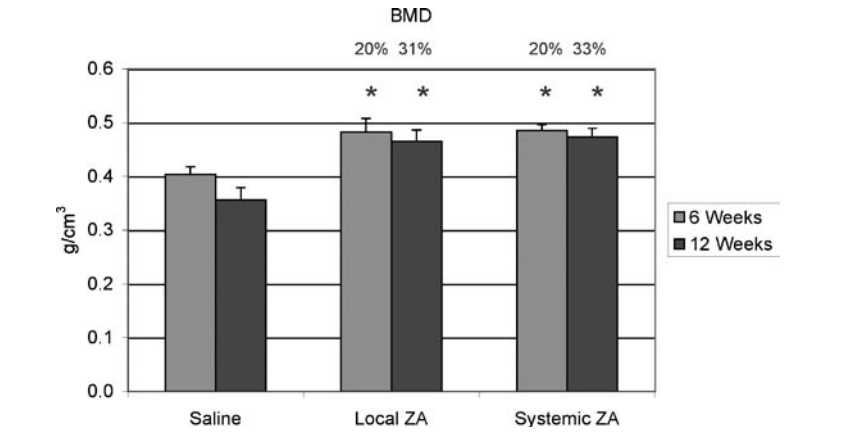

Figure 3: vBMD at 6 and 12 weeks: Local and Systemic ZA groups have significantly increased BMD than bone graft alone ($p<0.05$).

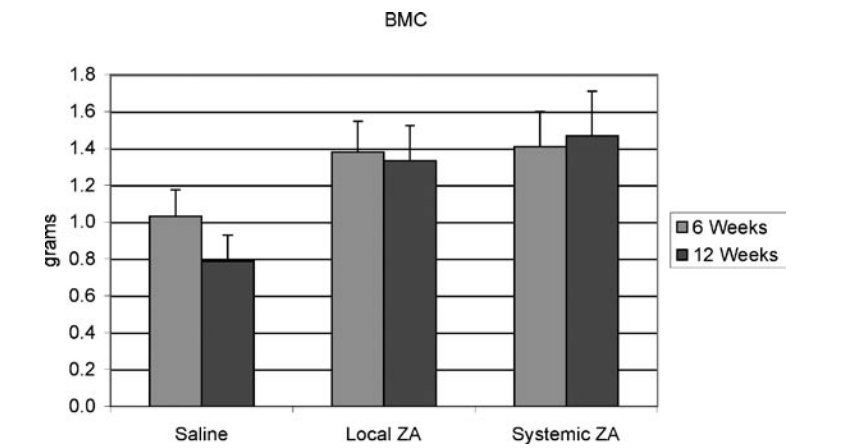

Figure 4: BMC at 6 and 12 weeks: Local and Systemic ZA groups have significantly more BMC than local bone graft alone ($p<0.05$).

The most important result to emerge from a recent study by Morone et al in NZ white rabbit L5-L6 spine fusion model was the observation that the peaks of gene expression in the central zone of the fusion mass lagged 1 to 3 weeks behind those in the outer zones. This correlates with the delay in bone formation in the central zone (seen histologically), and the fact that nonunions occur within the central zone of the fusion mass. Previous histological studies showed that healing of the fusion began at the decorticated transverse processes (outer zones) and progressed to the central zone by the fifth week. Remodeling and formation of a cortical rim and mature bone marrow occurred by the tenth week. Interestingly, we found that almost all of our nonunions occurred at the L7 TP junction and not in the central zone of the bone mass as has been described elsewhere. This may be due to the relatively smaller TP at L7 and therefore the corresponding reduced osteoinductive activity.

Boden's histological work also provided indications, at a histologic level, as to why nonunions in the central zone occur. Incorporation of autogenous bone graft into the spine fusion mass depends on the influx of osteoprogenitor cells and a vascular supply from the exposed bone marrow on the decorticated transverse processes in the outer zones. In other words, the central zone is compromised

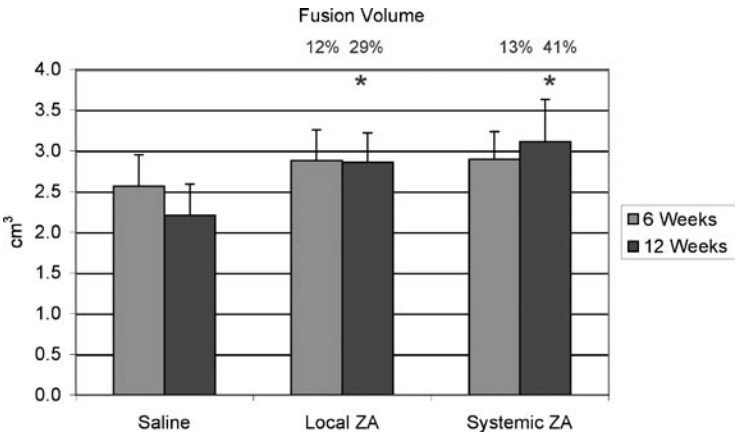

Figure 5: Total bone volume at 6 and 12 weeks: Fusion mass volume is significantly increased at 12 weeks in both treatment groups ($p<0.05$).

geographically. Eventually, the healing process extends to the central zone; however; in some cases it is too late because the bone graft has resorbed and a nonunion results.

In conclusion, systemically administered zoledronic acid increased fusion mass mineral density, content and volume, and led to a fusion rate of 63% by 12 weeks in an L6/L7 rabbit model of spinal arthrodesis using autograft. Locally applied zoledronic acid significantly delayed remodelling at the dose given in this study.

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Serine-Arginine Proteins Regulate Alternative Splicing of Type II Collagen

Eric O. Klineberg, M.D., Howard A. Chansky, M.D., Michael Blackburn, B.S., Anna Zielinska-Kwiatkowska, M.D., and Liu Yang, Ph.D.

In endochondral bone formation, chondrocytes differentiate from a resting to proliferative state followed by maturation and a terminally differentiated state. In the center of this rudimentary bone, proliferating chondrocytes can further differentiate into hypertrophic chondrocytes. These hypertrophic cells mineralize the surrounding matrix before undergoing apoptotic cell death. The cartilage matrix left behind then provides a scaffold for growth of osteoblasts and osteoclasts along with other cells that comprise mature bone. Terminal differentiation of hypertrophic chondrocytes is critical for the formation of bone and for remodeling of the endochondral matrix. This process involves the condensation of mesenchymal cells and their subsequent differentiation into proliferating chondrocytes.

The characteristic feature of articular chondrocytes is the expression of type II collagen (COL 2 gene). Type II collagen is the predominant form of collagen in the cartilaginous extracellular matrix. Alternative splicing is an essential step in gene expression and is known to affect important cellular processes such as tumor suppression, cell cycle control, apoptosis, and the development of the skeleton. Two procollagen transcripts are produced from the single type II collagen gene. COL 2A and COL 2B differ by the presence or absence, respectively, of exon 2 in the pre-mRNA transcript. The alternatively spliced exon has a highly conserved cysteine rich globular domain in the amino-propeptide. Alternative splicing of the COL 2 pre-mRNA is closely related to the state of differentiation of chondrocytes. While COL 2A is the predominant splicing product synthesized by immature proliferating cells, COL 2B is the primary product produced by hypertrophic chondrocytes. In addition, aberrant splicing of type II collagen is now implicated in several orthopaedic diseases including the Kniest form of spondyloepiphyseal dysplasia.

Chondrogenesis is regulated by a variety of growth and differentiation factors. Many transcription factors have been shown to be involved in the regulation of collagen genes, and studies from recent years have pointed to Sox9, a transcription factor with a high-mobility group domain, as one of the major regulators of collagen genes and chondrocyte differentiation. However, though Sox9 binds to a specific sequence in the promoter and enhancer regions of the COL 2 gene to transactivate these cartilage matrix genes in chondrocytes, ectopic expression of Sox9 in non-chondrogenic cells was not sufficient to have a measurable effect on collagen gene expression.

Serine-arginine (SR) proteins are a family of important splicing factors

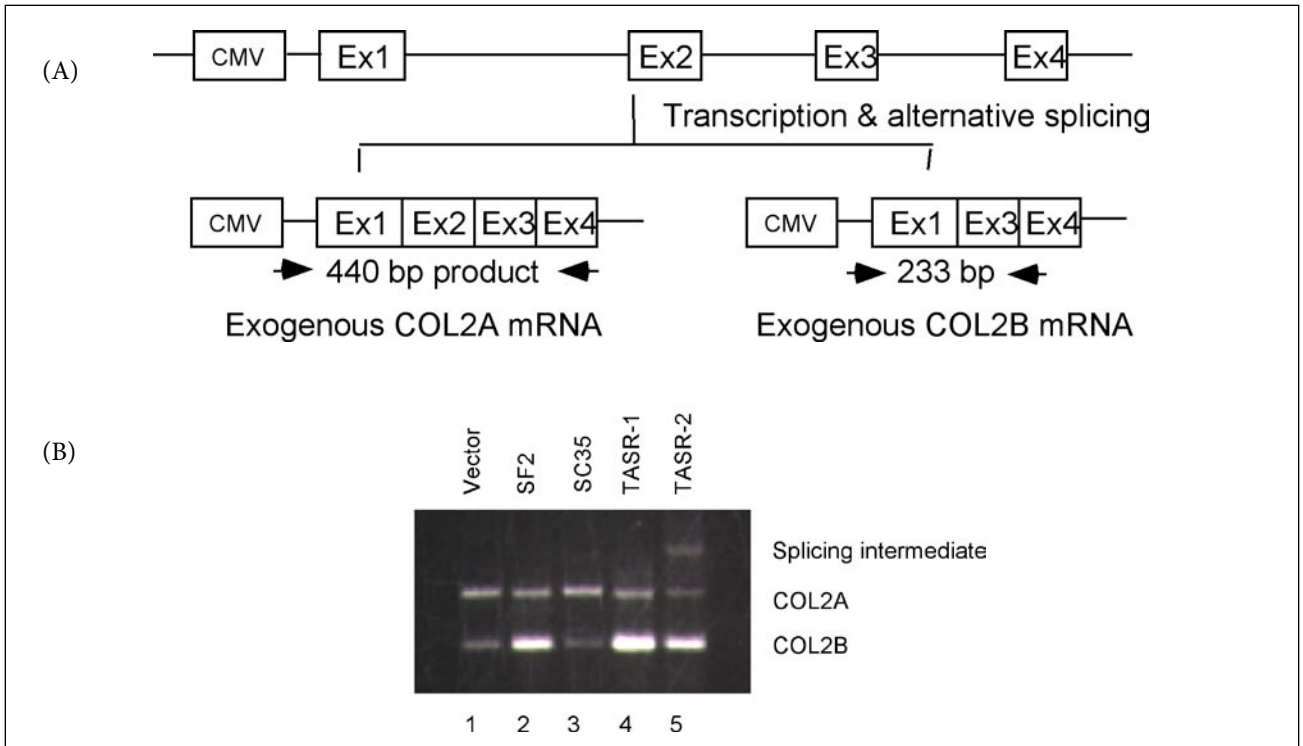

Figure 1: COL2 minigene construct and effects of SR protein on COL2 splicing. (A): DNA sequence corresponding to exon 1 through exon 4 of the mouse COL2 gene are included in the minigene construct. Expression of the COL2 minigene is driven by the CMV promoter. (B): The COL2 minigene was co-transfected into ATDC5 cells along with the empty pGC vector (lane 1), or pGC-SF2 (lane 2), pGC-SC35 (lane 3), pGC-TASR-1 (lane 4), or pGC-TASR-2 (lane 5). After 48 hours, RNA was isolated from the transfected ATDC5 cells for RT-PCR analysis of the alternatively spliced exogenous COL2 transcripts.

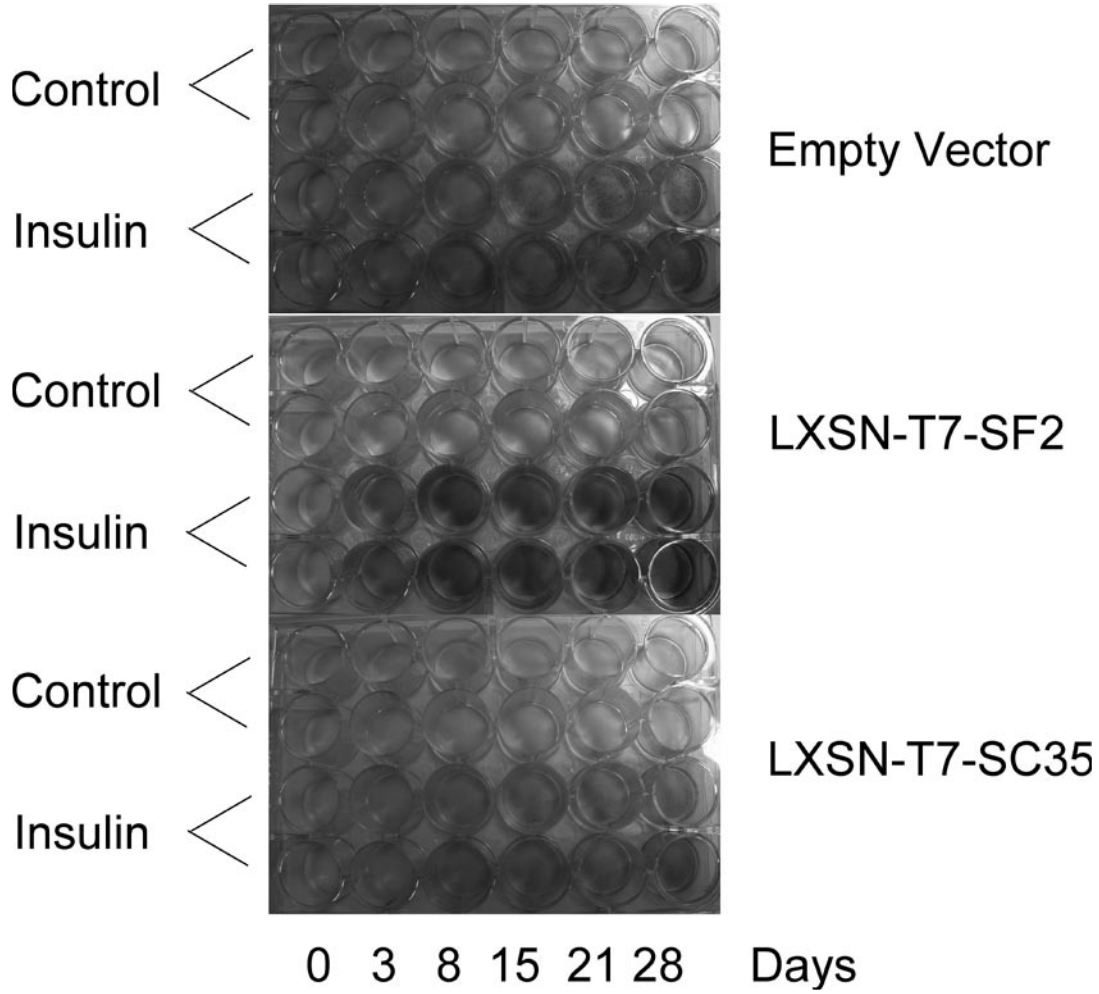

Figure 2: ATDC-5 cells stained for collagen with Alcian blue dye. ATDC-5 cells were transfected with empty vector, or the splicing factors SF2 or SC35. Single clones of ATDC-5 cells demonstrated increased collagen production at a faster rate when transfected with SF2 as opposed to SC35.

that regulate splice site selection in eukaryotic cells. The splicing of nascent mRNA precursors is an essential step for the expression of all intron-containing eukaryotic genes. Removal of intron sequences from nascent transcripts is mediated by the spliceosome, a large multicomponent complex. SR proteins are functionally redundant in the splicing of some introns but exhibit unique functions in the removal of others. There is also evidence that certain SR proteins are critical for tissue development at specific developmental stages and that their loss cannot be compensated for by the presence of other SR proteins. We are in the initial stages of studying the effects of the four most intensively investigated SR proteins – SC35, SF2, TASR-1, and TASR-2 - on alternative splicing of type II collagen and chondrogenic differentiation in ATDC5 cells.

Our model system employs mouse ATDC5 cells, a well-characterized chondrogenic cell line capable of differentiation into hypertrophic chondrocytes when induced by insulin or BMP-7. Advantages of using ATDC cells include their predictable expression of type II collagen and aggrecan as well as the onset of chondrogenic differentiation in response to BMP-7 or insulin. Our laboratory and others have demonstrated that ATDC5 cells are amenable to transfection as well as viral transduction. In addition, a recent study utilized ATDC5 cells to study regulatory elements in cartilage-specific splicing of COL II pre-mRNA.

Results

SR splicing factors modulate splicing of type II collagen

One of the characteristic features of chondrocytes is expression of the type II collagen (COL 2) gene. Alternative splicing of the COL 2 pre-mRNA is closely related to the differentiation status of chondrocytes. While COL 2A is the predominant splicing product in proliferating chondrocytes, hypertrophic differentiation of proliferative chondrocytes switches the alternative splicing to COL 2B.

The differentiation-dependent switch of COL 2 pre-mRNA splicing has been known for quite some time, but the underlying mechanism is not well understood. A mouse COL 2 'minigene" system (Figure 1A) has recently been developed that permits the study of alternative splicing of endogenous COL 2. The structure of the mouse COL 2 minigene as well as the COL 2A and COL 2B splicing

isoforms are illustrated in Figure 1A.

To investigate how COL 2 alternative splicing is regulated by trans-acting splicing factors, we obtained this COL 2 minigene construct (M. Bolander, Mayo Clinic) and co-transfected it into ATDC5 cells along with expression vector encoding SR proteins SF2, SC35, TASR-1 or TASR-2. In proliferating pre-chondrogenic ATDC 5 cells, as shown in Figure 1B, transfection of the COL 2 minigene gives rise to COL 2A as the major product with COL 2B as the minor product (Figure 1B, lane 1). Co-expression of the major SR splicing factor SF2 switches the splicing from COL 2A to COL 2B (Figure 1B, lane 2). By promoting splice site selection to COL 2A, co-expression of another major SR protein SC35 appears to antagonize the effect of SF2 in proliferating ATDC5 cells (Figure 1B, lane 3). While the sarcoma associated TASR-1 and TASR-2 function similarly to SF2 in promoting splicing to COL 2B (Figure 1B, lanes 4-5), TASR-2 may also interfere with the splicing process, leading to accumulation of an incomplete COL 2 splicing intermediate.

Specific patterns of SR protein expression correlate with the state of chondrocyte differentiation

We have observed that a combination of insulin and BMP-7 is more potent than either insulin or BMP-7 alone in stimulating the chondrogenic differentiation of ATDC5 cells. After 2 weeks of stimulation with these two factors, the ATDC5 cells start to assume the characteristics of hypertrophic chondrocytes as staining with Alcian blue demonstrates an abundance of sulfated glycosaminoglycan in the extracellular matrix. To examine the changes in SR protein expression profiles, proliferating as well as differentiated ATDC5 cells were lysed, separated by SDS-PAGE, and blotted with the m104 antibody that can recognize SF2 and SC35. Our results suggest that in proliferating ATDC5 cells, the SF2 protein level is low and barely detectable by the m104 antibody. However in hypertrophic ATDC5 cells, the amount of SF2 is significantly increased and thus may contribute to splice site selection favoring expression of COL 2B.

Discussion

Despite the fact that splicing of COL2 pre-mRNA plays a critical role in the function of articular cartilage, the molecular mechanism that regulates COL2 alternative splicing is poorly understood at the present time. Taking advantage of the recently established COL2 minigene system, we examined how individual SR splicing factors affect COL2 alternative splicing in proliferating ATDC5 cells. Since ATDC5 cells represent a widely used *in vitro* system capable of mimicking the multi-step differentiation of chondrocytes, our findings are likely to be relevant to alternative splicing of COL2 during chondrogenesis *in vivo*. We have identified for the first time that the SR protein SF2 may be one of the key factors controlling the switch of splicing from COL2A in proliferating chondrocytes to COL2B in hypertrophic cells. We are currently investigating how sustained expression of SF2 antagonists affect differentiation of ATDC5 cells and alternative splicing of COL2.

Major strides have been made in

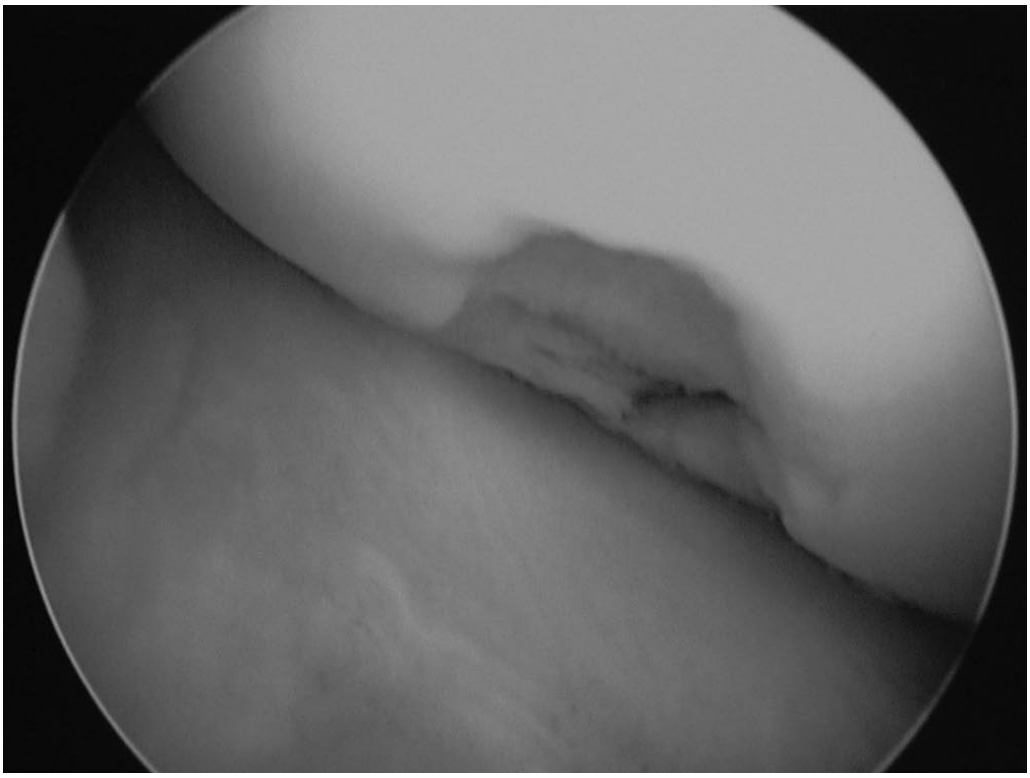

Figure 3: This large lesion of the medial femoral condyle is typical of osteochondritis dissecans, a common disease of children and young adults that is resistant to current treatments. Understanding the molecular regulation of cartilage biosynthesis is necessary if cartilage regeneration is to become a reality in the treatment of such diseases.

articular cartilage engineering and regeneration. However, there remain formidable barriers to predictable healing of articular cartilage. The exquisite gross and ultra structural features of cartilage must be restored by transiently stimulating the production and incorporation of cartilage extracellular matrix. Temporal and spatial regulation of chondrocyte differentiation and matrix elaboration will depend upon a deeper understanding of the normal biology of chondrocytes. In this study we have begun to investigate the role of SR splicing factors in collagen synthesis and chondrocyte growth and function.

Based upon the results of this study, in future work we will investigate both the effects of stable transfection of SR retroviral constructs on ATDC5 cells and the influence of SR proteins on collagen expression by mesenchymal stem cells in an environment simulating the three-dimensional structure of articular cartilage.

Acknowledgements

This work is supported by research grants from the National Institutes of Health, Veterans Affair Administration and the Orthopaedic Research and Education Foundation.

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Targeting of Ews/fli-1 By Rna Interference Attenuates the Tumor Phenotype of Ewing's Sarcoma Cells

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Despite advances in limb-sparing surgery, radiation therapy and chemotherapy, nearly one-half of children with Ewing's sarcoma succumb to the disease. Ewing's family tumors (EFT) share histological features as well as a recurrent and specifc chromosome translocation present in 85–90% of these tumors. The predominant t(11;22) translocation results in a chimeric oncogenic transcript fusing the a portion of the protein EWS with a portion of DNA-binding domain of the transcription factor FLI-1. Several lines of evidence indicate that EWS/FLI-1 related fusion proteins are necessary and suffcient to induce transformation both in cell culture and animal models. However the mechanism by which EWS/FLI-1 exerts its oncogenic effect is still unknown. In addition, the cell of origin of Ewing's sarcoma is uncertain thus further complicating the reliable identification of therapeutic molecular targets.

RNA interference (RNAi) is a recently described endogenous biological process that degrades specifically targeted messenger RNAs (mRNA). RNAi involves the introduction into animal cells of 21-nucleotide long RNAs ("short interfering" RNA or siRNA). These siRNAs result in sequence specific gene suppression of targeted mRNA. We hypothesized that siRNA would effciently and specifically down-regulate the chimeric EWS/FLI-1 protein leading to phenotypic changes in cell culture. Success with this approach could permit analysis of the effects of ESW/FLI-1 fusion protein in Ewing's sarcoma cell lines as opposed to surrogate cell lines. In the future it may also be possible to treat patients with Ewing's sarcoma by delivering siRNA that targets EWS/FLI-1 via gene therapy. In this study we have used synthetic siRNA, targeted against the type II fusion transcript present in the SK-ES cell line to gain insight into the functions of EWS/FLI-1 in Ewing's sarcoma cells and to test the feasibility of RNAi to treat fusion-induced sarcomas.

Results

Transfection effciency of SK-ES Ewing's sarcoma cells is optimized with electroporation: To investigate whether endogenous EWS/FLI-1 can be down-regulated by RNA interference, we obtained the SK-ES cell line that expresses the type II EWS/FLI-1 transcript most commonly found in Ewing's sarcoma. After testing a variety of approaches to deliver nucleic acid into SK-ES cells, including lipofection and calcium phosphate precipitation, we found that SK-ES cells can be effciently transfected by electroporation.

RNA interference effectively knocks down expression of EWS/FLI-1: To investigate whether the EWS/FLI-1 chimeric oncoprotein can be down-regulated in SK-ES cells by RNA interference, we designed four siRNAs targeting different regions of EWS/FLI-1. When introduced into SK-ES cells, the first three siRNAs did not significantly affect EWS/FLI-1 expression while siRNA-4 effectively knocked down expression of EWS/FLI-1. The level of β-actin protein in various samples was not affected by these treatments, indicating that knockdown of EWS/FLI-1 by siRNA-4 was not due to general suppression of gene expression. We also transfected SK-ES cells with siRNA targeting luciferase (siGL2), a gene not present in SK-ES cells. Similarly, SK-ES cells were treated in an identical fashion but were electroporated in the absence of any siRNA. Cells harboring non-functional control siGL2 as well as cells electroporated in the absence of any siRNA continued to express EWS/FLI-1, suggesting that knockdown of EWS/ FLI-1 is robust and specific to siRNA-4.

EWS/FLI-1 knockdown correlates with decreased proliferation and increased apoptosis: To study the cellular effects of EWS/FLI-1 knockdown in Ewing's sarcoma cells, SK-ES cells were electroporated with the non-functional siGL2 as a negative control, or with the functional siRNA-4 to specifically knock down EWS/FLI-1. As shown in Figure 3, SK-ES cells harboring the functional siRNA-4 proliferated

Picture 1: On the right side of the photograph is a scapula removed from a teenager with Ewing's sarcoma. The tumor arises from the bone of the scapula and can be seen filling the supraspinatus fossa (white arrow). On the left side of the photograph is a cadaveric graft that was used to reconstruct the scapula.

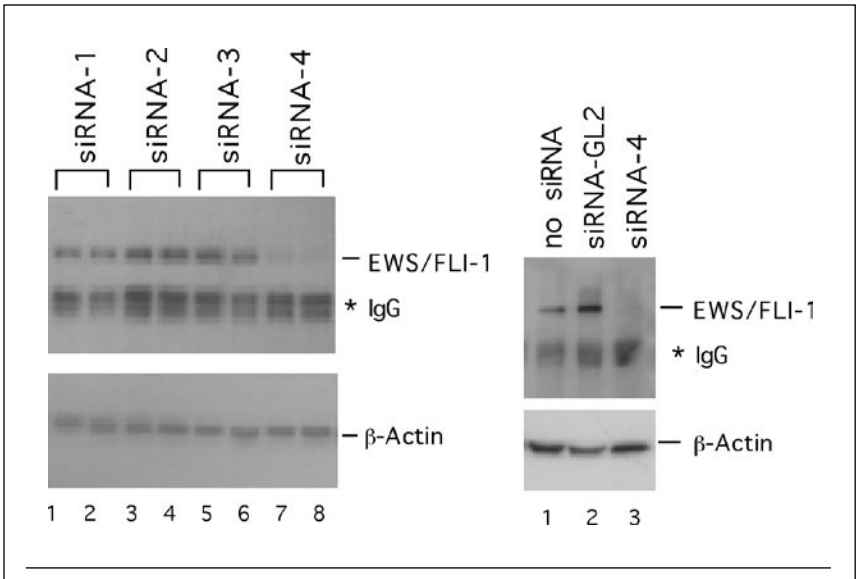

Figure 1: siRNA knockdown of EWS/FLI-1 in SK-ES cells. (Left panel) SK-ES cells were electroporated with different siRNA (lanes 1–8). Cell lysates were immunoprecipitated with an anti-FLI-1 antibody to concentrate EWS/FLI-1 protein for Western blotting (top panel). Each siRNA was applied at a final concentration of 20 nM (left lane for each siRNA) or 50 nM (right lane for each siRNA). The same lysates were also blotted with an anti-b-actin antibody to show equivalent loading of total protein. (Right Panel) Western blot after treatment with active siRNA-4 but including sham treatment (lane 1) and treatment with a negative control siRNA targeting luciferase (lane 2).

more slowly than cells harboring nonfunctional siGL2. Two days after electroporation we also observed more dead cells in siRNA-4 treated samples than in the siGL2 negative controls. To insure that this phenotypic response was specific to Ewing's sarcoma cells, identical experiments were performed in 293 cells and no differences were observed between siGL2 and siRNA-4 (Figure 3). We measured the apoptotic rate of SK-ES cells treated with the non-functional siGL2 or the functional siRNA-4 as wells as cells electroporated in the absence of siRNA. As shown in Figure 3, the functional siRNA-4 induced apoptosis in approximately three times as many cells as in the control cells treated with siGL2 or treated in the absence of siRNA. Thus, siRNA-4 targeting EWS/FLI-1 appears to possess anti-proliferative and pro-apoptotic activity in Ewing's sarcoma cells.

siRNA knockdown of EWS/FLI-1 impairs invasiveness of SK-ES cells: Ewing's sarcoma primarily metastasizes to the lungs. Based upon a previous study of breast cancer we hypothesized that the tissue-specific expression pattern of chemokine receptors fundamentally influences the distinct metastatic pattern of Ewing's sarcoma. Since the lung has been reported to express high levels of stromal cell derived factor-1 (SDF-1), we carried out expression analysis of the CXCR4 gene encoding the receptor for the SDF-1 chemokine. The CXCR4 transcripts were the only chemokine receptor consistently detected both in cultured Ewing's sarcoma cell lines and in primary Ewing's sarcoma specimens. To investigate whether the invasiveness of Ewing's sarcoma cells is enhanced by the chemokine SDF-1 (the ligand for the CXCR4 receptor that is expressed in Ewing's sarcoma cells), we established an in vitro invasion assay for SK-ES Ewing's sarcoma cells using Bio- Coat Matrigel transwell chambers with or without SDF-1 as the chemoattractant. SK-ES cells treated with functional siRNA-4 were dramatically less invasive than SK-ES cells treated with non-functional control siRNA. These results suggest that the presence of EWS/FLI-1 fusion protein is a prerequisite for in vitro invasion by SK-ES Ewing's sarcoma cells and that SDF-1 is a potent in vitro stimulus for invasion.

Discussion

In this study, targeted down-regulation of EWS/FLI- 1 by siRNA resulted in changes in the SK-ES Ewing's sarcoma cells consistent with reversion to, or assumption of, a less

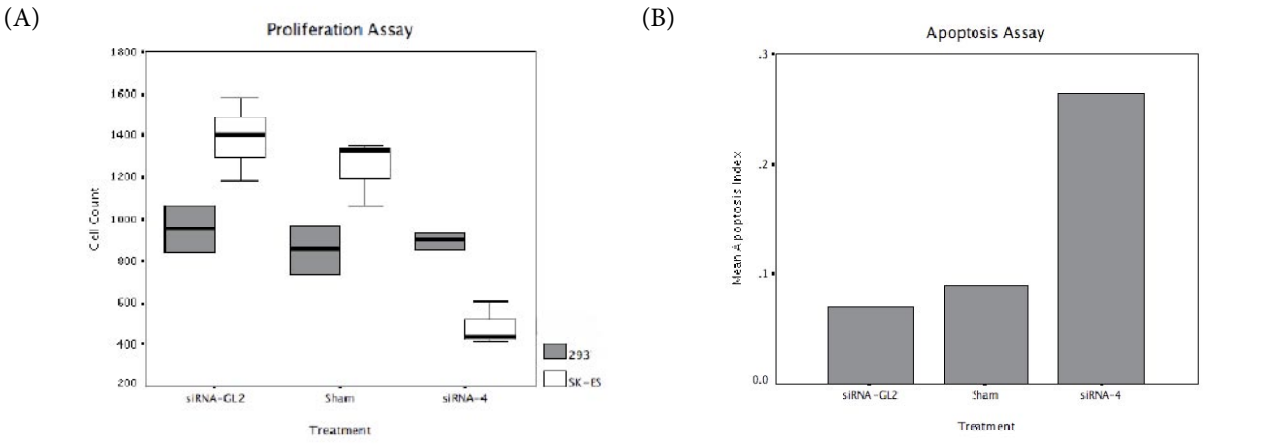

Figure 2: Effects of EWS/FLI-1 knockdown on proliferation and apoptosis. (A) SK-ES cells were counted 48 h after electroporation with either no siRNA, the non-functional control siRNA or the functional siRNA-4. (B) Two days later, apoptotic cells were labeled with annexin V-EGFP and counted using fluorescence microscopy. Cell number is shown as the average of cell counts in 10 high-powered fields after normalization to the total number of cells as determined in the proliferation assay±S.D.

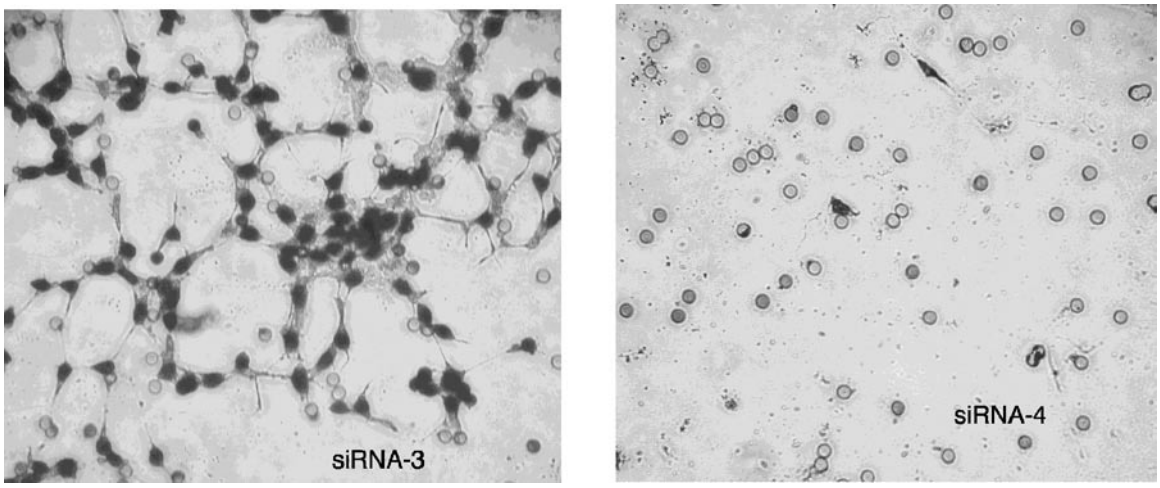

Figure 3: Effects of EWS/FLI-1 knockdown on invasiveness of SK-ES cells. SK-ES cells were electroplated with nonfunctional siRNA, and invasive cells found on the undersurface of the Matrigel insert were stained (left panel). SK-ES cells treated with the functional siRNA-4 were non-invasive with the 8 μm pores on the Matrigel clearly visible (right panel).

invasive phenotype. These changes include decreased proliferative capacity, increased apoptosis and decreased in vitro invasiveness––all consistent with at least partial reversal of the malignant phenotype. The lack of global down-regulation of transcription suggests that these changes are directly related to specific knockdown of the EWS/FLI-1 fusion protein. Ideally, the siRNA would be targeted against the sequence exactly at the fusion breakpoint, but this may not always be feasible due to the existence of a short identical sequence within the transcribed human genome or due to the variability in activity of different siRNAs. Since wild-type FLI-1 is not expressed in SK-ES cells, the observed effects with siRNA-4 are unlikely to be related to down-regulation of FLI-1.

The chemokine receptor CXCR4 plays a critical role in determining the metastatic potential of breast cancer cells as well as anatomic patterns of metastasis. We demonstrated that CXCR4 is expressed in both SK-ES Ewing's sarcoma cells and in tissue obtained from Ewing's tumors. Our study showed that siRNA targeting EWS/FLI-1 nearly eliminated the ability of SK-ES cells to invade through a Matrigel-coated membrane in response to SDF-1. These results suggest that the expression or function of CXCR4 may be directly or indirectly affected by down-regulation of EWS/FLI-1 in response to RNA interference. Real-time RT-PCR was therefore used to demonstrate that expression of CXCR4 mRNA is decreased by approximately 50% after treatment of SK-ES cells with siRNA-4 (data not shown). Thus, CXCR4 may be a critical factor in the invasion and metastasis of Ewing's sarcoma and expression of CXCR4 is repressed by knockdown of EWS/FLI-1.

The data presented in this study are consistent with the initial promising results of RNA interference used to target other gene products implicated in human disease. Our results show the feasibility of using RNA interference to specifically silence expression of the EWS/ FLI-1 fusion gene in a Ewing's sarcoma cell line. In addition to potentially salutary effects on the invasive and proliferative characteristics of Ewing's cells, RNA interference permits evaluation of the differential effects of the presence or absence of the chimeric fusion protein in Ewing's cells. We believe that short-interfering RNA delivered by viral vector may also be a promising therapeutic approach in the treatment of patients with Ewing's sarcoma.

Acknowledgements

This work is supported by a VA Merit Review Award (to H.A.C.), the Orthopedic Research and Education Foundation, the Florence and Marshall Schwid Memorial Foundation (to H.A.C.), and the National Institutes of Health (to L.Y.).

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Binding of Von Willebrand Factor A-like Domain of Matrilin-3 To Type IX Collagen

Jiann-jiu Wu, Ph.D., Dennis A. Hanson, Ph.D., and David R. Eyre, Ph.D.

Matrilins are a recently identified family of extracellular matrix proteins that contain von Willebrand factor A-like domains (vWFA), EGF-like domains and a C-terminal coil-coiled α-helix (Figure 1). The functions of matrilins are poorly understood but an adhesive role and binding to collagen, proteoglycan and other extracellular matrix component are indicated. Among the four members of the matrilin family, matrilin-1 (also known as CMP) and matrilin-3 are prominent in skeletal growth cartilages. Previous studies have shown that heterotetramers of matrilin-1/matrilin-3 and homotetramers of matrilin-3 are able to bind to collagen type IX in a Zn-dependent manner. Mutations in the vWFA domain close to the metal ion-dependent adhesion site (MIDAS motif) of human matrilin-3 have been identified as a cause of a mild form of multiple epiphyseal dysplasia, a rare heritable skeletal dysplasia that causes early onset severe osteoarthritis in hips and knees. Mutations in a homologous vWFA domain of the collagen α3(VI) chain have been linked to Bethlem myopathy. However, the protein consequences and precise disease mechanisms are not known. It is believed that these vWFA domains may mediate binding to collagen. Here we test the ability of the matrilin-3 vWFA domain to bind to cartilage type IX collagen using the recombinant protein.

Materials And Methods

The vWFA domain comprising residues 83-258 of human matrilin-3 was amplified by RT-PCR using a pair of custom designed oligonucleotide primers and RNA isolated from the Ch1 human chondrosarcoma cell line. The amplified cDNA was then cloned using a commercially available PCR cloning kit and subcloned via the primer encoded EcoR1 sites into the pET28a expression vector. Correct in-frame insertion, nucleotide sequence, and engineered stop codon were confirmed by standard DNA sequencing. The expression construct was then transformed into the expression host, E. coli BL21 (DE3) pLysS, and induced to make N-terminal polyhistidine-tagged recombinant protein by the addition of IPTG to the bacterial culture. The induced protein was recovered by lysing the resulting bacterial cell pellet with 1% n-octyl glucoside detergent and isolating the insoluble inclusion bodies.

Types II, IX and XI collagens were purified from fetal bovine epiphyseal cartilage by pepsin digestion and salt fractionation. Type IX collagen COL1 and COL2 fragments were recovered in the 2M NaCl precipitate and COL3 fragments in the 4M salt precipitate. Identities of the proteins in each fraction were confirmed by SDS-PAGE and N-terminal protein sequence analysis. Binding of recombinant human matrilin-3 vWFA domain to collagens was assessed using a solid-phase ELISA format. Native collagens and individual collagen α-chains were coated on 96-well plates and incubated with buffered solutions of recombinant vWFA preparations. Polyclonal antisera recognizing peptide sequences specific to the vWFA domain of matrilin-3 was used to assay for collagen binding.

Results

We have expressed the vWFA domain of human matrilin-3 gene in E. coli and assessed its binding affinity for different collagen types. The expressed protein was not secreted into the medium and was recovered in inclusion bodies. SDS-PAGE analysis of inclusion body protein showed an essentially pure preparation. Mass spectral analysis of

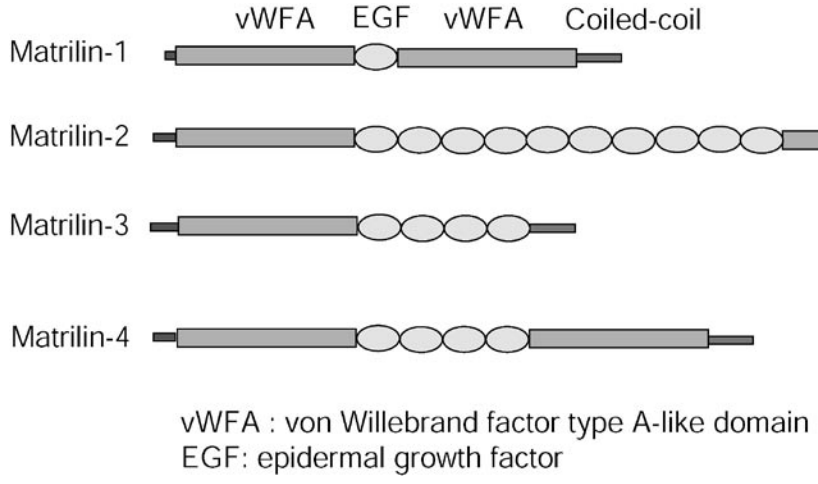

Figure 1: Modular structure of matrilin monomers.

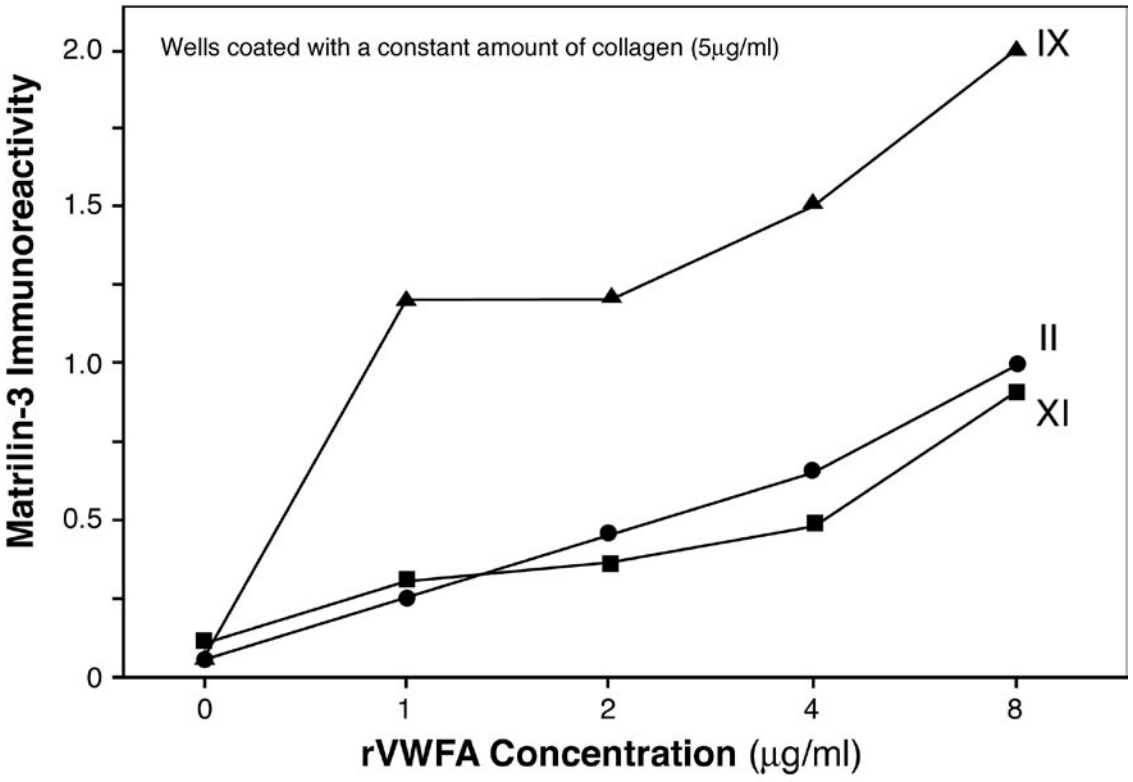

Figure 2: Binding of recombinant human matrilin-3 vWFA domain to types II, IX and XI collagens. Wells were coated with pepsin-derived collagen then incubated with increasing concentrations of recombinant vWFA.

tryptic peptides from an in-gel digest of the protein band confirmed an in-frame expression of the correct sequence.

Pepsin-solubilized types II, IX and XI collagen preparations were coated on 96-well plates. Serial dilutions of the recombinant vWFA were incubated in the wells to assess binding. The highest apparent binding affinity was found with pepsin-derived type IX collagen fragments in a concentration dependent manner (Figure 2). It was also found that addition of metal ions (e.g. 2mM $ZnCl_2$) was essential for the binding. Adding o-phenanthroline to the incubation mixture to chelate metal ions completely abolished the matrilin-3 vWFA to collagen interactions. A solid-phase binding assay was also used to localize the binding site for the vWFA domain within the type IX collagen molecule. Pepsin-derived COL1, COL2 and COL3 fragments were resolved on reverse-phase HPLC and analyzed for vWFA binding affinity. It was found that the recombinant vWFA domain bound selectively to the COL2 trimer, not the COL1 trimer (Figure 3). Recombinant vWFA also bound to the individual chains of the type IX COL3 domain, but with highest apparent affinity for α3(IX)COL3. Again, adding o-phenanthroline to the incubation mixture completely abolished these matrilin-3 vWFA/collagen interactions.

Discussion

vWFA domains occur in many extracellular matrix proteins, including all the matrilins and several collagens. The domain mediates protein-protein interaction; for instance, the vWFA domains in the α1 and α2 chains of human integrins α1β1 and α2β1 bind to a GlyPheHypGlyGluArg sequence in the type I collagen triple-helix. This sequence, however, does not occur in any of three type IX collagen gene products. Growth cartilage is enriched in heterotetrameric molecules of matrilin-1 and -3 subunits. The matrilin-3 chain contains a single vWFA domain and matrilin-1 contains two vWFA domains. The matrilin-1 trimer, prominent in tracheal cartilage, binds to type II collagen fibrils and to aggrecan. The collagen fibril network of hyaline cartilages develops as a heteropolymer of collagens II, IX and XI. In considering the likely functions of matrilins as matrix-adaptor or bridging molecules, it is possible that the different vWFA domains have evolved a selective affinity for different collagen subunits, and so participate in the assembly of the heteropolymeric fibril network.

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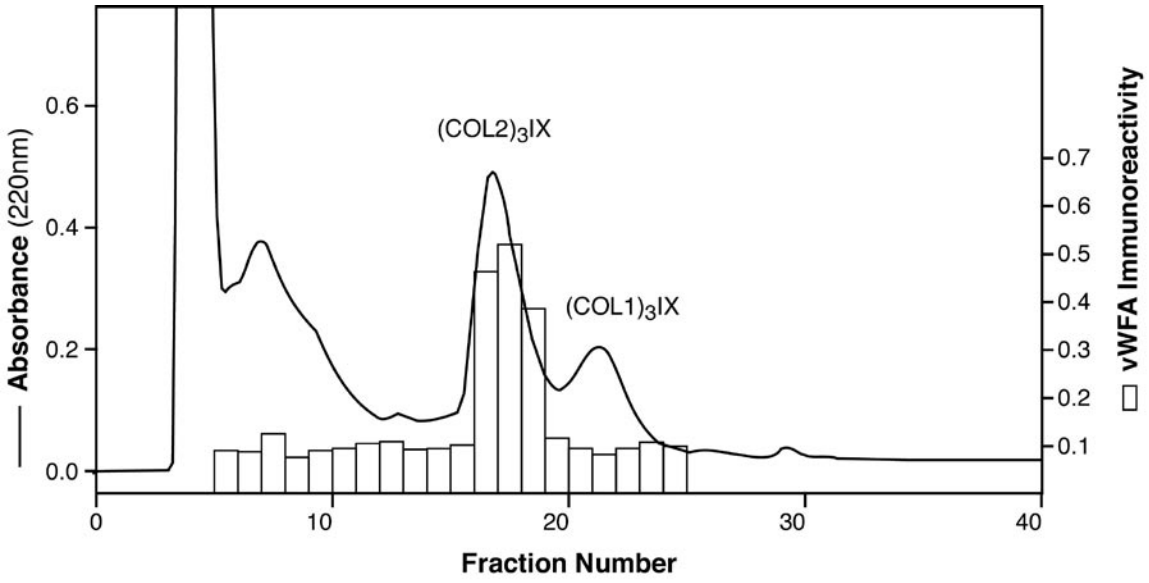

Figure 3: Binding of recombinant matrilin-3 vWFA to the collagen IX COL2 domain. Protein in each HPLC fraction was plated to assess vWFA binding affinity.

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Glenoid - Ream and Run Study

John M. Clark, M.D., Ph.D., Kristi Gibbs, B.S., John A. Sidles, Ph.D., Anthony Norman, B.S., and Frederick A. Matsen III, M.D.

The pain relief and functional improvement provided by total shoulder replacement surpass any other available treatment for shoulder arthritis. Unfortunately, the durability of these improvements is compromised by early failure of the polyethylene glenoid replacement component. The human glenoid is small, and in the case of arthritis, deformed by erosions. For this reason, the bony support for a glenoid component is limited. Loosening compounds the bone loss and salvage of a failed component can be prohibitively difficult. Younger, active patients are particularly vulnerable to these limitations.

As an alternative to replacement, surgeons at the University of Washington and other centers have adopted the strategy of *non-prosthetic glenoid arthroplasty*. In this approach, the glenoid is reamed to fit the prosthetic head of the humerus (Figure 1). The reaming removes minimal bone, and allows the surgeon to deepen, redirect, or enhance the concavity. To date, many patients return to a high level of activity, but the outcome has been variable. The reasons for this variable response have not been elucidated by existing clinical and experimental studies.

To define factors that might affect the outcome of such a metal on bone arthroplasty, and to establish a model for testing methods that could enhance remodeling of the glenoid, an animal model of non-prosthetic glenoid arthroplasty was developed.

Methods

Animals

Twelve, skeletally mature, female hounds, (Covance, Kalamazoo, MI), one year of age and weighing approximately 50lbs, were used in this study. Through a posterolateral approach, a custom made, stemmed humeral head replacement (DePuy, Warsaw, IN) was inserted into one shoulder of each of the dogs. All surgeries were performed under general anesthesia, and by the same orthopaedic surgical team. The study was performed under the approval of the Institutional Animal Care and Use Committee (IACUC) at Ethicon Endo-Surgery in Cincinnati, Ohio, where the study took place.

The right glenoid of twelve, skeletally mature, female dogs was reamed to a 30 mm diameter, removing all cartilage to bleeding trabecular bone. The native humeral head was excised and replaced with a stemmed, 28 mm diameter prosthesis (Figure 2).

Post-surgery, the operated limbs were loosely immobilized in a sling for seven days, and allowed ad libitum activity for the remaining study period. Fluorescent bone labels were administered monthly to identify bone formation. Six animals were sacrificed at 10 and 24 weeks each, and the intact glenohumeral joints were evaluated by gross examination, assessment of intrinsic stability, measurement of glenoid concavity (depth) and light microscopy of sections embedded in methylmethacrylate. Intact contralateral glenoids, and two that were freshly reamed, were also prepared for microscopy. The sections were evaluated for evidence of bone and soft tissue remodelling at the interface with the prosthetic humeral head (Figure 3).

Histomorphometry Technique

The structure of the glenoid articular surface articulating with the prosthetic humeral head was quantified by the following technique: each slide was scanned at a resolution of 1200 pixels per inch using a flatbed scanner (Epson Perfection 3200, Seiko Epson, Japan) and the image was exported to Photoshop. An arc with a 14 mm radius was fitted to the new glenoid surface on each scanned image of the reamed glenoids. A second, concentric arc with a 19 mm radius was then drawn, and the tissue captured by the parallel lines was analyzed by the following measurements (Figure 1B): 1) Maximum width of the surface; 2) Length of the contact surface articulating with the prosthesis; 3) Percentage of the contact surface consisting of reamed bone; 4) Percentage of the contact surface consisting of soft tissue; 5) Average thickness of the soft tissue measured at five standardized points; 6) Bone density (percent of total tissue area staining as bone)within the 5 mm arc; and 7) Bone density in an arc between 2 and 5mm

Group	Angle ß	Tissue Area (mm^2)	Bone Fraction %	Soft Tissue Thickness (mm)	Percent Surface Exposed Bone	Bone Density Beneath Surface
Normal glenoid*	79.3	114.2	28.3	0.56 +/- 0.03	0	14.85
Freshly Reamed	82.5	118.8	23.4	0.02 +/- 0.03	97.7	18.53
10 week Reamed	79.7	114.7	27.4	1.31 +/- 0.8	33.2	33.13
24 week Reamed	87.7	126.2	39.1	1.57 +/- 0.3	2.9	42.98

Table 1: Quantitative analysis of the response to reaming of the glenoid. *Contralateral shoulder of 24-week animals.

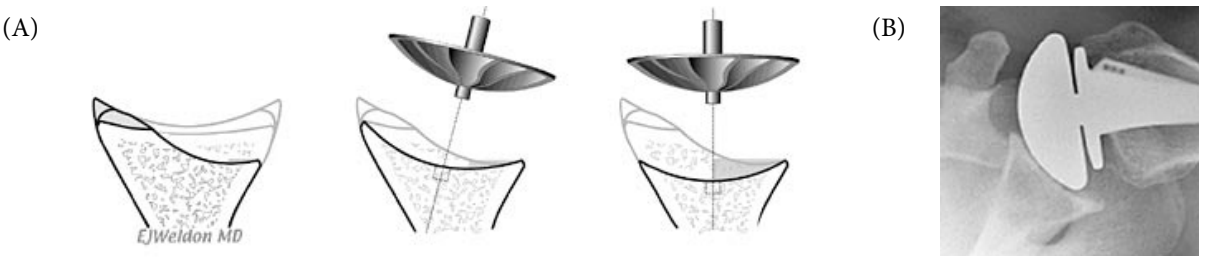

Figure 1: Non-prosthetic resurfacing of the glenoid. (A): Spherical reaming deepens the concavity, corrects any posterior erosion and corrects version. The result is an articular surface congruent with the humeral prosthesis and which optimizes stability. (B): In clinically successful cases, bony remodeling and a congruent "joint space" are observed over time.

from the articular surface. This second measurement excluded the layer of soft tissue that had formed on the surfaces of the 10 and 24 week specimens. For the intact "normal" glenoids, the thickness of articular cartilage was measured at five comparable points. To simulate reaming in this group, the 14 mm arc was positioned at the minimum depth necessary to exclude all articular cartilage. The socket width and bone density were measured exactly as had been done in the reamed groups. Mean values were calculated for all groups, and compared using unpaired t-tests. Significance was set at $p < 0.05$.

Figure 2: The 28 mm diameter humeral component articulated with a dog glenoid.

Results

All twelve joints remained located until the designated endpoints, with no deaths, dislocations or signs of infection. All animals limped, but shoulder girdle weight and motion improved between 10 and 24 weeks. Physical measurements showed that the depth and intrinsic stability of the glenoid had increased significantly by 24 weeks, when compared to both the intact and freshly reamed specimens.

Histological Findings

At 10 weeks, trabecular bone exposed by the reamer was partially covered by vascular, fibrous tissue that maintained a concave surface congruent with the implant. Where bone was still exposed, the severed trabeculae were viable up to the level of resection, and new lamellar bone deposited around them. The width of the articular surface was enlarged by new bone formed at the margins, and the density of the periarticular trabecular bone had increased by the deposition of appositional new bone. These changes were consistently more advanced at six months (Table 1). At 6 months, the articular surface was completely covered by soft tissue, and much of this tissue was fibrocartilage rather than the fibrous tissue, which predominated at 10 weeks (Figures 4, 5, 6; Table 1).

Discussion

Hemiarthroplasty, in which the convex side of a joint is replaced with a polished metal surface, has been a common orthopaedic procedure for over a half century. For the arthritic hip and shoulder, some have achieved remarkable function and durability. Prosthetic replacement of the socket was added because such "total"

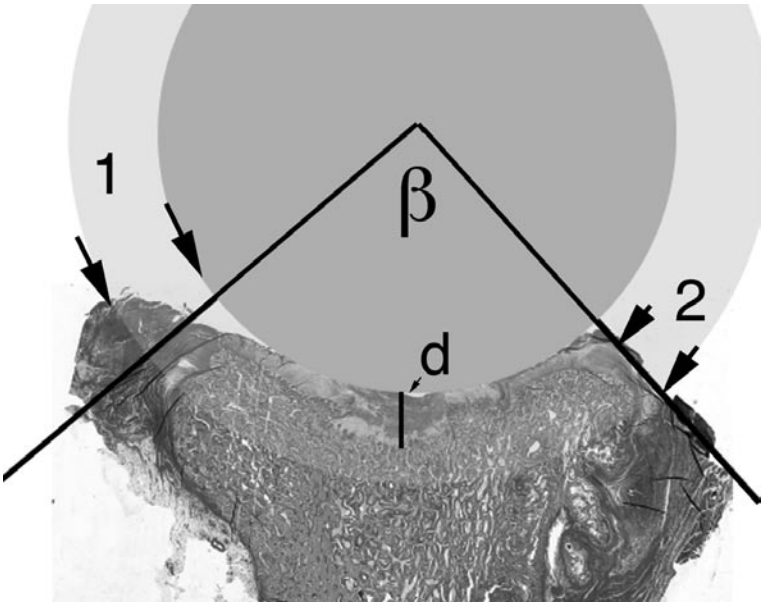

Figure 3: Method for quantitative analysis of the reamed glenoid surfaces. The width of the bony glenoid was defined as the bone captured by the angle ß. Thickness of any soft tissue covering the surface (d) was measured at five equally spaced points. The area fraction of trabecular bone was measured in the arc within five millimeters of the articular surface (1) and between 2 and 5 mm from the surface.

replacements provided more consistent improvements in pain and motion, and gave the surgeon an additional means to correct deformities. Also, total joint replacement was thought to prevent further erosion of the bone, a common problem with hemiarthroplasty. Interest in hemiarthroplasty has resurged as the limitations of polyethylene components have been recognized. Yet, at this time, we do not clearly understand why this procedure works well in some patients and fails in others.

Large clinical series and limited animal studies indicate that the living tissue articulated against a metallic hemiarthroplasty generally responds in one of two ways: (1) in successful cases, a stable soft tissue layer lines the socket; (2) in failures, any existing soft tissue interface dies or is eroded, and the bony socket also erodes. A poor fit between ball and socket probably plays a central role in the failures. Reaming allows the surgeon to control congruity, but removes remaining cartilage or other soft tissue and places the metal prosthesis directly against freshly cut bone.

This is the first study to show the fate of reamed bone articulated with a metallic prosthesis. Remarkably, the interface not only remained viable, but also demonstrated a remodeling response with several desirable features. Specifically, the articular surface was smooth, congruent with the metallic implant and supported by new bone formation peripherally and centrally. Of equal importance, the bone was replaced by soft tissue that, by six months, resembled fibrocartilage by morphological criteria. Normal articular cartilage is unsurpassed as a bearing surface, because it is avascular aneural (insensate) and smooth, but fibrocartilage, such as that found in tendon pulleys and the menisci, seems to tolerate compression and motion adequately. For this reason, the histologic appearance of the six-month specimens is highly encouraging.

This was a short study. The biological surface formed at six months in this nonprosthetic arthroplasty was evolving. Therefore, longer periods of observation, including attention to the function of the dog's forelimb will be needed. Comparable studies in animals used the hip joint, and

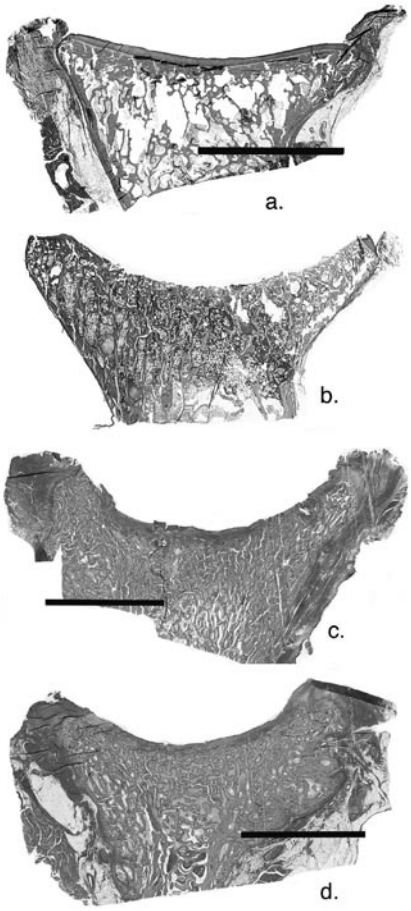

Figure 4: Glenoid preparations studied here. (A) Normal glenoid (B) Freshly reamed glenoid (C) Reamed glenoid at 10 weeks (D) Reamed glenoid at 24 weeks (Goldner's trichrome stain, bar = 1 cm) At all time points following surgery, the radius of the reamed glenoid matches that of the prosthesis. Trabecular bone exposed by the reamer (2b) was partially replaced by soft tissue at 10 weeks, and completely covered at 24 weeks.

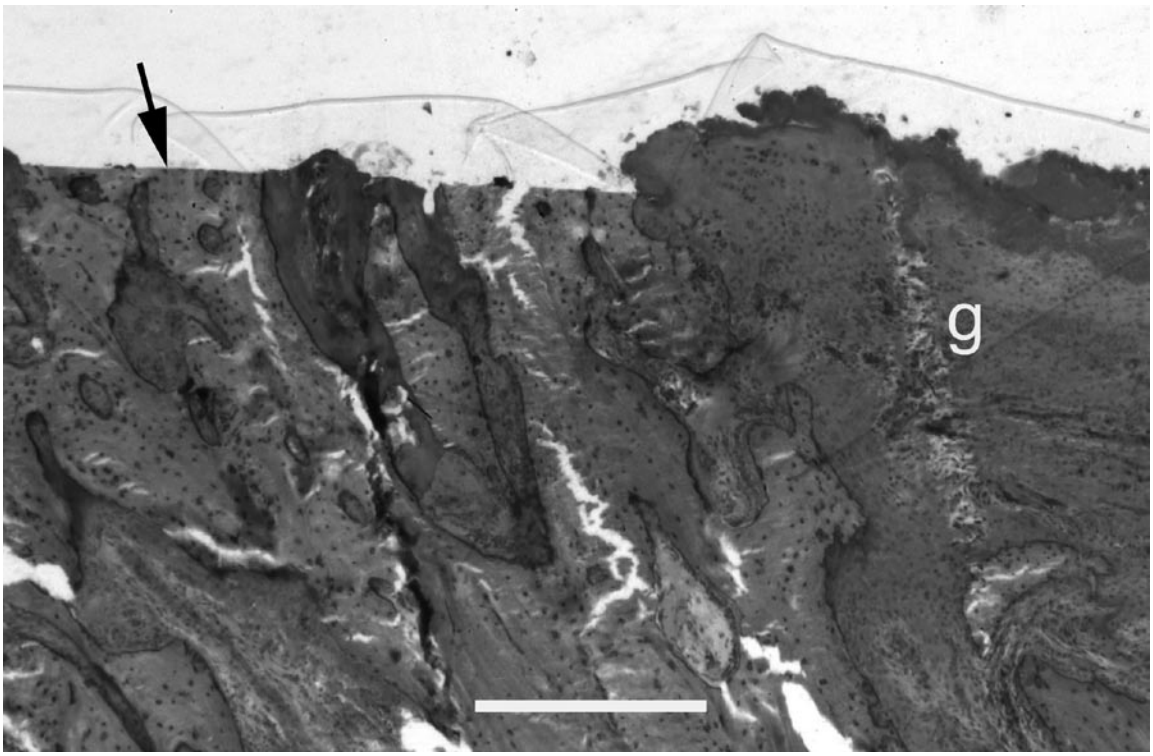

Figure 5: Exposed trabecular bone at articular surface, 10 weeks. Where bone was in contact with the prosthesis, the exposed trabeculae (arrow) were still cleanly transected. Tissue in the marrow spaces usually was structurally similar to the fibrous, vascular granulation tissue (g) that covered the surface in other locations (bar = 100 μm)

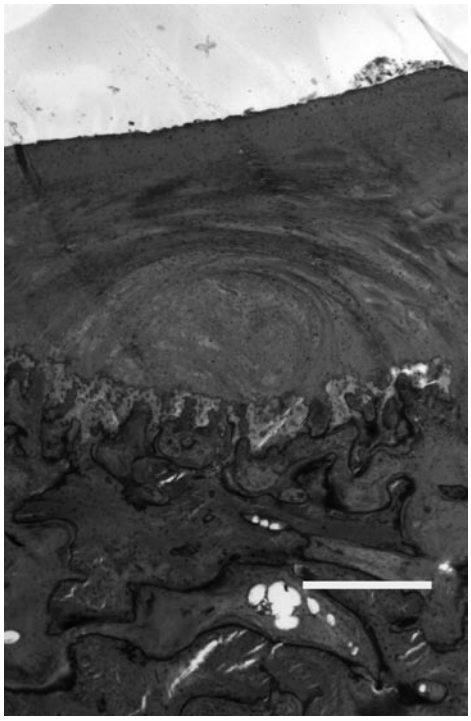

Figure 6: Soft tissue on articular surface of a 24-week specimen with histological features typical of fibrocartilage: round cells in lacunae; yellow background stain and distinct red collagen fibers that assume tangential orientation at surface. Calcified fibrocartilage is visible at base (bar = 100 μm).

suffered from complications such as dislocation, infection and component migration. This shoulder model avoided technical problems, and generated a consistent biological response. As such, it provides a solid foundation for further investigation.

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Injury Trends Among Helmeted and Non-Helmeted Skiers and Snowboarders

Ian Butler-Hall, M.S. and John W. O'Kane, M.D.

Ski helmets have been used for many years amongst competitive racers, but only recently have found their way onto the heads of the general skiing public. Over the past 8 years, helmet use has grown significantly among both skiers and snowboarders. It is known that head injuries are the leading cause of death of skiers and recent studies suggest that snowboarders are at higher risk of serious head and neck injuries than skiers. Helmet use has been shown to reduce the incidence of head injuries. Some have suggested though, that wearing helmets may actually increase the overall injury rate by increasing risk taking behavior, impairing vision or hearing, changing weight distribution about the head, or through some other mechanism. They suggest helmet use not be encouraged for skiers and snowboarders pending further research. This study attempts to analyze injury patterns in skiers and snowboarders with and without helmets, hypothesizing that there will not be an increase in overall injuries in helmeted participants.

Methods

Information on skier/snowboarder injuries was obtained from the Stevens Pass Ski Patrol injury reports from the 2001-2002 ski season. This information was compiled by the Risk Management Department of Stevens Pass and provided to the author without personal identifiers. The data included injury type and location, skier age and sex, and whether the visitor was a skier or snowboarder and wearing a helmet or not. Injury type categories included "fracture," "strain/sprain," "dislocation," "bruise/contusion," "puncture/laceration," and "concussion." The injury data included all injuries reported to and recorded by the Stevens Pass Ski Patrol during that season. A total of 1488 injuries were reported. After excluding injuries from non-skiing or snowboarding activity, pre-existing injuries exacerbated on the mountain, and those injuries caused by a chair-lift, 1292 traumatic ski and snowboard injuries were analyzed.

The number of total skier visits for the season was also given by Stevens Pass (492,783). Neither records of total skiers and snowboarders nor helmet use of the general population are kept by Stevens Pass. An estimation of the total skier/snowboarder and helmet/no helmet breakdown was made by counting visitors at the top of several different chairlifts. Counts were performed at different days at different times for one hour at each chairlift. Observers recorded equipment type and helmet use for each visitor that exited the chairlift. In all, 4901 visitors were counted; 2111 skiers without helmets (43.1%), 646 with helmets (13.2%), 1536 snowboarders without helmets (31.3%), and 608 with helmets (12.4%). These percentages were applied to the total skier days of 492,783 to extrapolate the estimated denominators of 212,256 skiers without helmets, 64,954 skiers with helmets, 154,441 snowboarders without helmets, and 61,133 snowboarders with helmets for the season.

Injuries to skiers and snowboarders with and without helmets were compared within groups (skiers with helmets to skiers without helmets, etc). Chi-squared tests were applied to each injury category and subset as well as group and overall totals. Statistics were considered significant at a p-value of .05 or less. Relative risk and 95% confidence intervals were calculated in those categories which were shown to be statistically significant by the chi-squared test.

Picture 1: An example of helmeted skiers.

Results

Overall results for skiers with and without helmets are listed in Table 1. Amongst skiers, those with helmets sustained 83 total injuries and those without helmets had 397 injuries ($p<.01$) with a relative risk (RR) of 0.6832 for those wearing helmets. Significant injury type/location categories included overall strains/sprains with injuries to 44 helmeted and 252 non-helmeted skiers respectively ($p<.001$ and RR of 0.5706). Within the sprain/strain category, significantly injured body areas included neck/back ($p<.05$) and knee ($p<.01$).

Overall results for snowboarders with and without helmets are listed in Table 2. Within the categories of snowboarders, those with helmets sustained 154 total injuries and those

	Ski (+)*	% of injuries	per 100,000 skiers	Ski (-)*	% of injuries	per 100,000 skiers	__ *	p-value	RR*	95% CI*
Approx. Skiers	64954			212256						
Total Injuries	83		127.8	397		187.04	**10.1854**	**0.0014**	0.6832	.53936 - .86538
Fractures										
Total	18	21.687	27.71	52	13.1	24.499	0.2034	0.6519		
Neck/Back	0	0	0	3	0.756	1.4134	0.077	0.7814		
Head/Face	0	0	0	2	0.504	0.9423	0.003	0.9563		
Shoulder/C	4	4.8193	6.158	10	2.519	4.7113	0.019	0.8904		
Arm	2	2.4096	3.079	6	1.511	2.8268	0.098	0.7542		
Hand/Wrist	2	2.4096	3.079	6	1.511	2.8268	0.098	0.7542		
Hip/Thigh	2	2.4096	3.079	4	1.008	1.8845	0.008	0.9287		
Lower Leg	6	7.2289	9.237	15	3.778	7.0669	0.3093	0.5781		
Ankle/Foot	1	1.2048	1.54	3	0.756	1.4134	0.266	0.606		
Other	1	1.2048	1.54	3	0.756	1.4134	0.003	0.9563		
Sprain/Strain										
Total	44	53.012	67.74	252	63.48	118.72	**12.1202**	**0.0004**	0.5706	.4143 - .7858
Neck/Back	0	0	0	15	3.778	7.0669	**4.59**	**0.0321**		
Shoulder	6	7.2289	9.237	21	5.29	9.8937	0.022	0.882		
Arm/Elbow	0	0	0	3	0.756	1.4134	0.077	0.7814		
Hand/Wrist	1	1.2048	1.54	11	2.771	5.1824	0.799	0.3714		
Hip/Thigh	3	3.6145	4.619	12	3.023	5.6536	0.09845	0.7537		
Knee	28	33.735	43.11	166	41.81	78.207	**8.7616**	**0.003**	0.5512	.3694 - .8226
Ankle/Foot	6	7.2289	9.237	24	6.045	11.307	0.1969	0.6572		
Other	0	0	0		0	0				
Dislocation										
Total	5	6.0241	7.698	16	4.03	7.5381	0.047	0.8284		
Shoulder	4	4.8193	6.158	16	4.03	7.5381	0.01	0.9203		
Other	1	1.2048	1.54		0	0	0.393	0.5307		
Bruise/Laceration/Abrasion/Puncture										
Total	13	15.663	20.01	65	16.37	30.623	1.99	0.1583		
Head/Face/	3	3.6145	4.619	29	7.305	13.663	3.524	0.0604		
Upper Extr	2	2.4096	3.079	9	2.267	4.2402	0.003	0.9563		
Lower Extr	4	4.8193	6.158	20	5.038	9.4226	0.6122	0.4339		
Torso	4	4.8193	6.158	7	1.763	3.2979	0.431	0.5115		
Concussion	3	3.6145	4.619	12	3.023	5.6536	0.0984	0.7537		

*Ski (+) denotes skiers with helmets
Ski (-) denotes skiers without helmets
__ = Chi squared value or Chi Squared with Yate's correction if expected values are less than 5
RR= Relative Risk; CI= 95% Confidence Interval

Table 1: Ski Statistics.

	Board (+)	% of injuries	per 100,000 skiers	Board (-)	% of injuries	per 100,000 skiers	__ *	p-value	RR	95% CI
Approx. Skiers	61133			154440.9						
Total Injuries	154		251.91	658		426.05	**35.394**	**<.0001**	0.59126	.49624 - .70448
Fractures										
Total	40	25.97	65.431	173	26.29	112.02	**9.6893**	**0.0018**	0.58412	.41421 - .82373
Neck/Back	2	1.299	3.2716	13	1.976	8.4175	1.009	0.3151		
Head/Face		0	0	1	0.152	0.6475	0.231	0.6308		
Shoulder/C	4	2.597	6.5431	36	5.471	23.31	**6.6368**	**0.0099**	0.2807	.09992 - .7886
Arm	6	3.896	9.8147	33	5.015	21.367	3.2316	0.0722		
Hand/Wrist	19	12.34	31.08	58	8.815	37.555	0.5143	0.4732		
Hip/Thigh	1	0.649	1.6358	6	0.912	3.885	0.165	0.6846		
Lower Leg	3	1.948	4.9073	6	0.912	3.885	0.001	0.9748		
Ankle/Foot	3	1.948	4.9073	13	1.976	8.4175	0.331	0.5651		
Other	2	1.299	3.2716	7	1.064	4.5325	0.001	0.9748		
Sprain/Strain										
Total	63	40.91	103.05	279	42.4	180.65	**16.649**	**<.0001**	0.57046	.43407 - .7497
Neck/Back	5	3.247	8.1789	22	3.343	14.245	1.2869	0.2566		
Shoulder	11	7.143	17.994	50	7.599	32.375	3.202	0.0735		
Arm/Elbow	5	3.247	8.1789	11	1.672	7.1225	0.06586	0.7974		
Hand/Wrist	18	11.69	29.444	73	11.09	47.267	3.2973	0.0693		
Hip/Thigh	1	0.649	1.6358	5	0.76	3.2375	0.033	0.8559		
Knee	15	9.74	24.537	60	9.119	38.85	2.5799	0.1082		
Ankle/Foot	7	4.545	11.45	53	8.055	34.317	**8.2304**	**0.0041**	0.33366	.15171 - .73384
Other	1	0.649	1.6358	5	0.76	3.2375	0.033	0.8559		
Dislocation										
Total	6	3.896	9.8147	32	4.863	20.72	2.9553	0.0855		
Shoulder	5	3.247	8.1789	30	4.559	19.425	3.4122	0.0647		
Other	1	0.649	1.6358	2	0.304	1.295	0.202	0.6531		
Bruise/Laceration/Abrasion/Puncture										
Total	31	20.13	50.709	105	15.96	67.987	2.0738	0.1498		
Head/Face/	13	8.442	21.265	37	5.623	23.957	0.1369	0.7113		
Upper Extr	8	5.195	13.086	19	2.888	12.302	0.02148	0.8834		
Lower Extr	5	3.247	8.1789	26	3.951	16.835	2.2823	0.1308		
Torso	5	3.247	8.1789	23	3.495	14.892	1.519	0.2177		
Concussion	14	9.091	22.901	69	10.49	44.677	**5.3963**	**0.0201**	0.51258	.28859 - .91043

*Board (+) denotes snowboarders with helmets
Board (-) denotes snowbowarders without helmets
__ = Chi squared value or Chi Squared with Yate's correction if expected values are less than 5
RR= Relative Risk; CI= 95% Confidence Interval

Table 2: Board Statistics.

	% of sample	Total (est)	Total injuries	% of all injuries	per 1000 skier days
Ski (-)	43.07	212255.6	397	30.73	1.87
Ski (+)	13.18	64953.6	83	6.424	1.28
Total Ski	56.25	277209.2	480	37.15	1.73
Board (-)	31.34	154440.9	658	50.93	4.26
Board (+)	12.41	61132.8	154	11.92	2.52
Total Board	43.75	215573.7	812	62.85	3.77
Total Helmet	25.59	126086.4	237	18.34	1.88
Total w/o helmet	74.41	366696.5	1055	81.66	2.88
Total	100	492783	1292	100	2.62

Table 3: Injury Rates.

without helmets had 658 injuries ($p<.0001$), with RR 0.5973 for those wearing helmets. Snowboarders with helmets sustained 40 fractures while those without helmets had 173 ($p<.01$, RR= 0.5841). Shoulder/clavicle fractures was the only significant subset of that category (4 and 36 for helmeted and non-helmeted snowboarders respectively, $p<.01$, RR= 0.2807). There were significantly less sprain/strains sustained by snowboarders with helmets than those without (63 and 279 respectively, $p<.0001$, RR= 0.57046), and within that category, the ankle/foot subset of sprain/strains showed significantly fewer injuries in those with helmets than those without (7 and 53 respectively, $p<.01$, RR= 0.3337). Helmeted snowboarders sustained significantly fewer concussions (14 and 69 respectively, $p<.05$, RR= 0.5126).

Comparing overall injury rates for skiers and snowboarders, those that wear helmets were injured significantly less overall as compared to their unprotected counterparts (Table 3).

Discussion

These data do not reveal a significantly lower incidence of concussions among helmeted skiers, but helmeted skiers do have an overall reduction in total injuries and specifically a reduction in total lower extremity (and knee only) and neck/back injuries. There were fewer concussions amongst helmeted skiers, and future studies with more accurate counts of total helmeted and un-helmeted skiers may demonstrate a significant reduction in the risk of concussion. Helmeted snowboarders had fewer head/face injuries, concussions, upper and lower extremity injuries, total sprain/strains, and total fractures. Helmets appear to have a stronger association in reduction of injuries amongst snowboarders than skiers.

Further study is necessary to determine if the skiers/snowboarders who wear helmets are self-selected and may be safer people in general, or if wearing a helmet actually changes behavior patterns. In either case, these data do convincing demonstrate that in this population, wearing a helmet does not result in increased injury rates via increases in risk taking behavior or other mechanisms. As there is currently no good data demonstrating that helmets increase the risk of injury, it seems prudent based on available information to recommend helmets for skiers and snowboarders. Considering all of the available literature, young male snowboarders are the group most likely to benefit from helmet use.

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Overcoming A Genetic Predisposition Toward Lack of Mechanical Responsiveness Using Rest-inserted Loading

Ted S. Gross, Ph.D., Sundar Srinivasan, Ph.D., and Sandra. L. Poliachik, Ph.D.

A number of recent studies have highlighted the genetic contribution to bone's ability to respond to mechanical loading. Identification of mouse strains with substantially different bone material properties and response to mechanical stimuli has enabled increasing mechanistic exploration of genetic disposition towards altered mechanosensitivity. In particular, the C3H/HeJ mouse has been observed to possess a greatly diminished ability to respond to exogenous mechanical loading. We have recently observed that the strategy of inserting a rest interval between each cycle of mechanical loading dramatically enhances the osteogenic response of low magnitude loading in the C57/B6J mouse, a strain noted for its sensitivity to mechanical loading. In this study, we hypothesized that rest-inserted loading would overcome the inability of the C3H mouse to respond to moderate physiologic magnitude mechanical loading.

Methods

Three groups of mice were utilized in the study: 1) 16 wk old C57/B6J mice (n= 7), 2) 16 wk old C3H/HeJ mice (n=6), and 3) 32 wk old C3H/HeJ mice (n=8). This design enabled comparison of the response to rest-inserted loading of same aged C57 and C3H mice (@ 16 wk) and a comparison of mice with similar levels of bone formation at the initiation of the experiment (16 wk C57 vs. 32 wk C3H). Loads were applied to the right tibia of each mouse using a non-invasive murine loading device. Each of the mice underwent a 3 wk protocol in which the right tibia was loaded 3 d/wk with 50 cycles of loading each separated by 10 s of rest. Calibration tibia were scanned at 18 μm voxel resolution (Scanco μCT-20) and resulting scans were used to develop a finite element model of the combined tibia and fibula of each two calibration mice. Once validated via the measured strains, the finite element models were used to quantify peak induced strains on both the periosteal and endocortical surfaces for each group. End loading conditions for each experimental group were adjusted such that peak induced strains were anticipated to be similar for each of the three groups through the tibial midshaft. All mice received calcein injections (IP, 15 mg/kg) on days 10 and 19, with the mice sacrificed on day 21. Following sacrifice, 300 μm thick mid-diaphyseal cross-sections were taken from the right (exp) and left (intact contralateral) tibiae and were mounted and ground to 100 μm for assessment of dynamic indices of bone formation. On both endocortical and periosteal surfaces, standard measures of mineralizing surface (MS), mineral apposition rate (MAR), and surface referent bone formation rate (BFR) were quantified. Between group differences were assessed using the Kruskal-Wallis non-parametric test with Mann-Whitney follow up, while the non-parametric Wilcoxon tests were used to assess differences between the experimentally loaded tibia and intact contralateral control tibia.

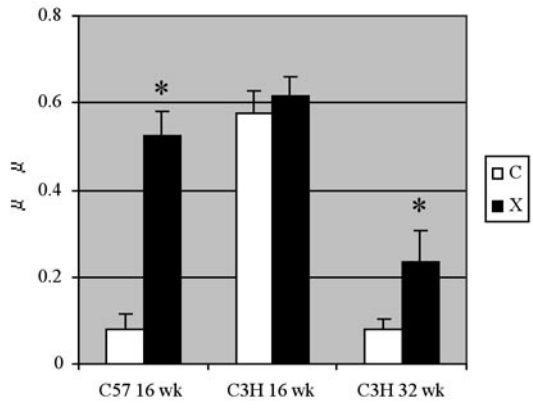

Figure 1: Periosteal bone formation rates for mice subjected to moderate magnitude rest-inserted loading. Asterisk indicates significant increase in loaded versus intact contralateral tibia.

Results

At the midshaft sites at which bone formation rates were assessed, peak normal strains induced in each of the groups were similar at the periosteum, but were significantly higher at the endocortical surface of the C57 at 16 wk as compared to the C3H @ 16 wk and 32 wk due to the shape of the bone (i.e., a thinner cortex). At the periosteum, all bone formation measures were elevated in 16 wk C3H contralateral tibia compared to the C57 and 32 wk C3H mice. At the endocortical surface, the MS (p=0.01), MAR (p=0.02), and BFR (p=0.02) were enhanced by loading only in the C57 mice. As observed previously, rest-inserted loading significantly enhanced periosteal MS (p=.01), MAR (p=0.02), and BFR (p=0.02) over control levels in C57 mice. Neither periosteal MS, MAR, nor BFR were altered by loading in 16 wk C3H mice. However, periosteal MS (p=0.01), MAR (p=0.05), and BFR (p=0.03) were each enhanced by rest-inserted loading in 32 wk C3H mice (Figure 1). The BFR achieved in the loaded C57 and 16 wk C3H mice exceeded that observed in the 32 wk C3H mice (both p=0.01).

Discussion

This study examined the ability of rest-inserted mechanical loading to stimulate bone formation in C3H mice. When the C3H skeleton is actively modeling (as was evidenced at 16 wk), our results support previous observations that the C3H mouse does not respond to mechanical loading. Previous studies have explored this concept in depth and have found that normal strains nearly 3 fold greater than induced in this study remain ineffective in provoking an osteogenic response in C3H mice between the ages of 9 and 20 wk. Thus, during vigorous periosteal modeling under genetic control, it appears that mechanical loading provides minimal additional benefit for enhanced osteoblastic activity.

However, we were able to significantly enhance all bone formation parameters when the same rest-inserted regimen was applied to 32 wk C3H mice. Interestingly, the decreased BFR response in 32 wk C3H vs 16 wk C57 mice exposed to similar loading protocols occurred primarily due to reduced MAR (48% of C57 levels). This result suggests that C3H mice are not necessarily unresponsive to mechanical stimulation, but rather, that their genetic predisposition constrains the ability to sustain biosynthetic activity. In a broader context, this study suggests that the strategy of rest-inserted loading may have wide application to a heterogeneous population, some of whom are, undoubtedly, less responsive to the benefits of skeletal loading.

Acknowledgements

Supported, in part, by NIH AR48102.

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Functional Outcomes of High-Energy AO/OTA C3 Bicondylar Tibial Plateau Fractures Treated With Dual Incisions and Medial and Lateral Plating

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Most reports of functional outcomes of tibial plateau fractures combine heterogenous groups of fracture patterns. Others that report the outcomes of high-energy bicondylar tibial plateau fractures frequently group injuries of varying articular severity. Additionally, several studies suggest that residual articular incongruity of the tibial plateau does not compromise long-term functional outcomes. The purpose of this paper is to report the functional outcomes of high-energy AO/OTA C3 bicondylar tibial plateau fractures operatively stabilized with medial and lateral plating using anterolateral and posteromedial surgical approaches, and to correlate the adequacy of operative reduction with functional outcome.

Methods

Between 1994 and 2001, all patients sustaining an intra-articular fracture of the proximal tibia were identified from a prospectively designed orthopaedic database. Eighty-three patients sustained 83 tibial plateau fractures classified as AO/OTA type 41-C3. All 83 patients were treated with medial and lateral plate fixations using two surgical incisions. The use of a single midline anterior surgical approach was abandoned prior to the study period, and similarly, fixed-angle screw/plate devices were not yet available. Indications for medial plating were to neutralize the medial metadiaphyseal injury and/or to stabilize displaced medial articular fracture fragments.

Of the original 83 patients, 41 were available for minimum two-year follow-up evaluations and completed the Musculoskeletal Function Assessment (MFA). Patients' charts were reviewed to determine age, gender, injury mechanisms, presence of other injuries, associated soft tissue injury, initial and definitive management, and complications. There were 23 male and 18 female patients with an average age of 46 years (range, 21-72). The mean time of follow-up was 55 months (4.6 years) (range, 30-104 months). Twenty-four patients (58%) were treated with temporary spanning external fixation prior to definitive ORIF. The average delay to definitive fixation was 8.75 days (range 0-30). Associated open wounds were observed in 12% and compartment syndrome diagnosed in 10%. Thirty-nine percent of patients had associated meniscal injuries diagnosed at the time of open reduction and fixation.

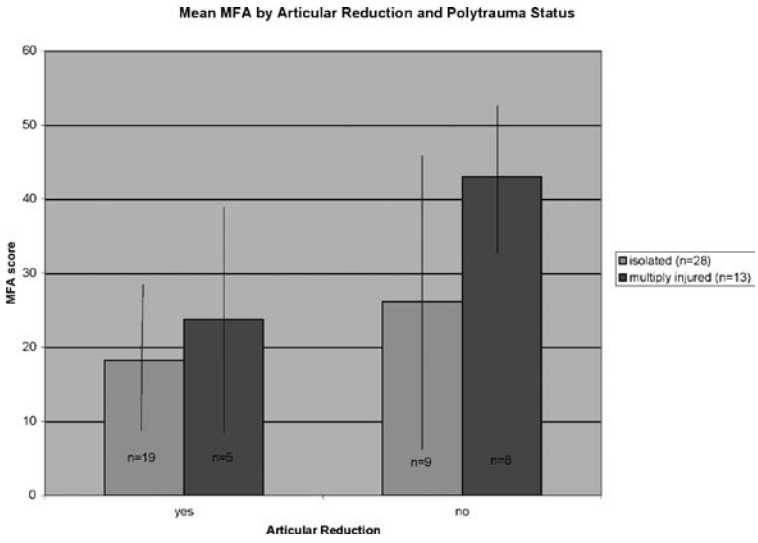

Figure 1: Mean MFA versus the presence or absence of satisfactory articular reduction. Patients are stratified according to the presence or absence of multiple injuries.

Two fellowship trained orthopaedic traumatologists blinded to the MFA scores independently assessed the quality of reduction on intraoperative and immediate post-operative plain radiographs using 4 radiographic parameters: articular reduction, sagittal alignment, coronal alignment, and condylar width. Each parameter was scored as satisfactory or unsatisfactory using the following endpoints, determined a priori: articular reduction (<= 2mm step/gap), coronal alignment (+/- 5°), sagittal alignment (+/- 5°), and condylar width (<= 5mm). Statistical analysis was performed using a regression model.

Results

Of the 41 patients, 2 incurred deep wound infections (4.9%) and 3 developed superficial complications (7.3%). Ten patients (24%), exclusive of those with deep infections, underwent hardware removal for relief of local symptoms.

Complete radiographic information was available for 31 patients. By definition, all patients sustained displaced lateral articular injuries, with 90% demonstrating lateral comminution and depression. The medial sided articular injuries were characterized by separation of the entire medial plateau in 32%, while 68% had significant medial plateau articular displacement. Of these, 66% were simple fractures, 19% were comminuted, and 14% demonstrated comminution with articular depression.

Seventeen patients (55%) had a satisfactory articular reduction, 28 patients (90%) had satisfactory coronal plane alignment, 21 patients (68%) demonstrated satisfactory sagittal plane alignment, and all 31 patients

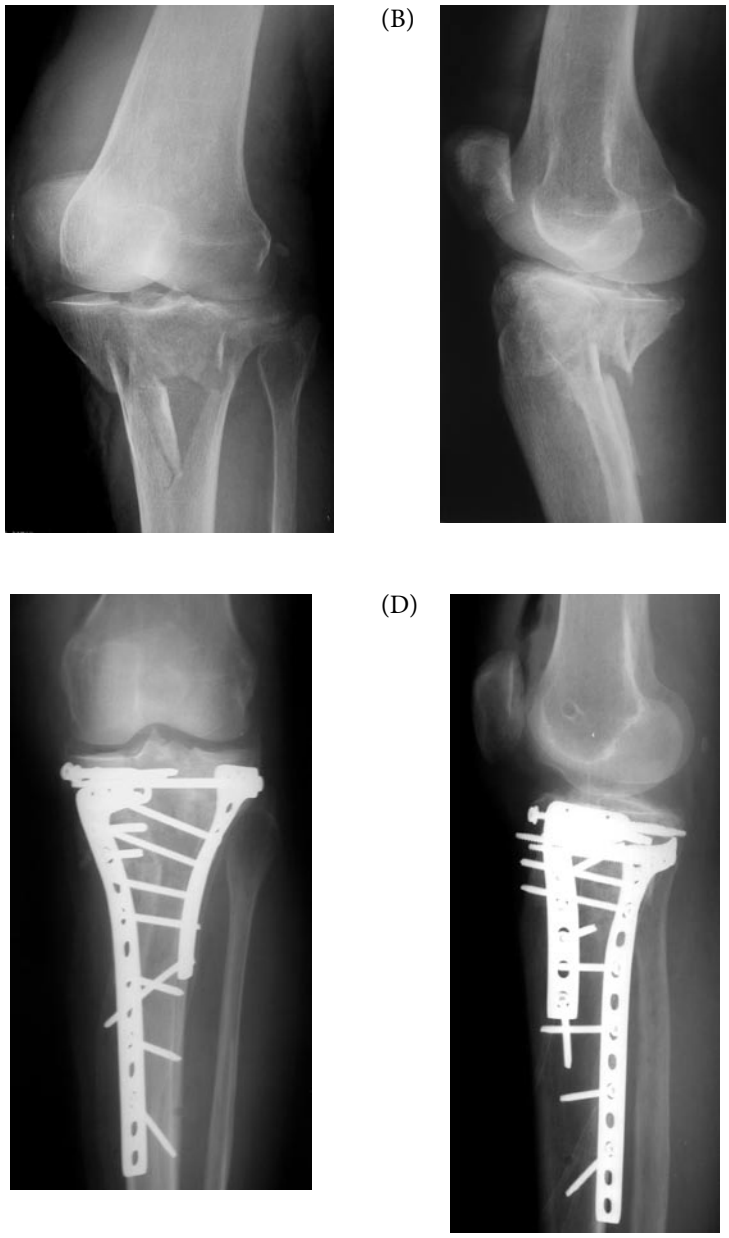

Figure 2 : (A), (B). Injury anteroposterior and lateral radiographs of a 48 year-old woman sustaining a comminuted bicondylar tibial plateau fracture after being involved in a motor vehicle collision. (C), (D). Immediate post-operative radiographs after open reduction and internal fixation using two surgical approaches with medial and lateral plating. Her reduction was scored as satisfactory on all four radiographic parameters.

demonstrated satisfactory plateau width.

The mean MFA was 24 (range, 1-63). Age and the presence of multiple injuries were statistically associated with a higher (worse) MFA score (p=0.037 and p=0.014, respectively). For this study, patients were considered to be multiply injured if they achieved an Injury Severity Score (ISS) greater than or equal to 18 or had associated lower extremity displaced intra-articular fractures requiring operative reduction and fixation. Of the 13 patients classified as multiply injured, 5 had an ISS of 18 or greater, and 8 patients had associated intra-articular lower extremity fractures requiring operative fixation. Twenty-eight patients were therefore considered to have isolated C3 bicondylar tibial plateau fractures (Table 1). When age and the presence of associated multiple injuries were accounted for, regression analysis demonstrated that a satisfactory articular reduction was significantly associated with a lower (better) MFA score (p=0.033) (Figure 1). Though not statistically significant, sagittal plane alignment and the overall reduction trended toward lower MFA scores (p=0.076 and p=0.067, respectively). When compared to normative data (MFA in normal population = 9.3), patients sustaining C3 bicondylar tibial plateau fractures treated with demonstrate significant residual dysfunction.

Discussion

Medial and lateral plate fixation of bicondylar tibial plateau fractures using a single incision has historically been associated with unacceptably high deep sepsis rates. More recent reports have demonstrated acceptable wound complications using a two-incision approach. This study was performed to evaluate the functional outcomes of a homogenous group of fractures treated with a consistent surgical method, and to identify which reduction parameters are associated with improved outcomes. To create as homogeneous fracture group as possible, only C3 bicondylar tibial plateau fractures were evaluated, as C1 and C2 fractures are associated with simple articular injury patterns and consequently, have demonstrated improved outcomes when compared to the C3 patterns. Accordingly, 68% of this study group sustained injury to the articular surface of the medial plateau, in addition to substantial articular injury of the lateral plateau.

A potential criticism of our methodology is that several reports have suggested that the accuracy and reproducibility of plain radiographic measurements of articular congruity may be suboptimal. Improved measurement accuracy has been demonstrated with CT scanning, particularly when evaluating fractures of the acetabulum and distal radius. The patients in this study, however, only obtained pre-operative CT scans and, therefore, we do not have the benefit of this potential improved radiographic accuracy. Unlike the reports that have identified problems with the validity of plain radiographic measurements, the reduction parameters evaluated in this study are continuous data that has been ordered into a dichotomous response, essentially decreasing the tolerance limits of the parameters evaluated. This may increase the

Patient	Age	MFA	Artic. Reduction	Multiply Injured	Assoc. Ortho Fx
1	58	1	no	1*	Calcaneus
2	52	3	yes	0	
3	57	5	no	0	
4	37	5	no	0	
5	46	6	X	0	
6	56	6	X	0	
7	39	7	X	0	
8	70	8	yes	0	
9	70	8	X	0	
10	72	10	no	1*	Calcaneus
11	49	11	no	0	
12	54	11	yes	0	
13	55	12	yes	0	
14	21	16	no	1*	Calcaneus, Talus
15	44	17	X	0	
16	46	17	no	0	
17	45	17	X	0	
18	32	17	no	0	
19	55	18	X	0	
20	54	19	yes	0	
21	33	21	no	0	
22	51	21	no	0	
23	41	24	no	1†	
24	39	24	yes	0	
25	53	25	no	1*	Pilon, Patella
26	39	28	yes	0	
27	52	28	yes	1†	
28	42	31	no	0	
29	36	31	no	1†	
30	33	36	no	0	
31	43	36	X	0	
32	48	39	yes	0	
33	36	40	X	0	
34	37	41	no	1*	Tib plateau
35	52	42	no	1*	Dist femur
36	35	43	yes	1†	
37	34	44	X	1*	Talus, Patella
38	56	48	yes	1*	Dist femur
39	39	53	yes	1†	
40	39	54	yes	0	
41	56	63	yes	0	

Table 1: Patient data chart. X = radiographs unavailable, 0 = isolated injury (n=28), 1 = multiply injured patient (n=13), * = associated intra-articular lower extremity fractures requiring operative management (n=8), † = Injury Severity Score (ISS) >18 (n=5)

validity of our radiographic assessments. While there is no data on the validity of radiographic measurements of articular congruity following ORIF of tibial plateau fractures, either using continuous or dichotomous variables, this may represent a potential limitation of our study.

Contrary to the majority of reports evaluating the surgical management of tibial plateau fractures, this study has demonstrated that an accurate reduction of the articular surface is correlated with an improved outcome and should be the primary surgical goal in the treatment of these injuries (Figure 2). The anterolateral and posteromedial approaches allow access to the major articular fracture components and can be performed with acceptable complication rates.

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The Impact of Educational Intervention on Provider Confidence and Competence in Performing a Simple Surgical Task

Seth S. Leopold, M.D., Hannah Morgan, M.D., Nancy J. Kadel, M.D.,
Gregory C. Gardner, M.D., Douglas C. Schaad, Ph.D., and Fredric M. Wolf, Ph.D.

A consensus is emerging regarding the positive correlation between provider volumes and patient outcomes following medical procedures, non-orthopaedic surgical interventions, and orthopaedic surgery. It is also recognized that for many complex new procedures there exists a so-called learning curve, and that providers who are new to a procedure may experience more complications than physicians who have performed the intervention in question more times. Much of this literature is derived from the general surgery experience during the transition from open to laparoscopic proceduress, and clear "threshold" numbers that will permit acceptable competence of particular procedures remain elusive for most interventions.

But at some point on the learning curve, each individual provider must decide that (s)he is qualified to perform a procedure. Since there is no certification process for individual orthopaedic procedures, this decision will necessarily be made by individual surgeons, who presumably will base this choice on his/her level of confidence, background, education, and skill. Minimally-invasive procedures are being developed and disseminated at a rapid rate in orthopaedic surgery, and most providers will need to learn these procedures in a context other than traditional residency training. As a result, understanding how providers arrive at the choice of whether they are ready to perform a particular task – and determining whether the choices they make are reasonable and safe – are important research questions, but to our knowledge, no work has been published on these topics. Moreover, relatively little is known about the efficacy of different methods used in medical education to teach psychomotor tasks, and while provider confidence with particular tasks has been studied to a limited degree, the relationship between a provider's self-perception of his/her psychomotor skills and objective competence hardly has been explored.

The present study tests the following hypotheses in the context of a simulated knee joint injection using anatomic models, which we considered to be a simple surgical task:

1. There is a relationship between a provider's confidence in the ability to perform a task and that provider's ability to perform the task competently
2. Psychomotor skills education improves the correlation between confidence and competence
3. Demographic variables are associated with differences in the provider confidence/competence relationship
4. More labor-intensive methods of instruction result in improved competence

Methods

Participants and Study Site

All participants at an approved continuing-medical education course taught by orthopaedic surgeons on the outpatient management of musculoskeletal disorders were invited to participate in this study, which took place over the course of an afternoon lab session on knee joint injections. Ninety-three licensed providers whose practices either included or may in the future include knee joint injections, agreed to participate. The education and practice backgrounds of the providers varied, but the group included M.D.'s, D.O.'s, nurse practitioners, and physician's assistants.

Study Intake, Baseline Questionnaires, and Pre-Test

All study participants received a 15-minute illustrated podium presentation on the indications for knee joint injection and aspiration, risks of the procedure, sterile technique, anatomic landmarks, needle position, and needle insertion for the superolateral approach. Participants then were asked to complete a background questionnaire that assessed each provider's type of practice (internal medicine, family practice, other), number of years in practice since completion of training, gender, age, number of knee injections/aspirations performed in the last year, and formal training in this procedure. Each provider was then asked to rate his/her self-assessed confidence at injecting a knee joint using the superolateral approach. A 10-point Likert scale was used for self-assessment of confidence, anchored by "not confident" (1 point) and "very confident" (10 points).

Next, all study subjects were asked to mark the relevant anatomic landmarks (superior pole of the patella and lateral border of the patella), simulate a sterile skin preparation and perform a knee joint injection using superolateral needle placement on custom-built anatomic knee models. The models have foam "tissues" in several layers that are designed to simulate the feel of injecting a human limb, and incorporate an electrical conductive system that provides audio feedback when the needle is positioned in the knee joint. The models were created to specifications designed to simulate a moderate knee-joint effusion. An overlay apparatus made for each model allowed to readily grade the accuracy of needle placement in a reproducible manner by trained preceptors, and the preceptors graded each injection attempt on a 10-point scale that included each of the following elements: simulating sterile skin preparation, marking anatomic landmarks that define the injection site, inserting the needle at the correct angle, gaining entry to the knee with as few repeat attempts as possible, and for gaining entry to the knee in as short a time as possible after the needle has been inserted. The participants were not informed that they were being timed during this exercise.

After performing the pre-instruction injection, each participant was asked to rate his/her own performance using a 10-point Likert scale, anchored with

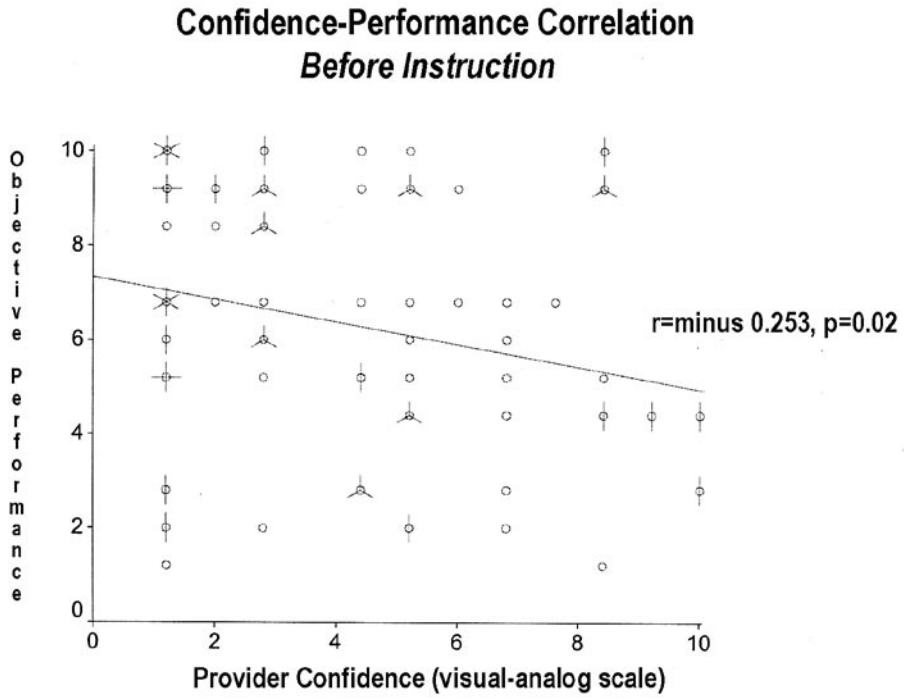

Figure 1: Before formal instruction, providers' self-expressed confidence was significantly but inversely related to objectively assessed performance at a simple surgical task (simulated knee joint injections on anatomic models).

"unsatisfactory" (1 point) and "very skillful" (10 points).

Randomization and Study Educational Intervention

Next, a table of random numbers, which was shielded from the investigators and the participants, was used to assign each study participant to receive further instruction on knee joint injection using the superolateral approach one of three ways:

1. A printed guide demonstrating the superolateral technique of knee joint injection
2. A CD-ROM video demonstrating the superolateral technique of knee joint injection
3. Hands-on instruction by a trained tutor

The printed guide included descriptions, and illustrations (line drawings and photographs) of the relevant anatomy and recommended needle placement and insertion. Providers assigned to this group were allowed to spend as much time reviewing the guide as they wanted, and they were permitted to refer to it during the study if they desired to do so. The CD-ROM video covered the same material and used the same static illustrations, but also included an audio component describing the procedure, and depicted a knee joint injection via the superolateral approach carried out in real-time. Participants who were randomized to receive hands-on instruction spent five to ten minutes with a trained preceptor (a fellow in adult reconstruction or a rheumatology or orthopaedic surgery attending surgeon), and then had the opportunity to perform supervised practice injections, with feedback from the instructor, until each participant indicated (s)he was comfortable enough to demonstrate an injection for testing purposes to a preceptor other than the one who provided the hands-on instruction.

Post-Test and Outcomes Assessment

Following instruction using one of the three methods described, each provider was again asked to rate his/her self-assessed confidence on injecting a knee joint on a Likert scale. Participants then again were asked to simulate a sterile skin preparation and perform a knee joint injection on the custom-built anatomic knee models, and this second effort was again graded by trained preceptors using the objective 10-point scale described earlier. To avoid bias, preceptors who performed hands-on instruction were not permitted to grade their own students on the second (post-instruction) knee injection. Following the post-instruction injection, each participant again was asked to rate his/her own performance using the 10-point Likert scale.

Results

Before instruction, participants' confidence was significantly but inversely related to objective performance standards (r=minus 0.253, p=0.02; Figure 1); that is, increasing confidence was actually correlated with poorer performance against the objective standard. After instruction, regardless of which teaching intervention students received, confidence was correlated with objectively-measured competent performance (r=0.24; p=0.04; Figure 2); however, this correlation was not nearly as strong as the correlation between participants' confidence and participants' own assessment of performance (pre-instruction r=0.42,

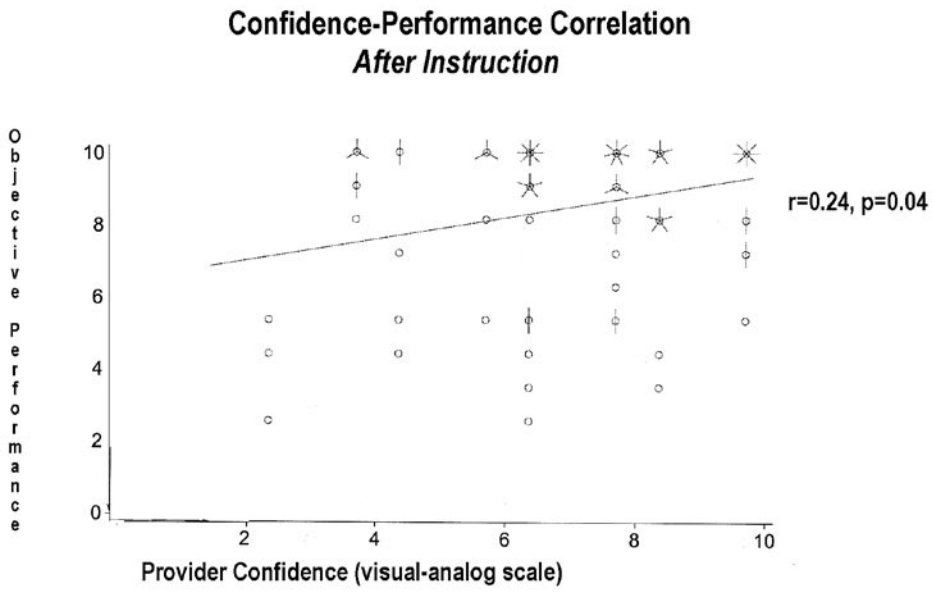

Figure 2: After formal instruction, providers' self-expressed confidence was significantly and directly related to objectively assessed performance at the same task; however, this correlation was weaker than that observed between provider confidence and providers' self-assessments of their own performance (r=0.72, p=0.001 after instruction), suggesting that providers persistently overestimated their skills even after instruction. These findings were not seen equally in all demographic and gender groups.

p=0.001; post-instruction r=0.72, p=0.001). These findings suggest that both before and after instruction, increasing levels of confidence among these providers was correlated with overestimation of their own skills at knee joint injection.

The inverse relationship between confidence and competence before formal instruction was largely driven by professional background (physician versus non-physician professional), gender, and age. Physicians (MD's and DO's) were significantly more confident than nurse practitioners and physician's assistants (5.3 versus 2.8 on the 10 point scale, p<0.001), but who did not score significantly higher on the pre-instruction competence scale (p>0.1). Analysis by gender identified that male participants were significantly more confident before instruction than female participants, but before instruction no significant skill differences between males and females were identified on the competence assessment. Similarly, before instruction, younger providers (dividing the group around the median age of 46 years) demonstrated a significant (p=0.047) and inverse relationship (r=minus 0.295) between confidence and objectively scored performance.

Objective measures of performance improved significantly across all groups after instruction (p=0.001); however, the most labor-intensive mode of instruction (hands-on teaching) did not improve performance significantly better than did less-intensive techniques (CD-ROM or printed technique manual).

Conclusions

The effects observed in this report, particularly the inverse relationship between providers' confidence and competence before receiving formal instruction, are not equally observed in all types of providers (physicians versus non-physician professional caregivers) or all demographic groups. The findings that age, gender, and professional training may result differentially in disproportionate or unrealistic self-assessments of psychomotor skills certainly warrant further study.

In the context of the simple psychomotor task studied in this report (simulated knee-joint injection), low-intensity didactic interventions – including a simple printed technique manual – were found to be as effective as high-intensity, hands-on efforts. We hypothesize that this same finding will not hold true for tasks of intermediate- or high-levels of complexity. Both this, and the impact of gender, age, and training on provider self-assessment of skills in more difficult surgical interventions, will need to be the subject of further inquiry.

This study demonstrated that even low-intensity forms of didactic instruction achieved significant improvements in provider confidence, competence, and the accuracy with which providers assess their own skills at performing simulated knee joint injections. However, the inverse relationship between providers' confidence and actual skill at performing even a simple surgical task before receiving instruction, and the consistent overestimation of providers' own skills even after instruction, should raise questions about how new, more complex procedures are introduced and how or when self-trained providers should begin to perform them.

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Evaluation of an Internet-Based, Patient-Centered Orthopaedic Information Tool

Seth S. Leopold, M.D., Kristen Shuyler, M.A., Mark McKenna, B.S., Doug Brock, Ph.D., and Frederick A. Matsen III, M.D.

The Internet is a vast and growing source of information. It has doubled in size annually for the past 11 years, and it is estimated that over 150 million individuals access the 2.2 million publicly accessible websites. Unfortunately, while there is no shortage of data on line, it can be difficult for a visitor to the World Wide Web to separate readable, high-quality, relevant, brand-neutral medical information from the ample supply of untested folk remedies, testimonials, and advertisements that are posted on line. And while patient self-management programs for common orthopaedic conditions such as arthritis and back pain have been shown to be worthwhile, the Internet can subvert such efforts with information on those same topics that is often harmful or distracting.

Numerous studies have documented the generally poor quality and low information content of websites that purport to share knowledge on orthopaedic topics. Despite this, a majority of orthopaedic patients who use the internet do so to research medical topics, a finding mirrored in the population at large.

In view of these findings, the cliché "knowledge is power" easily evolves into a concept of knowledge as therapy, and physicians have an obligation to offer such therapy on the Internet that meets the standards of quality that apply in other arenas.

With those issues in mind, we designed an internet-based system that offers an easily accessible, intuitive reference for laypeople seeking orthopaedic information. The present report seeks to evaluate the effectiveness of this tool in three domains that were important to the original team that created the website: authoritativeness, responsiveness, and accessibility.

Methods

Authoritativeness: Two tests were performed to evaluate the site with respect to this domain. First, the overall quality of the website was evaluated against the Journal of the American Medical Association's "Guidelines for Medical and Health Information Sites on the Internet". Next, the study team performed an internal website audit to profile the authors who have provided content on the site, including the following parameters: fellowship training, years in practice, faculty rank, number of peer-reviewed publications, and level of participation in the peer review process.

Responsiveness: A detailed, three-month logfile and content analysis of website statistics was performed, to determine the frequency and outcome of natural-language searches performed on the site, as well as the disposition of all queries that were forwarded to the webmaster for further assistance during the period of study. As a secondary endpoint of responsiveness, an evaluation of visitor ratings of the content pages visited was made.

Accessibility : 48 randomly selected natural-language questions submitted to *UW ORTHOSOURCE* over the last 12 months (four per month during the period of study) were entered verbatim back into *UW ORTHOSOURCE* as well as into Google and PubMed. The first 5 answers returned from each source were analyzed in a blinded fashion for Flesch-Kinkaid reading level and for relevance (proportion of search results that were obviously off-point). Summary statistics are presented regarding the sources of information returned by the Google searches, in terms of the proportion of sites that were of commercial, non-profit, educational, or other origin.

Results

Authoritativeness: The site met all 33 applicable JAMA guidelines. All website contributors are fellowship-trained; contributors published a mean of 44 journal articles, and serve on the peer-review process of 2.4 national journals.

Responsiveness: Visitors hit the site 365,668 times for an average of 6.6 minutes, and performed 2690 searches. The mean content-page utility rating was 4 of 5 ("very useful"). Visitors submitted 533 questions requesting additional medical information; this represents 19.8 percent of all searches, and 0.15 percent of visits. The content manager responded to 100 percent of those questions.

Accessibility: Readability of the site's content was intermediate between Google and PubMed. Flesch-Kinkaid grade level was 9.8 for Google searches, 11.3 for *UW ORTHOSOURCE*, and 12.0 for PubMed ($p<0.01$). *UW ORTHOSOURCE* yielded the most on-topic search results ($p<0.05$). Sixty-one percent of Google searches (269 of 445) returned ".com" websites, suggesting for-profit content.

Discussion

Investigations by the University of Washington's Program for Educational Transformation Through Technology (PETTT) concerning the needs of learners at large, including individuals seeking health-related information, have consistently pointed to the following critical elements of a knowledge-sharing system:

(1) trustworthiness of the information
(2) "searchability"
(3) organization
(4) immediate access
(5) ability to re-access information and to share with family and friends
(6) ability to understand the information

It can be seen that item (1) is a comment on authoritativeness, while (2) and (3) relate to responsiveness and (4), (5) and (6) concern accessibility. As a scalable tool for pure knowledge distribution, the Internet offers advantages over office calls, printed brochures and even physician visits.

The present report used established definitions and tools to confirm a high level of authoritativeness, responsiveness, and accessibility of

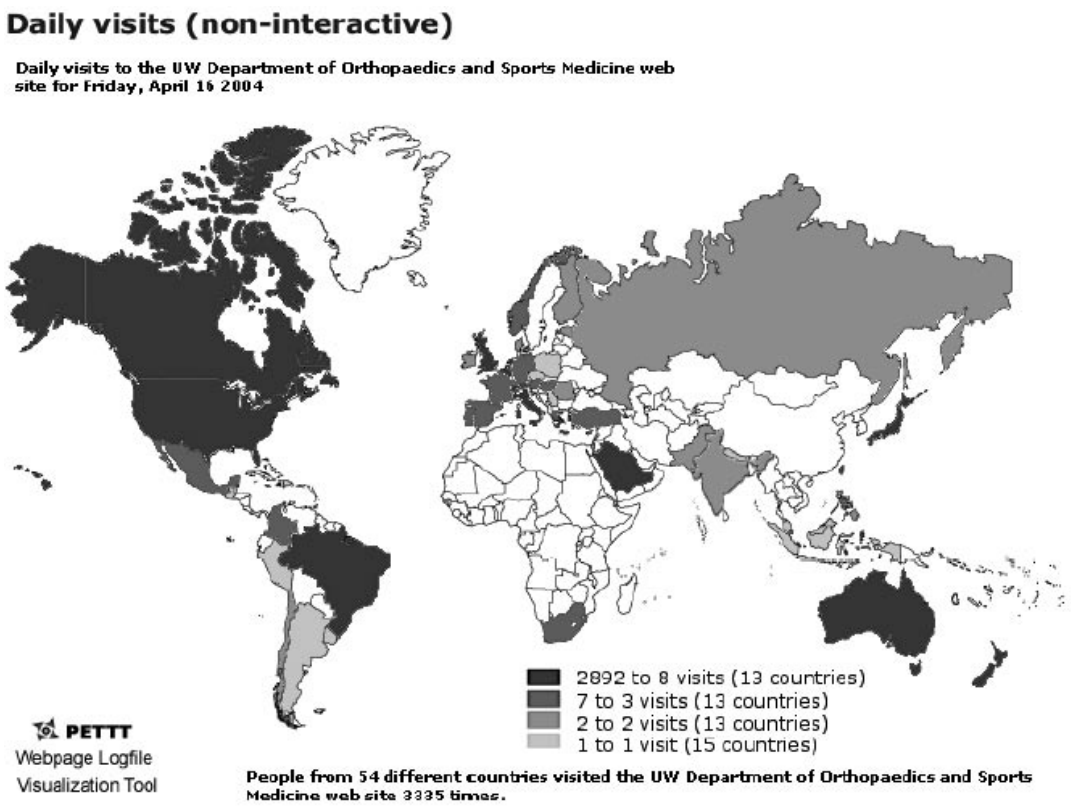

Figure 1: The host website for UW ORTHOSOURCE (www.orthop.washington.edu) is visited by thousands of people from dozens of countries on a daily basis. This map shows that on a typical single day, over 3300 visitors from 54 countries spent time learning about musculoskeletal health on this site.

a prototypical educational website designed to return high-quality medical content when queried using a natural-language search engine.

Authoritativeness or quality has been defined in numerous ways. Some studies have made descriptive characterizations of surveys of search results; others have reified authors' subjective assessments of content appropriateness or perceived validity. Simulated peer-review processes have also been used to compare the scientific or clinical validity of pages returned from (usually commercial) search engines. That approach has the advantage of familiarity to clinicians who rely on and trust the peer-review process to establish content reliability. However, since *UW ORTHOSOURCE* returns content from thousands of templated article sections across disciplines including orthopaedic surgery, rheumatology, and internal medicine, as well as on "lifestyle" topics relating to self-care and living well with musculoskeletal illness and disability, assembling a panel of expert peer reviewers to assess the quality of content of this breadth would have been impractical. The present study used an audit of content authors' academic credentials as a surrogate measure of authoritativeness; with a mean of over 40 peer-reviewed articles published and participation in the peer-review process of multiple specialty journals, the site scored well in this area. The site also met all relevant JAMA criteria for medical websites; these criteria are designed to help minimize barriers to the use of the Internet for physician-patient information transfer.

Responsiveness is more than a webmaster replying consistently to specific visitor queries, although by that standard the site also scored extremely well. At its essence, responsiveness is the ability of an educational site to identify and provide for the needs of its visitors. The format for the site was created following interview sessions, forums, and directed surveys that collected the opinions of hundreds of patients regarding which elements of website design are important to them, and what topics should be covered in articles about medical conditions and surgical procedures. Based on the results of that research, a set of content templates was created, upon which all the site's content is based. Finally, the inclusion of a natural-language search engine that helps visitors find content responds to the expressed desires of on-line health-information seekers; a robust query function in sites visited for health-related topics is consistently listed as an important feature to these users. It is likely that this accounts for the high level of satisfaction of the site's users (four of a possible five stars, on average, for content pages).

Accessibility can be defined as the potential for patients and other seekers to find relevant and interpretable information easily. Accessibility, then, really is a combination of "findability," "usability," and relevance. To keep the site scoring high on search engines, the webmaster works with subject-matter experts to update content pages regularly, the information architecture of each page is structured to keep the

educational content visible to tools that search the web, and the site maintains robust topical links to other sites when it is appropriate to do so. Success of the steps taken by the site's web developers are validated by the statistics of website visitors; during the three-month detailed audit, visitors from over 50 different countries hit the site over 360,000 times (Figure 1). Over the past two years, there have been nearly 3 million visits to the site. Readability, defined loosely as the extent to which information is comprehensible to a given class of people, represents a necessary but not sufficient criterion for determining accessibility. Based on grade-level analysis (Flesch-Kinkaid score), material from the site was intermediate in difficulty between material identified on Google and references found on a typical Medline search. With respect to relevance, natural-language searches on *UW ORTHOSOURCE* provided significantly more on-topic results than either Google or PubMed.

Over 60 percent of the search results (269 of 445) from Google in the present report yielded sites whose suffixes indicate for-profit origins (".com"). While commercial origin does not discredit the information posted on line, there is ample evidence that commercial sites impact visitors differently than non-commercial ones and that the quality of the information posted differes between ".com" and ".edu" sites. Advertising was the focus of 80.8 percent of websites (69 of 73) about back pain in a recent report. Other work has suggested that the proliferation of commercially-oriented health information websites on the Internet can be confusing or frankly misleading to patients and other seekers.

It is worth noting that a majority of in-office patient requests – 80.2 percent of requests in one study (619 of 772) – are for information, not for physician action. Other studies have found that education-based self-management programs, whether in-person or internet-based can improve health status and possibly health-care utilization. Web-based tools like *UW ORTHOSOURCE* offer the potential to unite the skills and abilities of faculty content creators and internet technology experts to provide a service for patients that, working alone, neither group would be able to offer. The system enables faculty to share their knowledge broadly in a way that is scalable. The system enables the webmaster to manage queries to a high level of visitor satisfaction in a way that creates an interactive environment for patients, with a minimum of administrative time, and without engaging in activities that could be construed as being the unauthorized practice of medicine. Tools like *UW ORTHOSOURCE* appear to offer opportunities to meet the demand for information and education in a scalable manner, in order to utilize in-office visits in a way that is more productive and satisfying for patients and more effective for orthopaedic surgeons.

Acknowledgements

The authors gratefully acknowledge the University of Washington for its University Initiatives Fund Interdisciplinary Projects Grant (The Program for Educational Transformation Through Technology), which supported the work presented in this report.

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Severe Infection and Toxic-shock-like Syndrome Caused By Group A Streptococcus in Children With Septic Arthritis and Osteomyelitis

Annie C. Links, M.S. and Gregory A. Schmale, M.D.

In the 19th century, the mortality rate for septic arthritis exceeded 50%. Modern medicine and the routine use of antibiotics in fighting infection have led to a drop in this mortality rate to nearly zero. Yet various strains of Group A Beta-hemolytic Streptococcus (GABHS) remain quite virulent, producing life-threatening illnesses despite early and appropriate treatment. During the year 2003, five patients were treated at Children's Hospital and Regional Medical Center (CHRMC) Intensive Care Unit (ICU) with Group A Streptococcal bacteremia associated with bone and joint infections. These infections typically led to prolonged ICU stays, intubation, hypotension requiring pressors, and coagulopathy, with multiple operating room trips and long-term antibiotic treatment. Unlike previous reports from this institution, these infections were not preceded by recent varicella infections.

Group A Streptococcus accounts for 10% of all cases of pediatric osteomyelitis and septic arthritis and is the second most common infectious agent after Staphylococcus aureus, which causes 80-90% of pediatric bone infections and most joint infections. Yet, during the same time period, no child required ICU treatment for systemic shock from Staphylococcus aureus bone or joint infection at Children's Hospital.

Streptococcal Toxic Shock Syndrome (STSS) is a severe illness associated with Group A Streptococcal infection. The clinical manifestations in children include hypotension and multi-organ involvement, with two or more of the following: renal impairment, coagulopathy, abnormal liver function tests, acute respiratory distress syndrome, generalized erythematous macular rash, or soft tissue necrosis.

Cases

A retrospective review of patients admitted and treated for septic arthritis and osteomyelitis revealed five during the calendar year 2003 with significant hypotension, ICU admission, respiratory distress and Group A Streptococcal bacteremia. Patients were typically treated with antibiotics until their serum inflammatory markers normalized.

Case 1: A previously healthy 14 1/2 year-old girl presented with one week of fever, right ankle and thigh pain. Blood cultures grew GABHS.

On hospital day (HD) 2, mental status changes and respiratory distress required ICU transfer. She underwent urgent excisional debridement of a right lateral thigh abscess; right ankle, left elbow and wrist aspirations, and bilateral hip and left shoulder aspirations. Two days later she underwent repeat debridements of infected sites.

She was hospitalized for 25 days and treated with antibiotics for 44 days.

Case 2: A previously healthy 3 year-old boy with fever and three days' refusal to walk needed ICU admission after initially presenting to an outside hospital with seizures and hypotension requiring pressors. Blood cultures grew GABHS; GABHS also grew from a bedside knee-joint aspirate. On HD 2, the knee was formally irrigated and debrided in the operating room.

He received 7 days of ICU care and 47 days of antibiotics and was back to baseline 50 days after admission.

Case 3: A previously healthy 14 year-old boy presented at an outside hospital with two days of right-sided joint pain. His right wrist, elbow and ankle were swollen. He developed hypotension, fever, macular rash, pulmonary edema and acute renal failure. Blood cultures grew GABHS.

Over the next two weeks, he was taken to the operating room on four separate occasion for the following: aspirations of the right knee and tibia; right ankle, elbow and dorsal hand irrigation and debridements; right hip and wrist irrigation and debridements; repeat wrist and dorsal hand wash-outs; right volar wrist, flexor tendon sheath, and palmar bursal drainage, and right carpal tunnel release.

He was hospitalized for 23 days and treated with antibiotics for a total of 70 days. Three weeks after discharge, radiographs demonstrated right carpal joint obliteration. Right hand weakness

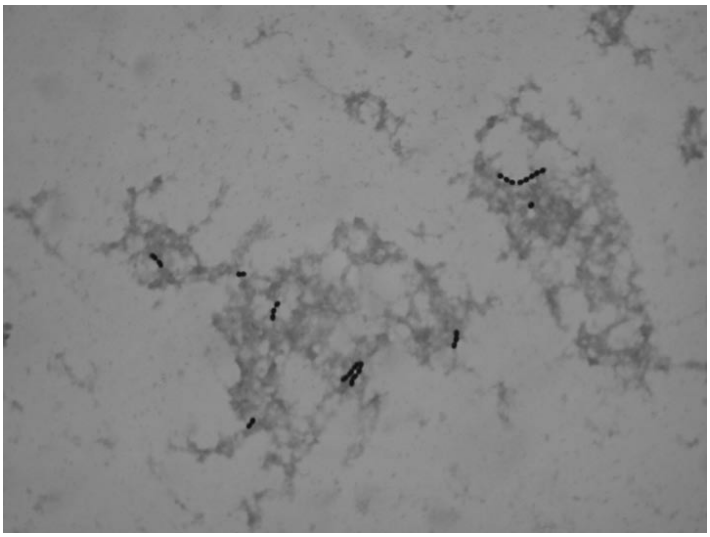

Figure 1: GABHS, gram stain from aspirate, courtesy of Dr. Ajit Limaye.

Patient	Hypotension	Respiratory distress	ARDS	High LFTs	Abnormal renal function	Coagulopathy, thrombocytopenia, or anemia	Extremity Involvement
1	X	X		X		X	Osteomyelitis, first metatarsal; septic ankle, shoulder, wrist, hip, elbow
2	X					X	Osteomyelitis, distal femur; septic knee
3	X	X		X		X	Septic elbow, wrist, knee, ankle, hip
4	X	X	X	X	X	X	Osteomyelitis, distal femur; septic knee
5	X	X		X	X	X	Osteomyelitis, proximal tibia; septic hip

Table 1: Multi-system involvement spectrum in five pediatric patients with severe Streptococcal infection.

with decreased wrist motion persisted at 5-months follow-up.

Case 4: A previously healthy 14 year-old boy presented to an outside facility with right thigh pain of 2 weeks duration. He was febrile, hypotensive, in respiratory distress and required pressors, intubation and transfer to Children's. Blood cultures grew GABHS. He developed acute respiratory distress syndrome and a right superficial femoral deep venous thrombosis.

Over the next week he was taken to the operating room on two separate occasions for right knee irrigation and debridement with biopsy of the distal femur and irrigation of the subtalar, talonavicular, and first MTP joints.

He was hospitalized for 25 days and treated with antibiotics for 67 days.

Case 5: A previously healthy eight year-old girl presented to an outside hospital with right leg pain of eight days duration. Profound hypotension necessitated transfer to CHRMC where she required intubation, pressors, blood product transfusions and prolonged ICU care. Blood cultures grew GABHS.

She was taken to the operating room on multiple occasions for repeat irrigations and debridements of the left hip and right proximal tibia. Nine days after her first hip arthrotomy, her hip was noted to be dislocated, and she underwent a repeat washout of the hip with a closed reduction and spica casting.

She was initially hospitalized for 54 days; two-weeks after discharge she was readmitted for repeat right tibia irrigation and debridement. Overall, she underwent six operations and 245 days of antibiotics. Follow-up five months later revealed full strength and motion of the lower extremities.

Conclusion

These cases highlight the severity of systemic involvement for five children with Group A Streptococcal bone and joint infections. Most patients were treated elsewhere before requiring intubation for respiratory distress or pressors for hypotension. The typical patient needed multiple trips to the operating room for repeat irrigation and debridement of infected bones, joints, and overlying soft tissues to limit tissue destruction. Early diagnosis and aggressive treatment of bone and joint infections may reduce long-term musculoskeletal sequelae and decrease ICU stays and mortality rates.

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Vehicle Design Factors Affecting Occupant Pelvic and Chest Forces in Near-side Impact ("T-bone") Automobile Crashes

Allan F. Tencer, Ph.D., Robert Kaufman, Christopher Mack, and Charles Mock

In order to reduce injury during a car crash, the mechanism of occupant injury and the crash factors affecting injury potential must be defined. In a two vehicle near-side 90 deg ("T-bone") collision, the door panel is punched into the occupant by the striking vehicle, Figure 1, before the vehicle starts to accelerate sideways. Figure 2 shows the effect on the occupant in a sequence of clips from an NCAP (New Car Assessment Program, US DOT) side impact collision with a moving deformable barrier. The chest and pelvis are the most likely regions of the body to be injured in side impacts, and the predominant injurious contact in pelvic and chest injuries is with the door panel. In US-NCAP testing, chest injury potential is measured from instrumented crash dummies placed in the vehicle, using the TTI (Thoracic Trauma Index) based on accelerations at rib 4 and 8 and vertebra T12 adjacent to the driver's door) and pelvic injury from peak pelvic acceleration. NCAP tests allow study of vehicle design factors that may protect or contribute to occupant chest and pelvic injuries, since all parameters of the test, except the vehicle under study, are held constant. Vehicles must pass this crash test (Federal Motor Vehicle Safety Standard 214) in order to be sold in the US. Studying vehicle design factors in this controlled setting can provide insight into how to further protect against these injuries.

Methods

NCAP (new car assessment program) side impact tests performed by the National Highway Traffic Safety Administration (NHTSA) on vehicles from model years 1999-2003 were studied from data available at www.dms.dot.gov, docket 3835, where complete reports of each test are posted. A total of 164 separate tests were analyzed. In the test, the vehicle is instrumented at the door, door sill and frame, and center of gravity and at least 3 crash dummies are positioned in the vehicle in the driver's, front passenger's, and rear passenger's seats. A moving deformable barrier, weighing about 1363 kg, basically a vehicle chassis with a standard crushable front end, is pulled into the driver's side front door at a 27 deg angle at about 61 Kph (38 mph). The dependent variables selected for study were the TTI, calculated from acceleration at rib 4, rib 8, and T12, and pelvic peak acceleration. The independent variables were, vehicle weight, wheelbase, door length from its forward end to the center of contact with the barrier, and distance of the driver's dummy left hip to the door panel. Variables related to the structure and strength of the door included the maximum amount of driver's door crush or intrusion, the peak acceleration of the door, and the maximum velocity of the door during impact. Further, the effects of a thoracic side airbag on chest accelerations, and a center console on pelvic accelerations were determined. In addition, 19 vehicles were studied at a large local salvage yard. A frame was mounted onto the driver's door and the stiffness of the armrest was determined. Data were analyzed using a standard multiple linear regression with 9 variables.

Field studies were performed as part of CIREN (Crash Injury Research and Engineering Network, National Highway Transportation Safety Administration). This consists of an analysis of actual crashes experienced by consenting patients at Harborview and 9 other trauma centers around the US. The crashes selected all involved side impacts with focus on injuries to the pelvic, thoracic and abdominal regions. Each crash site had scaled documentation of the roadway, traffic controls, road surface type, conditions, and road grade at both pre- and post-impact locations. Exterior inspections of the vehicle yielded angle of impact and speed change, a measure of crash severity. An inspection of the interior of the vehicle from which the injured person had been removed was performed to determine points of occupant contact and restraint system use. With Institutional Review Board approval, the injuries were assessed by examining the patient's medical records and imaging studies.

Results

NCAP data showed that the following variables correlated in descending order of importance with decreasing

Figure 1: Example of the door punch mechanism from NCAP test, left, just prior to impact, center, door contacts shoulder, right, door contact dummy along side, dummy is still in upright position.

Figure 2: Example CIREN (Crash Injury Research and Engineering Network, NHTSA) side impact in which the occupant sustained abdominal and chest injuries. Note the location of the protruding armrest relative to the seat. Arrows indicate the locations at which the occupant contacted the door.

pelvic acceleration of the driver's crash dummy during impact, Table 1: increasing vehicle weight, less door intrusion, lower door velocity difference calculated from, peak door velocity-final door (or vehicle) velocity, lower arm rest stiffness, and lower door peak acceleration. Lower door intrusion, and velocity are characteristics of stronger doors. However, amount of door intrusion did not correlate to either vehicle weight or wheelbase indicating that larger heavier vehicles do not necessarily have stronger doors. Findings were similar for TTI (thoracic trauma index) except that door velocity had more influence, and door intrusion had less. TTI was lowered about 15% with a thoracic airbag, p =0.01. Pelvic acceleration was lowered about 12% if a stiff center console was not present (p = 0.05). The vehicle weight and post impact door intrusion between groups in both airbag and console comparisons were not significantly different.

A total of 38 CIREN cases of near side impacts were selected with occupants receiving either a thoracic, abdominal or pelvic injury. For the thoracic injury subgroup, the mean struck vehicle speed change after impact was 25 mph (after impact the struck vehicle was pushed sideways at 25 mph), the AIS score was 4.2 with the main injury source being the door panel that intruded laterally, an average of 34cm. Injuries included multiple rib fractures with associated hemothorax, or pneumothorax with lung contusions and lacerations. For the abdominal injury subgroup the mean speed change was 23 mph and mean AIS was 3.3 with the main injury source being the armrest where the door panel had intruded laterally an average of 30cm. Injuries included 9 occupants with spleen lacerations or contusions, 3 with liver lacerations or contusions, 3 with kidney contusions, 2 with diaphragm lacerations, and 2 involving retroperitoneum hemorrhage. The pelvic injury subgroup had a mean vehicle speed change of 22 mph, mean AIS of 3 with the door panel that intruded an average of 25cm as the main injury source. Injuries included fractures to the pelvic region with 11 also involving the sacrum.

Discussion

Studying vehicle design with the goal of lowering side impact occupant accelerations and injuries demonstrates that several key factors strongly affect resulting occupant forces. Vehicle weight and the extent of door intrusion are the most significant variables. Door velocity as it is pushed by the striking vehicle into the occupant space, and the stiffness of the armrest are also important. Heavier vehicles will experience lower side accelerations, however heavier, higher center of gravity sport utility vehicles have been prone to a separate injury mechanism in these tests, rollover upon impact which was not considered in this analysis. Door intrusion can be lowered by either making the doors and door structure (the B pillar or center pillar between the doors, and the roof and door sill) stronger or moving the occupant farther inboard from the side of the door. Separate analyses showed that there was no correlation between the amount of door intrusion and either vehicle weight or wheelbase. Therefore larger SUVs do not necessarily have stronger doors. Vehicles with thoracic side airbags and lacking stiff center consoles provide better side impact injury protection. A list of the performance of all 164 tested vehicles is available by contacting the author.

CIREN data indicates that door intrusion in the range of 25-35 cm

PELVIS dependent variable	pelvic r2 = 0.85	CHEST dependent variable	TTI r2=0.80
vehicle weight	0.06	vehicle weight	0.01
maximum door intrusion	0.04	maximum door velocity	0.31
max door -final vehicle velocity	0.22	max door -final vehicle velocity	0.35
arm rest stiffness	0.29	front door edge to impact distance	0.42
door acceleration	0.30	maximum door intrusion	0.59
maximum door velocity	0.53	door acceleration	0.65
vehicle wheelbase	0.57	arm rest stiffness	0.83
dummy left hip to door	0.98	vehicle wheelbase	0.99
front door edge to impact distance	1.00	dummy left hip to door	0.99

Table 1: Results of a multiple linear regression using the variables listed. The probability of the correlation of each variable is listed. (for example p = 0.06 gives a 94% chance that vehicle weight correlates to pelvic acceleration, while p = 0.98 gives only a 2% chance that dummy left hip to door distance correlates to pelvic acceleration).

has the potential for the creation of serious chest and pelvic injuries. This information may provide guidelines for the design of more effective doors. One benefit of the development of the side impact standard was the requirement that after 1997, all vehicles be equipped with a side impact beam in the door to stiffen it. It may be worthwhile to reconsider the design of this door stiffening beam to produce more resistance to impact.

The side impact test as currently performed does have limitations which should be recognized. The formulation of TTI does recognize the effects both of age and weight, however the test is performed using a side impact dummy which represents only the 50th percentile male. Older drivers and those of shorter stature should consider that the measured probability of injury to them is higher than that reported in NCAP crash tests. The use of TTI as a chest injury criterion is also under investigation. Some authors have shown that the stored energy criterion (integral of contact force and chest deflection) and maximum chest deflection (D max) are better predictors than TTI of the number of ribs fractured in impact tests. One separate goal of this research is to compare various injury predictors. The moving deformable barrier which represents the striking vehicle, simulates a smaller (about 3000 lb) sedan. It does not simulate the higher bumper and greater mass of a light truck or SUV which make up half the passenger vehicles in the current US fleet. Higher bumpers tend to override the door beam causing the upper part of the door to tilt inwards, increasing door intrusion into the occupant space.

In summary, vehicles tested in the US DOT new car assessment program crash tests showed a wide range of results in terms of accelerations transmitted to crash dummies in a side impact. Specific factors reducing crash accelerations include a heavier vehicle with stiffer doors, a softer armrest, a thoracic side airbag, and no center console.

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Perioperative Complications after Open Reduction and Internal Fixation of Posterior Pelvic Fractures

Andrew T. Howlett, M.D., Sean E. Nork, M.D., and M.L. Chip Routt, Jr.,M.D.

Unstable pelvic ring disruptions are difficult to manage for various reasons. Pelvic related hemorrhage and associated injuries have been responsible for high mortality rates in these patients. Delayed and poorly aligned healing, especially of the posterior pelvis after trauma, adversely impacts clinical outcomes. Effective treatment of unstable pelvic ring injuries includes accurate restoration of the injured structures, particularly the posterior pelvic anatomy. Numerous techniques attempt to provide excellent reduction and stable fixation of the injured pelvic ring. Recently, manipulative reduction with percutaneously inserted internal fixation has become popular due to improved intraoperative fluoroscopic imaging, diminished operative times and blood losses, and very low infection rates. Unfortunately, all pelvic ring injuries cannot be effectively managed using such percutaneous techniques. Instead these injuries require open reduction and internal fixation (ORIF) of the posterior pelvic disruption using an open dorsal pelvic operative exposure. Open posterior pelvic surgical approaches have been criticized because of reported wound complication rates as high as 25%. Other hazards of open posterior pelvic surgical approaches include excessive bleeding due to intraoperative vascular injury or loss of pelvic tamponade, neurologic injury from attempted reduction maneuvers or from inaccurate implant placement, prolonged operative times, and the need for prone patient positioning. We report our perioperative complications related to ORIF for displaced posterior pelvic ring disruptions with particular attention to wound, vascular, and neurologic complications.

Methods And Results

We reviewed 437 consecutive patients treated operatively for unstable pelvic ring disruptions at Harborview Medical Center from January 1, 1999 through December 31, 2002. Of these, only 23 patients (5.3%) underwent posterior pelvic ORIF using dorsal surgical exposures. One pediatric patient was excluded, leaving twenty-two adult patients for evaluation. Of the twenty-two adults, eight were females and fourteen were males, with an average age of thirty-eight years (range 17 to 57). Injury mechanisms varied, but were all due to high energy traumatic events. The patients reflected a polytraumatized population with a mean Injury Severity Score (ISS) of 22 (range 17 to 37). Nine patients (41 %) presented with associated peripheral neurological injury. None had associated spinal fracture requiring decompression or operative stabilization.

Operative procedures were performed according to the patient's specific injury pattern and overall clinical condition. The indications for posterior pelvic ORIF included eleven patients with displaced sacral alar fractures and associated significant neuroforaminal osseous debris, one patient with sacral dysmorphism which precluded safe percutaneous management, one patient with failed closed management, and one patient with failure of percutaneous fixation alone. In eight other patients, the posterior pelvic fracture pattern and displacement mandated open treatment.

Accurate open reduction and internal fixation of the posterior pelvic ring injuries were accomplished using a variety of surgical techniques dependent on the specific pattern of pelvic ring disruption, all through an open posterior pelvic exposure. Operative blood losses averaged 700 cc (range of 250 cc to 8 liters). Two patients had excessive intraoperative bleeding. One patient with a crescent iliac fracture/SI dislocation had a superior gluteal vein laceration with 1.2 liters operative blood loss. In the second patient, an intraoperative loss of 8 liters was experienced due to her traumatic iliac vein laceration which responded to packing. Three patients had avulsed fifth lumbar nerve roots noted intraoperatively. Immediate postoperative CT scans were reviewed to assess implant safety and fracture reduction. All implants were accurately located. Twenty-one fracture reductions were classified as

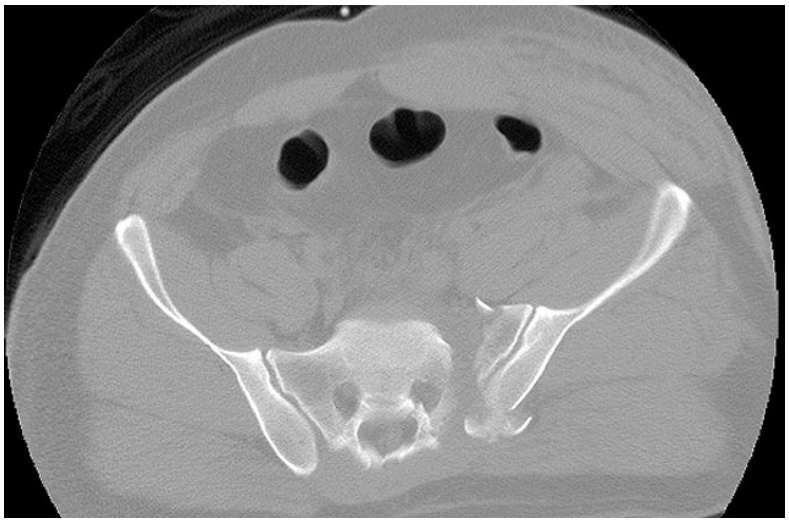

Figure 1: This patient was injured in an automobile accident sustaining displaced pelvic ring injuries, including left sided sacral alar and posterior iliac fractures and a symphysis pubis disruption. The pelvic computed tomography(CT) axial image demonstrates the sacral and iliac fracture displacements.

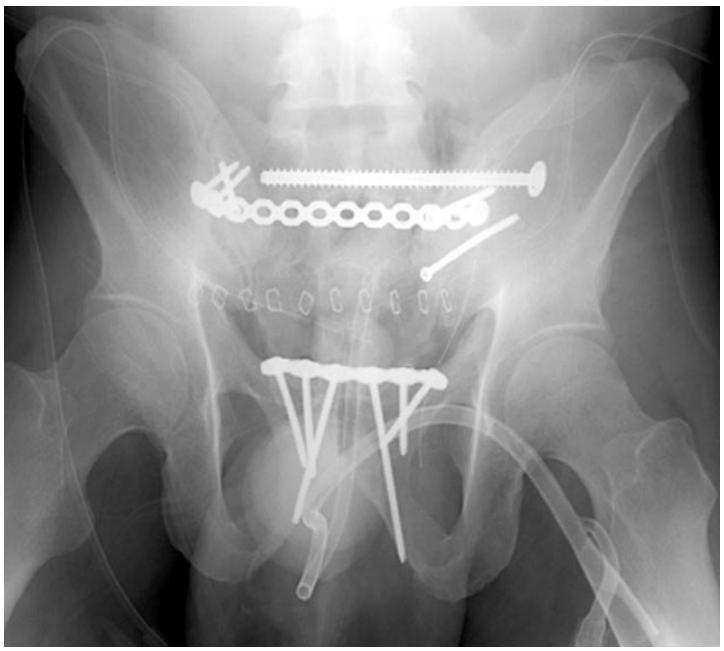

Figure 2: Open reduction and internal fixation (ORIF) through a dorsal pelvic surgical exposure was selected, along with symphyseal ORIF using an anterior approach.

excellent, while the remaining patient had a good reduction.

Follow-up was avaliable for all patients averaging 14 months (range 12-20). There were no deaths. Wound complications occurred in three patients, including one deep wound infection, one wound hematoma, and one wound required twelve days of suction drainage after surgery. The deep wound infection occurred in a mentally impaired patient who digitally probed her dorsal pelvic wound on several occasions while on the ward. Three patients developed deep venous thromboses, all were superficial femoral vein locations with one being bilateral. One patient developed a sacral nonunion. He was the only patient who had a wide osseus resection prior to nerve root decompression. In all others, the nerve root decompressions were performed using the fracture interval. For the remaining twenty-one patients, radiographic union with complete fracture consolidation without loss of fixation was achieved by four months.

These twenty-one patients were also full-weight bearing five months after injury (average 4.3 months). Overall, final radiographic studies at the time of last clinic visit included twenty-one excellent reductions and one poor reduction. Two patients required removal of prominent hardware with resolution of symptoms in both patients.

A total of 13 complications in eight patients were identified. Four patients had numerous complications, including two patients with two complications and two patients with three complications each.

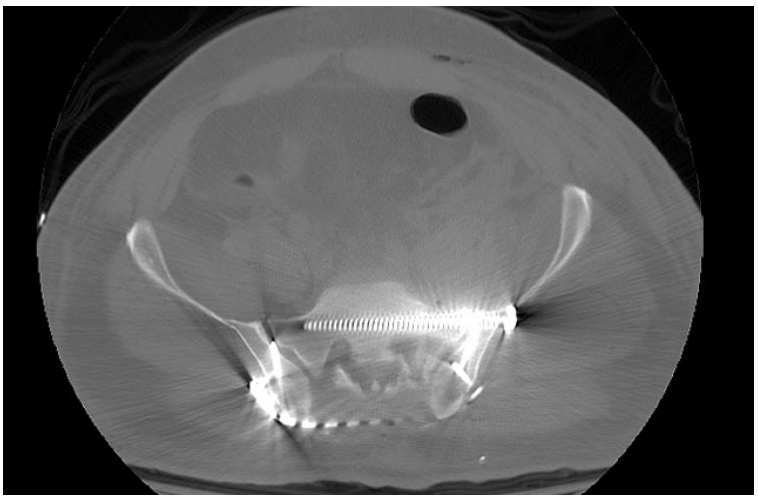

Figure 3: The pelvic CT scan after surgery demonstrates the reduction quality and implant safety.

Discussion

This study demonstrates that an open posterior surgical exposure of pelvis for the treatment of unstable pelvic ring injuries need not be considered a high-risk procedure, especially regarding wound complications. Our deep wound infection rate (4.5%) is quite low when compared to prior studies (17-25%). Open posterior pelvic surgery using a dorsal surgical exposure was indicated rarely in our overall group of patients with unstable pelvic injuries. We used the presence of significant neuroforaminal osseous debris, sacral dysmorphism, and certain posterior pelvic fracture patterns, which preclude percutaneous management, as indications for an open posterior approach.

Surprisingly, eight of nine patients (89%) in this series had at least some improvement of peripheral neurologic function and four patients (44.4%) had complete resolution of their neurologic deficits after surgical decompression, fracture reduction and stabilization. No patient had evidence of iatrogenic nerve injury resulting from surgical technique or implant placement, and no patient had worsening of his or her preoperative neurologic status. A few factors may help explain the significant rate of neurologic improvement in the patients presented in this study. If preoperative imaging demonstrates osseus debris within the neural tunnels, then open nerve root decompression should be performed in conjunction with fracture reduction and stabilization. Early stabilization may also play a role in improving neurologic function. Accurate reduction of the fracture and rigid stabilization may protect injured nerve roots. Obviously, avulsed nerve roots will not demonstrate improvement regardless of operative

Patient	Fracture	Preoperative Gibbons	Preoperative Motor Loss	Preoperative Dysathesias	Bowel/ Bladder Loss	Postoperative Gibbons	Neurological Recovery
1	C1.1	4	S1 (0/5)	S1-S3	Yes	2	S1 Motor (5/5), S1 Sensory
2	C3.3	3	L5 (0/5)	L5	No	0	Resolved
3	C1.1	3	L4/L5/S1 (0/5)	L4-S1	No	3	L4/S1 Motor (4/5), L4/S1 Sensory
4	C1.1	3	L5/S1 (0/5)	L5/S1	No	3	S1 Motor (5/5) S1 Sensory
5	C1.1	3	S1 (0/5)	S1	No	2	S1 Motor (5/5)
6	C1.1	3	L5/S1 (0/5)	None	No	0	Resolved
7	C1.1	3	L5/S1 (0/5)	L5/S1	No	3	S1 Motor (5/5), S1 Sensory
8	C1.1	3	S1 (0/5)	S1	No	0	Resolved
9	C1.1	4	S1 (0/5)	S1-S3	Yes	0	Resolved

Table 1: Summary of Preoperative and Postoperative Neurological Status and Associated Fracture Pattern.

intervention, but adjacent levels may be improved and was demonstrated in two patients in this series. Excessive intraoperative bleeding complicated the operative course of two patients in this series. Despite prophylactic treatment for DVT, three patients developed detectable thrombi without associated pulmonary embolism. This emphasizes the importance of continued clinical surveillance despite the presence of prophylactic treatment. Fixation failure occurred in two patients. One was minor, and the other graded as a "good" rather than "excellent" reduction at final follow-up.

Summary

Open posterior pelvic surgical exposure for unstable pelvic ring injuries is an effective, yet infrequently needed, method for accurate fracture reduction and stabilization, and associated nerve root decompression. Wound infections occur infrequently, especially in compliant patients. Operative blood loss is related to associated local vascular injury, rather than fracture bleeding. Other than complete avulsions, nerve root injuries recover after surgical decompression, accurate fracture reduction and stabilization. Fixation failure is related to poor compliance with rehabilitation. Indications for open posterior pelvic reduction and fixation include osseus debris within the sacral nerve root tunnel, inability to obtain satisfactory manipulative reduction, and the inability to use percutaneously inserted posterior pelvic fixation screws.

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	Number of Patients	Percentage
Total Patients	22	-
Total Wound Complications	3	13.6 %
Wound Infection	1	4.5 %
Wound Hematoma	1	4.5 %
Prolonged Drain Output	1	4.5%
Loss of Fixation	2	9 %
Nonunion	1	4.5 %
Deep Venous Thrombosis	3	13.6%
Excessive Intraoperative Bleeding	2	9%
External Fixator Pin Site Infection	1	4.5%

Table 2: Summary of complications.

Treatment of Isolated Perilunate and Lunate Dislocations With Combined Dorsal and Volar Approach and Intraosseous Cerclage Wire

James Verheyden, M.D. and Thomas E. Trumble, M.D.

This study was performed to determine the clinical outcome of patients with perilunate and lunate dislocations treated with a combined dorsal and volar approach and intraosseous cerclage wire. Twenty-two patients were for a dorsal perilunate or lunate dislocations acutely with repair of both the scapholunate interosseous ligament (SLIL) and lunate-triquetrum interosseous ligament (LTIL) to reconstruct the injured ligaments and restore carpal kinematics.

Introduction

Isolated perilunate dislocations are relatively rare injuries and are among the most challenging carpal injuries to treat. Perilunate dislocations are less common than perilunate fracture-dislocations in a ratio of one to two. It has become accepted that anatomic reduction of the normal intercarpal relationships is the key to successfully restoring normal wrist biomechanics and preventing chronic instability and/or scapholunate advanced collapse (SLAC). It has also become accepted, that closed treatment of these injuries does not reliably restore these complex intercarpal relationships. Acute perilunate dislocations are usually relatively easy to reduce. However, maintenance of this reduction and maintenance of normal intercarpal relationships is often difficult. Because of difficulties with residual carpal instability and progressive arthritis with resultant pain and loss of motion after closed treatment, most surgeons favor open reduction for these injuries. Open reduction allows good visualization of the injury and facilitates anatomic reduction and repair. Unfortunately, the optimal surgical approach has not been identified and most series have contained patients with both perilunate and perilunate-fracture dislocations.

When treating perilunate and lunate dislocations, we believe that the key to a successful long-term result is a strong repair of the scapho-lunate interosseous ligament (SLIL). We have found that internal fixation with Kirshner (K) wires does not help to compress the scaphoid and lunate together, to protect the SLIL repair, during the critical period of ligamentous healing. We believe that an intraosseous cerclage wire, however, can effectively and reliably reduce and restore normal scapholunate alignment and decrease tension on the SLIL repair during the critical period of ligamentous healing.

This report details the subjective and objective outcomes of one surgeon's results after reconstruction of twenty-two isolated perilunate injuries using a combined dorsal and volar approach with an intraosseous wiring technique.

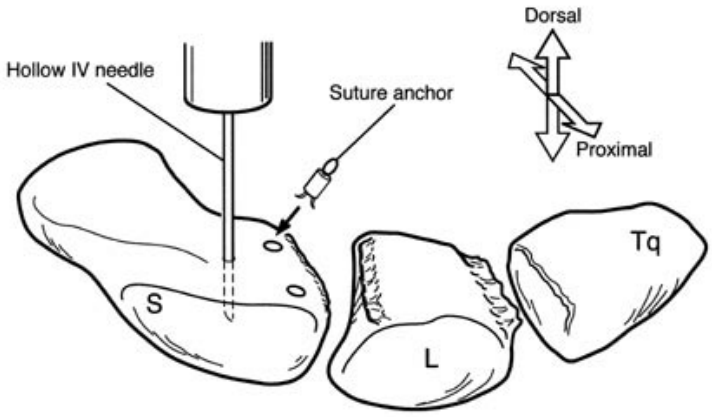

Figure 1: Placement of 18 guage intravenous catheter in proximal pole of scaphoid and placement of suture anchors for later repair of scapholunate ligament disruption.

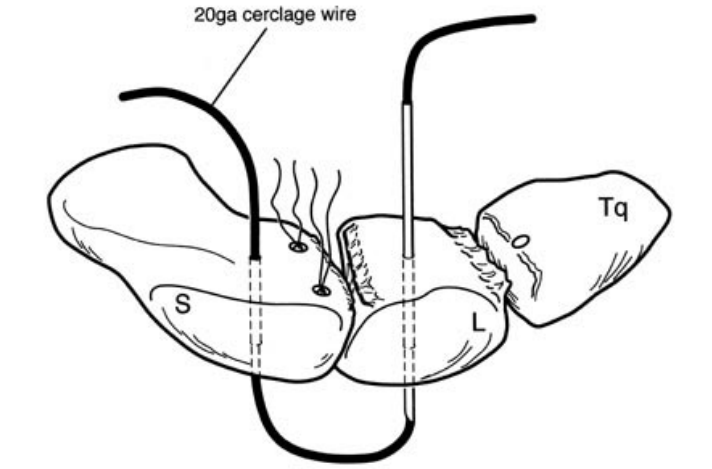

Figure 2: A 20 guage wire is passed from dorsal to volar through the proximal pole of the scaphoid and from volar to dorsal through the lunate.

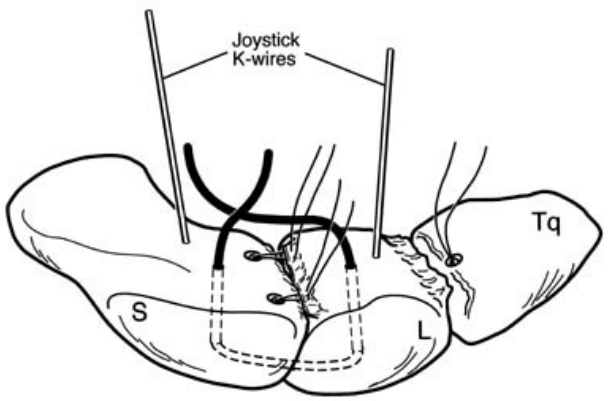

Figure 3: Kirschner wires are used as joysticks to anatomically reduce the scaphoid and lunate. Sutures from the bone anchors are passed through the scapholunate ligament, but are not tied.

Methods

A combined dorsal and volar approach with an intraosseous wiring technique was used to treat twenty-two isolated perilunate and lunate dislocations.

Operative Technique

A standard dorsal longitudinal approach was used. The extensor retinaculum was identified, the third dorsal compartment was released, and the extensor pollicus longus (EPL) tendon was retracted radially. The fourth dorsal compartment was sharply elevated off the capsule and a longitudinal capsulotomy was made to expose the scapholunate and lunotriquetral ligaments. A separate eight cm palmar approach using an extended carpal tunnel incision that crossed the wrist crease was then made. The transverse carpal ligament was released and the carpus internally stabilized with an intraosseous wire technique that Almquist and associates initially used for chronic complete scapholunate separation. Mini mitek (Ethicon, Piscataway, NJ) or Micromite (Linvatech 1.8 mm, Largo, FL) bone anchors were placed for later scapholunate interosseous ligament (SLIL) repair. The suture anchors were routinely placed in the scaphoid, as this is where the scapholunate ligament usually avulses from. However, in a few instances, the scapholunate ligament avulsed from the lunate and the suture anchors were placed in the lunate. The hollow metal cannula of an 18 gauge intravenous catheter was then placed on a power wire driver. The trick is to remove the plastic hub without crushing the hollow metal cannula. This was best accomplished using a needle driver and gently twisting off the plastic hub. The hollow needle was then drilled from dorsal to volar through the proximal pole of the scaphoid as if the scaphoid was reduced (Figure 1). A 20 gauge wire was then passed through the needle from dorsal to volar (Figure 2). The cannula was then removed, and drilled through the lunate from dorsal to volar, again as if the lunate were

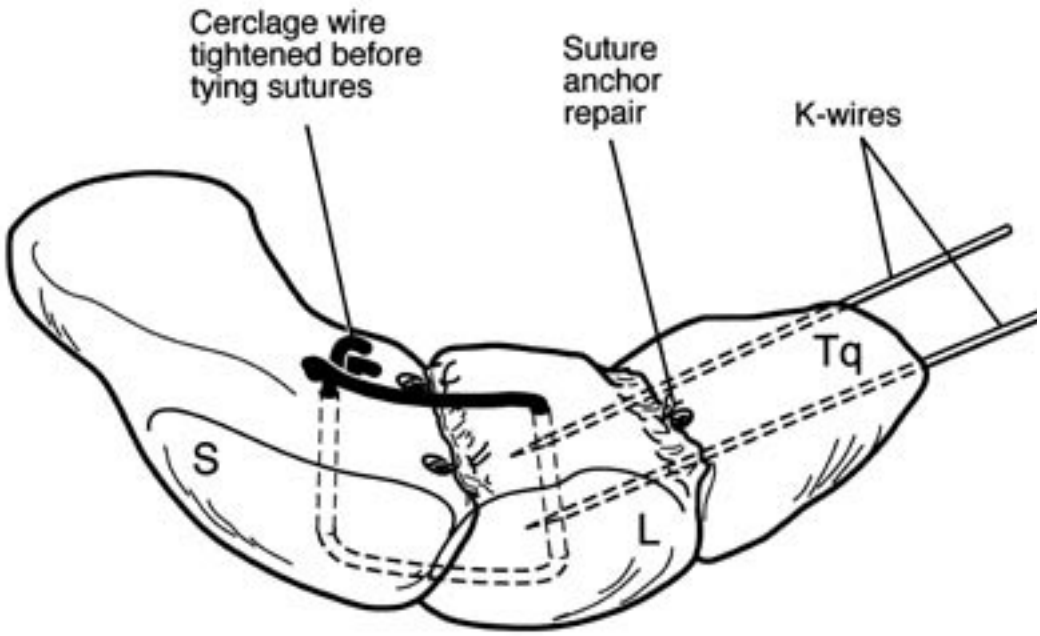

Figure 4: With the scaphoid and lunate anatomically reduced, the cerclage wire is tightened. Next, the sutures from the bone anchors are tightened. In a similar fashion, the triguetrum is reduced to the lunate and held in place with Kirshner wires prior to tying the bone anchor sutures.

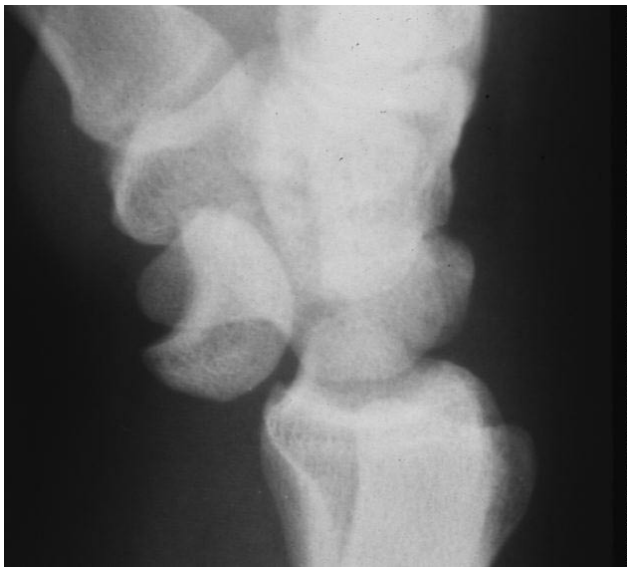

Figure 5: Preoperative lateral radiograph of volar lunate dislocation.

reduced. Note, to avoid retracting the flexor tendons, it is easier to pass the scaphoid wire first. The wire was then passed from volar to dorsal, through the hollow cannula, completing the circle. The bone anchor sutures were then passed through the torn SLIL. Dorsal Kirshner-wires were next placed in the scaphoid and lunate as joysticks. With the scaphoid reduced to the lunate, as confirmed by PA and lateral fluoroscopy, the cerclage wire was tightened. The bone anchor sutures were then tied to repair the ligament without tension (Figure 3). Bone anchors were then placed to repair the lunate-triquetral interosseous ligament (LTIL) if there was sufficient ligament dorsally for repair. Two 0.045 in Kirshner-wires were then passed across the triquetrum and into the lunate, under fluoroscopy, with the bones reduced. The LTIL bone anchor sutures were then tied, completing the repair (Figure 4). Tears in the volar capsular ligaments at the space of Poirier were repaired with interrupted sutures. Kirshner-wires were cut to retract under skin.

At the completion of surgery, patients were placed in a sugar tong splint. Patients returned for suture removal and splint change at ten to fourteen days and a short arm cast was applied. Range of motion exercises were initiated at six to eight weeks in a removable wrist splint. Kirshner-wires for LTIL repair were removed at eight weeks under local anesthesia. As wrist motion was regained, the cerclage wire often broke, as expected, and as noted

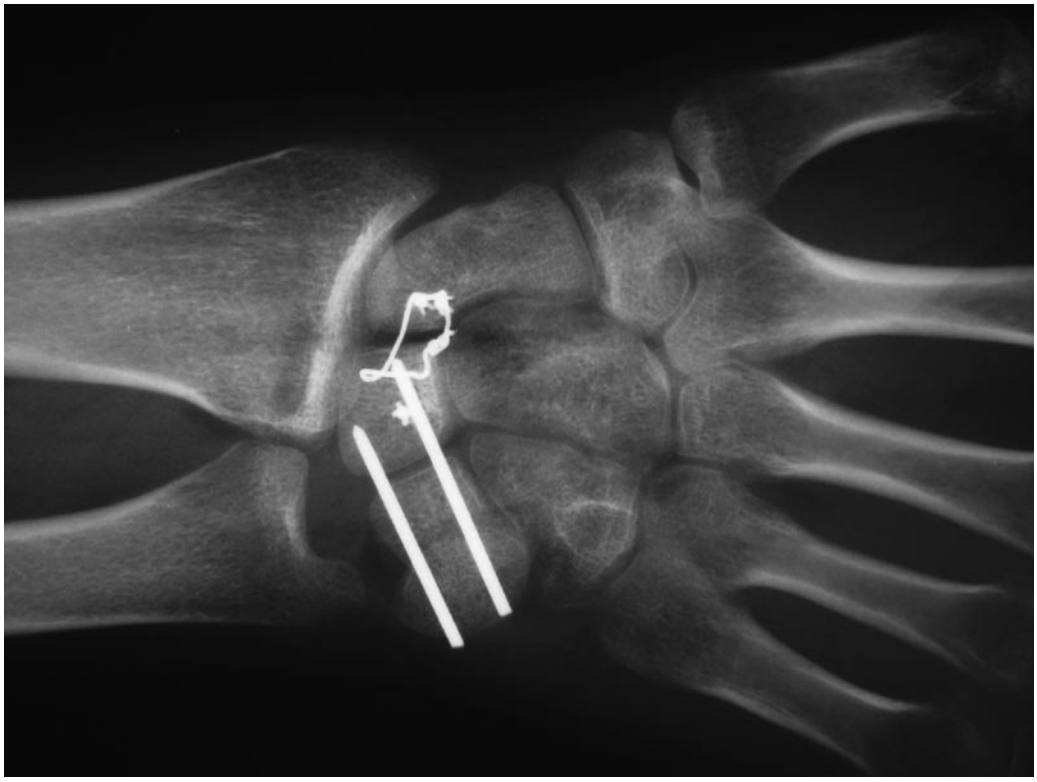

Figure 6: Postoperative PA and lateral radiographs of a volar lunate dislocation treated with a combined dorsal and volar approach using a 20 guage intraosseous cerclage wire.

by Almquist and associates.

The mean interval between injury and surgery was three days. Outcome was assessed after an average of forty-nine months. Subjectively, patients were assessed with a DASH questionnaire, and patients were asked to rate their overall satisfaction, pain relief, problems with activities of daily living, and return to work and previous activity status. Objectively, results were assessed by range of motion and grip strength measurements and initial postoperative radiographs were compared with final radiographs with regards to scapholunate angle and gap.

Results

Patient satisfaction was high in fifteen of twenty-two patients. Seven patients stated they had problems with activities of daily living (ADL's) after their injury. Only ten patients returned to the same job they had before their injury. However, all twenty-two patients were able to return to some type of work. Sixteen of the patients stated they were able to return to their previous level of activity. The wrist flexion-extension arc and grip strength averaged 80% and 77%, respectively, compared to the opposite side. Follow-up radiographs demonstrated no significant change in scapholunate angle or gap with time. As expected, the scapholunate cerclage wire frequently broke. The cerclage wire was removed in sixteen patients, twelve for broken hardware and four for pain.

Conclusions

Although isolated perilunate dislocations are among the most challenging wrist injuries to treat, our results show that a combined dorsal and volar approach with an intraosseous wiring technique can effectively restore normal intercarpal relationships, providing acceptable pain relief, functional motion and grip strength.

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Effect of Peri-Operative Epidural Anesthesia on Phantom Limb Pain and Residual Limb Pain

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Most persons who undergo limb amputation will experience some phantom limb pain (PLP); (Jensen 1985). For example, in a recent study of 255 community dwelling amputees, 72% of lower limb amputees experience PLP. PLP is usually episodic and not particularly disabling. Fortunately for most individuals the phantom pain episodes are not severe. However for a notable subset (14%), phantom pain is a significantly limiting problem (Ehde 2000).

A variety of mechanisms, both central and peripheral, have been proposed to explain the development of PLP. Persistent peripheral nerve discharges have been recorded after amputation, and others have postulated that hyperirritable foci develop in the dorsal horn of the spinal cord after peripheral nerve transection. The massive afferent barrage at the time of injury or amputation may create central changes that generate later pain or alternatively, the sudden loss of peripheral input may trigger central changes that result in deafferentation pain. Pre-emptive epidural anesthesia has been proposed as a possible mechanism to decrease long-term phantom pain.

Figure 1: Amputee golfing.

Bach (1988), Jahangiri et al (1994), Nikolajsen (1998), and Lambert (2001) have examined the prevention of PLP by perioperative epidural anesthesia. Initially, Bach and colleagues (1988), using bupivacaine and morphine for 3 days preoperatively reported a significant reduction in the intensity of PLP. Subsequently, Jahangiri and colleagues (1994) used an epidurally administered mixture of bupivacaine, clonidine, and diamorphine, intraoperatively and for 3 days post-operatively similarly demonstrated a reduction in PLP intensity at 1 year post-surgery. In contrast Nikolajsen and colleagues, using epidural bupivacaine and morphine administered 18 hours before surgery and continued for 3 to 7 days post-operatively, found no effect on the incidence of phantom limb pain at 3, 6, 9,or 12 months post surgery compared to a control group with sham epidural anesthesia and oral or intramuscular morphine. More recently, Lambert and colleagues (2001) compared epidural anesthesia with bupivacaine and diamorphine starting 24 hours before surgery and continuing for 3 days post-operatively, versus perineural anesthesia; there was no difference in PLP between the two treatment conditions at 1 year and the incidence was comparable to previous epidemiologic studies.

Objectives

(1) Can epidural anesthesia be found to reduce the incidence and/or severity of phantom limb pain or residual limb pain after lower limb amputation?

(2) Does epidural anesthesia improve pain control during hospitalization compared to patient controlled anesthesia (PCA)?

(3) Does epidural anesthesia influence hospital length of stay compared to PCA?

(4) Does perioperative epidural anesthesia affect the long-term functional status or psychosocial well being of the amputee?

Subjects

Study participants were solicited from consecutive admissions to a Level 1 regional Trauma Center, for lower limb amputation. Inclusion criteria included: (1) sufficient cognitive skills to understand the informed consent form and complete self-report questionnaires; (2) at least 18 years of age; (3) English speaking; (4) permanent home address for follow-up purposes; (5) patients who are scheduled for amputation. Exclusion criteria were: (1) significant lower limb phantom pain on the same or opposite side subsequent to a previous amputation; or (2) a medical condition in which a spinal epidural anesthetic would be contraindicated.

Study Design

A placebo controlled, two-group, randomized clinical trial was initially planned. All subjects were to be randomized into one of two groups: (1) perioperative spinal epidural anesthesia (treatment group) and (2) "sham" perioperative spinal epidural (control group). However, after several months, it became apparent that the number of subjects that were unwilling to be randomly assigned to one treatment or the other, or were otherwise not eligible to participate in the study presented accrual problems. Thus, we not only randomized all consenting eligible subjects, but also enrolled separately into a "non-randomized arm" those who met inclusion criteria but could not or were not willing to be randomized; these are referred to as "no epidural" or "non-randomized epidural" conditions. Average phantom limb pain intensity constituted the primary outcome variable and was measured daily postoperatively during hospitalization, and then at 1-, 6-, 12-, and 24-month postamputation

points. With the exception of the anesthesiologist, all study personnel and the participants in the randomized arm were blind to group assignment. The study protocol was approved by the University of Washington Human Subjects Committee.

Results

Subjects

There were 86 subjects initially enrolled in the study. Twenty-two were recruited into the randomized study (11 in the treatment arm and 11 in the control arm), 30 had non-randomized epidural anesthesia, and 34 were in the no epidural group. All subjects received patient controlled anesthesia (PCA). The average age of patients enrolled was 44 years. There were no significant differences in age between groups. The most common cause for amputation in our subject population was trauma (72%). Diabetes was next most common (14%), followed by infection (6%), vascular disease (4%) and other causes (gangrene, congenital anomalies- 4%). Causes were similar between subgroups, with trauma the most frequent cause in each group. The level of amputation in the study population was most commonly transtibial (69%), transfemoral (19%), midfoot (6%), through knee (5%) and other (2%).

Outcomes

Epidural bupivacaine had no influence on the incidence or intensity of PLP at 2 years in either the randomized or non-randomized groups, relative to standard care. Moreover, there were no significant differences in in-hospital pain measures between groups and no differences at 1, 6, 12, or 24 months in residual limb pain, depression, function, or satisfaction with life scores. It is concluded that epidural anesthesia given pre-operatively and 3 days post-operatively adds little to PCA and other standard analgesic treatments in the prevention of PLP. One interesting difference between our study and the studies that did report a significant effect for pre-operative analgesia is that patients in all treatment conditions in the current study received aggressive post-operative analgesia that included PCA. It is possible that the administration of immediate and aggressive analgesia during the post-operative period provided enough preventative care to overshadow any effects of the pre-operative epidural anesthesia. The overall low average pain scores at 2 years post-amputation with average PLP of 2 out of 10 in our entire study group is consistent with this conclusion. In contrast, previous cross-sectional studies of lower limb amputees have reported average pain intensity ratings of around 5 on the 0-10 scale.

With regard to in-hospital measures, participants in the treatment group tended toward less use of opiod analgesics, but this difference was not statistically significant, and patients who received epidural analgesia did not show better pain control during hospitalization than those with PCA alone. Finally, participants in the treatment group did not demonstrate a shorter length of hospitalization than the control group. While there was a significantly shorter length of stay in the non-randomized epidural group, compared to the no epidural group, our data suggests that the latter group was a sicker group (more emergent surgeries and more medical contraindications to epidural), which likely confounds the LOS data. No long-term impact on functional status or psychosocial well being of the amputee was found with perioperative epidural anesthesia.

Acknowledgements

This research was supported by a grant "Management of Chronic Pain in Rehabilitation" PO1 HD/NS33988, from the National Institutes of Health, National Institute of Child Health and Human Development (National Center for Medical Rehabilitation Research) and the National Institute of Neurological Disorders and Stroke.

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Mark A. Harrast, M.D.
Assistant Professor, Rehabilitation Medicine

John E. Olerud, M.D.
Professor, Division of Dermatology

Nathan J. Smith, M.D.
Professor Emeritus, Pediatrics

Michael D. Strong, Ph.D.
Research Professor, Surgery

Nicholas B. Vedder, M.D.
Professor, Plastic Surgery

Clinical Faculty

Sarah E. Jackins, R.P.T.
Assistant Professor, Rehabilitation Medicine

University of Washington

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University of Washington School of Medicine

Department of Orthopaedics and Sports Medicine

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4800 Sand Point Way NE
Seattle, WA 98105
(206) 987-1776

Harborview Medical Center
325 Ninth Avenue
Seattle, WA 98104
(206) 731-3466

University of Washington
Medical Center
Bone and Joint Center
4245 Roosevelt Way NE
Seattle, WA 98105
(206) 598-4288

VA Puget Sound Health Care System
1660 South Columbian Way
Seattle, WA 98108
(206) 764-2215

Graduating Residents
Class of 2004

Jon Braman, M.D.: Jon has accepted a 1 year fellowship with Evan Flatow at Mt. Sinai Hsopital in New York City. He plans a career focused on Shoulder and Elbow Surgery.

Mike McAdam, M.D.: After graduation Mike plans to complete a Sports Medicine Fellowship with Warren King in Palo Alto, CA, and then hopefully return to Seattle with his wife and child to begin practicing.

Jason Thompson, M.D.: Jason was selected for the highly competitive position of Spine Fellow in our Advanced Clinical Experience program at the University of Washington Department of Orthopaedics.

Alexis Falicov, M.D., Ph.D.: Alexis will be doing a 1 year fellowship in Spine at the Vancouver General Hospital in Vancouver, BC. He plans on getting an academic position in spine.

Thea Khan-Farooqi, M.D.: Thea plans to begin a career in general orthopaedics after moving to Charlotte, North Carolina.

Incoming Residents

Drew Fehsenfeld: Drew received his doctorate degree in Philosophy in Biomedical Sciences from Creighton University in 1999 and received his medical degree from the University of Texas medical School at San Antonio. Drew began a commitment to Habitat for Humanity that has lasted for over eight years. He is also a CPR instructor and organized TCU's first mass CPR Training day. He feels that orthopaedics is a field that will continue to challenge and fulfill him.

John Howlett: John received his MD degree from the University of California San Francisco, School of Medicine. John believes that the study of literature and medicine has provided the insight into the human condition and is looking forward to the varied clinical and academic possibilities a career in orthopaedics can offer. Personal interests include backpacking, trail running and reading.

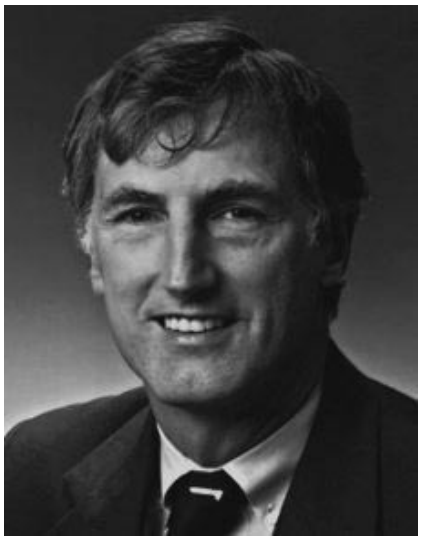
Michael Lee: Mike attended the Pomona College in Claremont, California where he received a BA degree in Neuroscience. He received his medical degree from the University of Washington. An elective rotation abroad in Ghana, West Africa impacted Mike's life. It greatly strengthened his personal and professional connection to orthopaedic surgery. Mike enjoys spending time reading, hiking and has completed two marathons.

Mark Freeborn: Mark attended the University of Washington where he received his Bachelor of Science degree in Psychology. He received his MD from the University of Michigan Medical School in Ann Arbor, MI. Mark's desire to practice medicine is traced to growing up in a household with foster children who were physically challenged. In his free time, Mark enjoys athletics.

Christopher Howe: Chris obtained his BS degree in Biology from the University of North Dakota. He earned his MD degree from the University of North Dakota School of Medicine. When growing up, Chris enjoyed spending time on his Grandfather's farm which set a pattern for decision making and problem solving. He and his wife Jen enjoy spending time in the outdoors and maintaining a healthy lifestyle.

Gregg Nicandri: Gregg obtained his BS degree in Biology from Pennsylvania State University. He received his MD degree from the Medical College of Virginia of Virginia Commonwealth University. Gregg enjoys writing, research and mentoring others. He believes the camaraderie and the challenge of team sports has been a benefit to his career in medicine.

2004 Department of Orthopaedics New Faculty



Theodore Wagner, M.D.

Dr. Theodore Wagner was born in Philadelphia, Pennsylvania. Dr. Wagner received his undergraduate degree from Trinity College in Hartford, Connecticut. He then returned to Philadelphia where he got his medical degree from Temple Medical School. He went on to an internship at Royal Victoria Hospital in Montreal, Canada. His residency was at the University of Washington here in Seattle. He then worked in our department before moving on to private practice at Orthopedic Physicians here in Seattle. In addition, he has been Director of the Spine Institute at Seattle's Swedish Hospital Medical Center. Dr. Wagner will serve as the Associate Chief of Spine Surgery at the University of Washington Medical Center.

Christopher Wahl, M.D.

Dr. Wahl was born in Anchorage, Alaska. He went to the University of Colorado, getting his degree in Architecture. He received his medical degree at Yale University School of Medicine. He completed his residency in orthopaedic surgery at Yale-New Haven Hospital in Connecticut. He was a fellow on the Sports Medicine and Shoulder Service at the Hospital for Special Surgery in New York. Afterwards, he was a A.O. John Border European Traveling Trauma Fellow under Professor Axel Ruter at the Clinic for Trauma and Restoration Surgery in Augsburg, Germany. He returned to Yale as an attending surgeon in 2002. Dr. Wahl will join the sports medicine team and specialize in shoulder and knee arthroplasty.

Research Grants
Department of Orthopaedics and Sports Medicine

National Institutes of Health (NIH)

Collagens of Cartilage and the Intervertebral Disc
David R. Eyre, Ph.D.

Pathology of Inborn Skeletal Diseases
David R. Eyre, Ph.D.

Skeletal Dysplasias
David R. Eyre, Ph.D.

Augmentation of Peak Bone Mass
Ted S. Gross, Ph.D.

Disuse Induced Osteocyte Hypoxia
Ted S. Gross, Ph.D.

Safety of Lumbar Fusion Surgery for Chronic Back Pain
Sohail K. Mirza, M.D.

Imaging of Molecules by Oscillator-Coupled Resonance
John A. Sidles, Ph.D.

*Chondrogenesis and Histone Modification Enzymes
Liu Yang, Ph.D.

TLS and TLS Fusion Proteins in Leukemia
Liu Yang, Ph.D.

Veterans Affairs Rehabilitation Research and Development Service

Ewing's Sarcoma Fusion Proteins and mRNA Splicing Factors
Howard A. Chansky, M.D.

The Effect of Foot Morphology on Foot Function
Bruce J. Sangeorzan, M.D.

The Epidemiology of Foot Structure and Ulceration in Diabetic Veterans
Bruce J. Sangeorzan, M.D.

Research Grants
Department of Orthopaedics and Sports Medicine

Rehabilitation Research and Development Center of Excellence for Limb Loss Prevention and Prosthetic Engineering
Bruce J. Sangeorzan, M.D.

Transtibial Amputation Management Strategies
Bruce J. Sangeorzan, M.D.

Orthopaedic Research and Education Foundation (OREF)

The Role of Wild-Type EWS and the EWS/FLI-1 Fusion Protein in the Genesis of Ewing's Sarcoma
Howard A. Chansky, M.D.

Splicing Factors Effect Chondrocyte Differential and Collagen Sythesis
Howard A. Chansky, M.D.
Eric O. Klineberg, M.D.
Liu Yang, Ph.D.

Journal of Bone and Joint Surgery Resident Journal Club
Seth S. Leopold, M.D.

Reduction of Total Knee Arthroplasty Risk in Morbiedly Obese Patients Using Laparoscopic Bariatic Surgery: A Prospective, Controlled Trial
Seth S. Leopold, M.D.

Overcoming Nerve Defect by Growth Factor Stimulated Regeneration Along Intact Nerves
Ben Dubois, M.D.
Thomas E. Trumble, M.D.

Toward Clinical Application of the Intact Nerve Bridge Technique:Longer Term Study in a Rabbit Model
Wren V. McCallister, M.D.
Thomas E. Trumble, M.D.

Centers for Disease Control

Chest Injuries Due to Motor Vehicle Side Impacts
Allan F. Tencer, Ph.D.

Research Grants
Department of Orthopaedics and Sports Medicine

American Society for Surgery of the Hand

Bridging Versus Non-Bridging External Fixation of Distal Radius Fractures: a Measure of Structural Rigidity in an Unstable Fracture Model
Thomas E. Trumble, M.D.

American Shoulder and Eldow Surgeons

Periosteal Arthroplasty of the Reamed Glenoid: A Histologic and Histomorphometric Study in a Rabbit Model of Non-Prosthetic Arthroplasty
Kevin L. Smith, M.D.

Council for Nail Disorders

Cells Involved in Human Digit Tip Regeneration
Christopher H. Allan, M.D.

Defense Advanced Research Projects Agency

Achieving Molecular Observation in Four Years
John A. Sidles, Ph.D.

The Accelerated Development of MRFM
John A. Sidles, Ph.D.

Florence and Marshall Schwid Memorial Foundation

The Role of Wild-Type TLS and the TLS/CHOP Sarcoma Fusion Protein in the Genesis of Myxoid Liposarcoma
Howard A. Chansky, M.D.

Genetics Institute

A Feasibility and Safety Study of rhBMP-2/ACS and Allograft Compared to Autogenous Bone Graft for Patients with Severe Tibial Shaft Fractures
Sohail K. Mirza, M.D.

Research Grants
Department of Orthopaedics and Sports Medicine

Integra Lifesciences Corporation

Comparison of Bioabsorable Tubes for Repair of Nerve Injury
Thomas E. Trumble, M.D.

National Science Foundation Engineering Research Center

Tissue-Engineered Digit Replacement
Christopher H. Allan, M.D.

Novartis Pharmaceuticals Corporation

Cartilage Collagen Study
David R. Eyre, Ph.D.

Orthopaedic Trauma Association

Immediate vs. Delayed Closure of Type II and IIIA Open Tibia Fractures
M. Bradford Henley, M.D.

Percutaneous Pinning versus Open Reduction and Internal Fixation of Proximal Humeral Fractures: A Prospective and Randomized Comparison of Outcomes
Sean E. Nork, M.D.

Ostex International, Inc.

Molecular Markers of Connective Tissue Degradation
David R. Eyre, Ph.D.

Pfizer, Inc.

Guinea Pig Osteoarthritis
David R. Eyre, Ph.D.

Research Grants
Department of Orthopaedics and Sports Medicine

Sevrain, Christophe J-P

Biomechanical Testing of a Cervical Spine Fixation Plate
Allan F. Tencer, Ph.D.

Synthes Spine Co.

Spine End-Results Research Fund
Frederick A. Matsen III, M.D.

The Boeing Company

Randomized Clinical Trial of Open versus Endoscopic Carpal Tunnel Release and Hand Therapy Comparing Patient Satisfaction. Functional Outcome and Cost Effectiveness
Thomas E. Trumble, M.D.

Tyco Healthcare

Interdiscal Electrothermography (IDET) in Cervical Discs
Allan F. Tencer, Ph.D.

Washington Woman's Foundation

Strengthening the Femoral Neck to Prevent Hip Fractures caused by Osteoporosis
Frederick A. Matsen III, M.D.

Whitaker Foundation

Examining Processes Underlying the Dramatic Osteogenic Response Elicited by Rest-Inserted Loading
Sundar Srinivasan, Ph.D.

Zymogenetics, Inc.

Study of zfgf5 and Cartilage
James D. Bruckner, M.D.

*will not officially start until 7/1/04

Contributors to Departmental Research and Education

April 2003 Through March 2004

We express our appreciation to all who have contributed to the work of the Department of Orthopaedics and Sports Medicine over the past year. Your assistance makes possible special research activities, educational programs, and other projects that we could not offer without this extra support from our alumni, faculty, and friends in the community. We owe a special thanks to the University of Washington Resident Alumni who have made significant contributions to help further the education of our current residents. We have tried to include in this list all who contributed; if anyone was overlooked, please be sure to let us know!

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1956
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1957
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Don Ericksen, M.D. ★★
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Oriente DiTano, M.D. ★

1999
Craig Boatright, M.D.
Jeffrey Garr, M.D.
John Michelotti, M.D. ★
Julie A. Switzer, M.D.
Thomas D. Chi, M.D. ★

2000
Brett Quigley, M.D. ★
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Daniel Jones, M.D. ★
Joel Hoekema, M.D. ★
Patrick McNair, M.D.

2001
Eric Novack, M.D.
Frederick Huang, M.D. ★
Matthew Camuso, M.D.
Michael Metcalf, M.D. ★
Richard Bransford, M.D.

2002
Timothy DuMontier, M.D.
Scott Hacker, M.D.
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William Sims, M.D. ★
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2003
Ben DuBois, M.D.
Andy Howlett, M.D.
Guy Schmidt, M.D. ★
Brian Shafer, M.D.
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2004
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We express our appreciation to all who have contributed to the endowments of the Department of Orthopaedics and Sports Medicine. Your assistance makes possible special research activities, educational programs, and other projects that we could not offer without this extra support from our alumni, faculty, and friends in the community. Additional Contributions to these and new endowments are most welcome! If you have any questions, please contact our Chair, Rick Matsen, or our Administrator, Diana Jansen.

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Sigvard T. Hansen Jr. Endowed Chair in Orthopaedic Traumatology

Jerome H. Debs Endowed Chair in Orthopaedic Traumatology

Endowed Chair for Women's Sports Medicine and Lifetime Fitness

Surgical Dynamics Endowed Chair for Spine Research

Douglas T. Harryman II/DePuy Endowed Chair for Shoulder Research

Synthes Spine End Results Endowed Chair

Zimmer Fracture Fixation Biology Endowed Professorship

Ostex Bone and Joint Research Endowment

Orthopaedic Traumatology Endowed Lectureship

John F. LeCocq Lectureship in Orthopaedic Surgery

Don and Carol James Research Fund in Sports Medicine and Fitness

Victor H. Frankel Award

Esther Whiting Award

Ed Laurnen Award

Spine Research Endowment