Chief Resident Research Presentations

Thursday
March 9, 2017
7:00–8:30 am

LOCATION
Richard L. Menschel Education Center
Hospital for Special Surgery
2nd Floor, 535 East 70th Street

Alexander Christ, MD
Elizabeth Cody, MD
Peter Derman, MD, MBA
Grant Garcia, MD

Michael Hendel, MD, PhD
Sravisht Iyer, MD
Joseph Liu, MD
Andre Shaffer, MD

Lewis Clark Wagner, MD, Award for Excellence in Clinical/Translational Orthopaedic Research
and
Russell F. Warren, MD, Award for Excellence in Basic/Translational Orthopaedic Research

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Presentation Schedule
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Richard L. Menschel Education Center
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7:00 am  Targeting Skeletal Metastases Using a Novel HPMA Copolymer Nanomedicine Delivery System
Alexander Christ, MD

7:11 am  MRI Validation of Tibial Tubercle Transfer Distance: A Clinical and Cadaveric Study
Joseph Liu, MD

7:22 am  Assessment of Backside Polyethylene Wear in Reverse Shoulder Arthroplasty
Michael Hendel, MD, PhD

7:33 am  Cervical Spine Fusion: Epidemiology, Complications, ED Utilization, Readmissions, & Revisions
Peter Derman, MD, MBA

7:44 am  Patient Factors Associated with Higher Expectations from Foot and Ankle Surgery
Elizabeth Cody, MD

7:55 am  The “Safe Zone” Technique Improves Suture Placement and Accuracy During Arthroscopic Remplissage: A Cadaveric Validation of A New Technique
Grant Garcia, MD

8:06 am  Anti-Sclerostin Antibody Enhances Spinal Fusion Volume and Mass but Does Not Improve Fusion Rates in Rat Spine Fusion Model
Andre Shaffer, MD

8:17 am  Locally Applied Simvastatin as an Adjunct to Promote Spinal Fusion in Rats
Sravisht Iyer, MD
Targeting Skeletal Metastases Using a Novel HPMA Copolymer Nanomedicine Delivery System

Alexander B. Christ, MD; Theresa Pazionis, MD; Chloeh Horowitz; Rajasekhar Vinagolu; Melissa Zimel, MD; Dong Wang, PhD; Steven R. Goldring, MD; P. Edward Purdue, PhD; and John H. Healey, MD.

Introduction:
Bone is among the most common sites for metastases from carcinoma, with an incidence of 35%–73% (1, 2). Current treatment strategies for skeletal metastases include radiation and systemic chemotherapy, both of which are associated with significant local and off-target complications. Recent advances in nanotechnology have led to the development of novel polymer-drug conjugates that selectively deliver chemotherapeutic agents to solid tumors (3 – 5). Our goal is to develop a nanoparticle system for drug delivery that selectively localizes to the sites of skeletal metastasis and provides a mechanism for regulated drug release while avoiding non-target organ and systemic toxicity.

Tumors differ from normal tissues by the presence of an immature capillary network with increased vascular permeability and impaired lymphatic drainage. These properties form the basis for the EPR (enhanced permeability and retention) effect, the proposed mechanism for preferential uptake and retention of nanoparticles to solid tumors (5 - 7). Using small animal models, we previously demonstrated selective delivery of polymer-drug conjugates to sites of injury and inflammation and showed that HPMA copolymers are internalized by both resident cells and infiltrating myeloid cells and sequestered in lysosomes (8 – 10). These findings confirm that the HPMA copolymer retention mechanism involves not only the EPR effect, but is also dependent upon cellular uptake and retention by tumor cells and other resident cell types, a process termed ELVIS (Extravasation through Leaky Vasculature and subsequent Inflammatory cell-mediated Sequestration).

Recent studies have shown that resident macrophages exert a significant influence upon tumor biology (11 - 13). These reports indicate that tumor-associated macrophages (TAM) represent a population of M2 cells that are immune-suppressive, promoting angiogenesis and supporting growth and development of metastasis. This has led to the concept of pharmacologically repolarizing these cells towards an immune-stimulatory M1 population capable of promoting a tumoricidal T-cell response. This study was undertaken to evaluate the potential efficacy of the HPMA copolymer system in specifically target TAMs associated with skeletal sites of breast carcinoma.

Materials and Methods:
Balb/c mice were inoculated with 10^5 4T1 murine breast carcinoma cells in approximately 100µL saline into the right proximal tibia via percutaneous injection, followed by a control injection of 100µL saline into the left proximal tibia. Serial radiographs using Faxitron small animal imaging were performed weekly until identifiable skeletal lesions had developed. HPMA copolymers conjugated to IRDye800CW (P-IRDye) and AlexaFluo488 (P-Alexa) were synthesized. Mice with radiographically-visualized tumors were injected via the retro-orbital venous plexus with 0.5mg P-IRDye and 0.5mg P-Alexa in 50µL normal saline, and copolymer localization was assessed over the following week using a live-animal near-infrared imager (Li-COR). Following necropsy, the sites of copolymer targeted tumors were collected and subjected to both histological analysis and collagenase digestion to prepare a single cell suspension. Dispersed cells were analyzed for P-Alexa uptake and phenotypic markers by flow cytometry.

Additionally, TAMs were isolated by positive selection of CD11b expressing cells using magnetic bead sorting. Real-time PCR was performed on these TAMs to evaluate expression of M1 and M2 markers.
In vitro studies were performed using fresh bone marrow macrophages (BMMs), which were exposed to 4T1 cells in culture over varying lengths of time. mRNA was then harvested from the BMMs and evaluated by real-time PCR for expression of M1 and M2 markers. These cells were also analyzed flow cytometry and fluorescence microscopy.

**Results:**

P-IRDye localization to the tumor was confirmed via Li-COR imaging. All tumors demonstrated increased signal at 24 and 48 hours compared to the contralateral leg. Further, P-Alexa uptake by both tumor cells and TAMs was confirmed with confocal microscopy and flow cytometry. Flow cytometric and cell sorting approaches provided an initial characterization of the TAM populations, and demonstrated robust expression of M2 surface markers.

Real-time PCR of TAMs isolated from mice tumors demonstrated gene expression consistent with the M2 phenotype. BMMs incubated with 4T1 cells initially displayed M1-like gene expression, but converted to M2-like gene expression when incubated with tumor cells for increasing periods of time.

**Conclusions:**

The primary goal of this study was to develop an in vivo murine metastatic tumor model in which to evaluate delivery of HPMA copolymers to TAM populations associated with sites of skeletal metastasis. All tumors showed preferential uptake of P-IRdye compared to the contralateral control limb, and the harvested tumors demonstrated increased uptake of P-Alexa into both tumor cells and infiltrating TAM populations.

In previously published work we observed preferential delivery and retention of HPMA copolymers to sites of inflammation and intracellular retention of the molecules within the lysosomal compartments of myeloid cells. Our study demonstrates that HPMA nanoparticles localize and are retained by cells at sites of metastatic tumors in a similar fashion, providing proof-of-principle that the HPMA system can be used as a drug-deliver system to selectively target TAM populations within skeletal metastatic sites and provide a mechanism for sustained therapeutic benefit while avoiding off-target toxicity.

This study has several limitations: First, intra-tibial injections do not perfectly mimic a metastatic model. In our initial studies we utilized an intra-cardiac injection model to produce skeletal metastasis. However, this resulted in a high mortality rate, small metastases that were difficult to detect, and neurological deficits. Therefore, we feel that intra-tibial injections are an adequate model in this proof-of-principle study. Second, tumors did not develop in all animals. This was likely due to the difficulty in delivering a uniformly tumorigenic number of cells in each injection. However, we have shown that a HPMA-copolymer nanomedicine delivery system can be used to target TAM populations in an in vivo murine metastatic carcinoma model. This model can be used for targeted drug delivery to metastatic cancer in bone, as well as to further explore the role of TAMs in promoting or preventing tumor growth.

**References:**


**Level of Evidence: IV**

**Funding Acknowledgement:** OREF Resident Clinician-Scientist Training Grant 2016-2017, Louis and Rachel Rudin Foundation Award 2016-2017, Center for Molecular Imaging and Nanotechnology at Memorial Sloan-Kettering Cancer Center (Project #302)

**IACUC Approval Number:** 05-14-08M
MRI Validation of Tibial Tubercle Transfer Distance: A Clinical and Cadaveric Study

Joseph N. Liu, MD; Douglas N. Mintz, MD; Joseph Nguyen, MPH; Jacqueline L. Munch, MD; Sabrina M. Strickland, MD; Beth E. Shubin Stein, MD

**Purpose:** Tibial tubercle osteotomy can treat moderate patellofemoral arthritis, patellofemoral overload, and/or patellar instability. Studies that validate tibial tubercle transfer distance or osteotomy angle have not been performed. The purpose of this study was to verify the amount of medialization and anteriorization estimated by surgeons intraoperatively by using postoperative axial imaging.

**Methods:** All patients undergoing anteromedialization osteotomies of the tibial tubercle by a single surgeon with pre- and postoperative magnetic resonance imaging (MRI) studies were included. Using MRI multiplanar reformats, distances that the tibial tubercle was translated medially (medialization) and anteriorly (anteriorization) were measured. In addition, the osteotomy angle was measured on the postoperative MRI. The measured values were compared with intraoperative estimates. Tibial tubercle osteotomies were then performed on 3 cadaveric knee specimens and imaged with pre- and post-procedure MRIs to correlate intraoperative measurements with MRI findings.

**Results:** The steepest osteotomy angle that could be performed without violating the posterior cortex and/or endangering the posterior neurovascular structures was 46.3 degrees.

**Conclusions:** Surgeons overestimate the anteriorization and medialization distances as well as the osteotomy angle in tibial tubercle osteotomies. Modifications of the anteromedialization osteotomy should be considered when more anteriorization is desired with tubercle transfers.

**Key Terms:** Anteromedialization, tibial tubercle transfer, patellofemoral, osteoarthritis, patellofemoral overload, knee pain

**Level of Evidence:** IV

**IRB Approval Number:** 2014-051 and 2015-250
Backside Polyethylene Wear in Reverse Shoulder Arthroplasty

Michael D. Hendel, MD; Michael Schwartz, BS; Chelsea Koch, BS; Xiang Chen, MS; Timothy Wright, PhD; Andreas Kontaxis, PhD; Lawrence V. Gulotta, MD
Hospital For Special Surgery, New York, NY, USA

Introduction: Reverse Shoulder Arthroplasty (RSA) indications have expanded in recent years to include younger, more active patients, highlighting the importance of implant durability and longevity. The mechanisms of long-term RSA failure remain uncertain and further investigation is needed. Aseptic loosening from implant associated osteolysis has been reported in RSA, and may contribute to premature implant failure. Polyethylene debris (PE) has been associated with osteolysis and aseptic loosening in hip and knee arthroplasty, and it has been proposed that RSA polyethylene components may produce increased PE wear particles when compared to conventional anatomic total shoulder implants due to increased articular surface area. In the RSA, PE wear on the articular side has been previously investigated, but no study to date has investigated backside PE wear between the liner and the humeral metal component. The purpose of this study was to evaluate retrieved RSA PE liners for both articular and backside surface wear in a series of failed arthroplasties.

Methods: Twenty-two RSA humeral PE liners were retrieved between 2005 and 2014 and collected for analysis. The average patient age at surgery was 65 ± 8 years. The average time at which implant was extracted was 16 ± 21 months. Diagnosis at the time of revision was dislocation (10), infection (4), loosening (2) mechanical failure (3), and unknown (3). Liners were examined under light microscopy (10-30x mag.) by two independent graders. The damage on the articular and backside of the liner surface was then graded using a modified Hood scoring system. Damage scores were graded on a scale of zero to three in each quadrant both on the articular and backside of the implant. The location and damage modality was then compared between the articular and backside of the implant.

Results: Damage was observed on the articular surface in all 22 liners, and on the backside in 20 liners. The average total damage score was significantly higher on the articular surface than on the backside (16.27 ± 6.92; 4.65 ± 3.27; p<0.001). Damage scores were not significantly different among quadrants on the backside (p = 0.44) or the articular surface (p = 0.13). The most common mode of damage was scratching and pitting on both the articular and backside. Deformation on the inferior aspect of the articular side of the liners was also frequently noted, consistent with scapular notching.

Conclusions: This short-term retrieval study demonstrated backside PE damage occurs on the humeral component of RSAs. As expected, there was significantly greater damage to the articular side of the liner. Wear to the backside was present in over 90% of the liners, with a trend toward increasing wear in the superior quadrant. The extent to which this is clinically significant remains to be determined. The role of backside wear in RSA and its overall contribution to PE particulate disease and osteolysis is unclear and further investigation is warranted.

Figure 1: Example of Pitting (left) to the backside of a liner, and deformation at the inferior aspect on the articular surface shown here (right).

Figure 2: Total damage score was significantly lower on the backside surface than the articular surface (5.3 ± 4 versus 16.5 ± 7; p<0.001). Damage scores were not different among quadrants on the backside (p=0.44) or the articular surfaces (p=0.13).

Level of Evidence: IV

IRB/IACUC Approval Number: #24097
Demographic, Clinical, and Operative Factors Affecting Long-Term Revision Rates After Cervical Spine Arthrodesis

Derman PB, Lampe LP, Hughes AP, Pan TJ, Kueper J, Girardi FP, Albert TJ, Lyman S

Background: Limited data exist on long-term revision rates following cervical spine arthrodeses. The purposes of this study were to define reoperation rates after primary cervical arthrodeses and to identify risk factors for revisions.

Methods: New York State's all-payer health-care database was queried to identify all primary subaxial cervical arthrodeses occurring in the 16 years from 1997 through 2012. A total of 87,042 patients were included in the study cohort. Demographic information was extracted. Patients' preoperative medical comorbidities, surgical indications, and operative approaches were assembled using codes from the ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification). The cohort was followed to revision surgical procedures, death, or the end of the study period. All subsequent contiguous spinal arthrodeses, including in the subaxial cervical spine, were considered revisions. The overall revision risk and the risk associated with various preoperative characteristics, surgical indications, and operative approaches were assessed using a Cox proportional hazard model.

Results: During the study period, 6,721 patients (7.7%) underwent revision. The median time to revision was 24.5 months. The probability of undergoing at least one revision by 192 months was 12.6%. Arthrodeses performed via anterior-only approaches had a significantly higher probability of revision (p < 0.001) at 13.4% (95% confidence interval [95% CI], 12.9% to 13.9%) than those performed via posterior approaches at 7.4% (95% CI, 6.6% to 8.4%) or circumferential (anterior and posterior) approaches at 5.2% (95% CI, 4.0% to 6.8%). This relationship persisted in multivariate analysis; compared with anterior surgical procedures, there was a significantly lower risk of revision (p < 0.001) for posterior surgical approaches at a hazard ratio of 0.76 (95% CI, 0.69 to 0.84) and circumferential approaches at a hazard ratio of 0.53 (95% CI, 0.42 to 0.66). Patient age of 18 to 34 years, white race, insurance status of Workers' Compensation or Medicare, and surgical procedures for spinal stenosis, spondylosis, deformity, and neoplasm were associated with elevated revision risk. Arthrodeses spanning few levels and those performed for fractures had a lower revision risk.

Conclusions: Primary subaxial cervical spine arthrodeses had a probability of revision approaching 13% over a 16-year period, with elevated reoperation rates in patients undergoing anterior-only surgical procedures. Age, race, insurance status, surgical indication, and number of spinal levels included in the arthrodesis were also associated with reoperation risk.

Level of Evidence: Therapeutic Level III

IRB/IACUC Number: #11073
Patient Factors Associated with Higher Expectations from Foot and Ankle Surgery

Cody, Elizabeth A.; Mancuso, Carol A.; Burket, Jayme C.; Marinescu, Anca; MacMahon, Aoife; Ellis, Scott J.; HSS Orthopaedic Foot and Ankle Surgery Group (Roberts, Matthew M.; Drakos, Mark C.; Deland, Jonathan T.; Levine, David S.; Demetracopoulos, Constantine A.; Kunas, Grace)

Introduction:
Few authors have investigated patients’ expectations from foot and ankle surgery, and standardized means of assessing expectations are lacking. Managing patients’ preoperative expectations may help improve their ultimate satisfaction with surgery. In a previous study, we developed a valid and reliable patient-derived expectations survey for patients undergoing foot and ankle surgery. In this study, we aimed to examine relationships between patients’ preoperative expectations and their demographic and clinical characteristics. We hypothesized that patients with more disability and those with anxiety or depressive symptoms would have greater expectations.

Materials and Methods:
All adult patients scheduled for elective foot or ankle surgery by one of six orthopaedic foot and ankle surgeons were screened for inclusion from August 2015 through March 2016. Patients were enrolled in person or by telephone. Preoperatively, all patients completed the Foot & Ankle Surgery Expectations Survey in addition to the Foot & Ankle Outcome Score (FAOS), Short Form (SF)-12, Patient Health Questionnaire (PHQ)-8, Generalized Anxiety Disorder 7-item scale (GAD-7), and pain visual analog scale (VAS). The expectations survey contains 23 expectations categories, each with five answer choices ranging from “I do not have this expectation” to “complete improvement” expected. It is scored from 0-100, with higher scores indicating more expectations. Differences in the expectations score with categorical variables were assessed with t-tests and single factor analysis of variance (ANOVA). Differences in the number of expectations and the number of expectations with complete improvement expected were assessed with Mann-Whitney U and Kruskal Wallis tests. Correlations between expectations and continuous variables were assessed with simple linear regression.

Results:
352 patients with an average age of 55 ± 15 (range, 18 to 86) were enrolled. Expectations were not significantly related to age. On average, women expected to achieve complete improvement more often than men (p = 0.011). Other factors that were significantly associated with higher expectations (p < 0.05) included non-Caucasian race, workers’ compensation, use of a cane or other assistive device, diagnosis of ankle instability or osteochondral lesion, and greater medical comorbidity (Table). Patients with hallux valgus or mid- or hindfoot arthritis had significantly lower expectations than patients with other diagnoses. Patients with a history of prior orthopaedic surgery or current narcotic medication use were less likely to expect complete improvement. Worse function and quality of life (as assessed by all FAOS subscales and the SF-12 physical and mental components), more depressive and anxiety symptoms, and higher pain VAS scores were associated with higher expectations scores and more expectations (p < 0.01 for all).

Conclusions:
The results of this study may help inform surgeons’ preoperative discussions with their patients regarding realistic expectations from surgery. Generally patients with worse function and more disability had higher expectations from surgery. Addressing these patients’ expectations preoperatively may help improve their ultimate satisfaction with surgery.

Level of Evidence: Level II, cross sectional study.

Table. Expectations scores and numbers of expectations are listed for groups of interest, with p-values representative of the difference between the group of interest and all other patients. Higher expectations scores indicate more expectations. *p < 0.05.

<table>
<thead>
<tr>
<th></th>
<th>Mean expectations score (range, 0-100)</th>
<th>p-value</th>
<th>Mean number of expectations (range, 0-23)</th>
<th>p-value</th>
<th>Mean number of expectations with complete improvement expected (range, 0-23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=352)</td>
<td>60.3 ± 18.7</td>
<td>n/a</td>
<td>16.3 ± 4.4</td>
<td>n/a</td>
<td>8.1 ± 6.8</td>
<td>n/a</td>
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<td>Male sex (n=120)</td>
<td>57.1 ± 18.1</td>
<td>0.663</td>
<td>15.9 ± 4.5</td>
<td>0.172</td>
<td>6.7 ± 6.5</td>
<td>0.011*</td>
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<tr>
<td>Female sex (n=232)</td>
<td>61.8 ± 18.8</td>
<td></td>
<td>16.6 ± 4.3</td>
<td></td>
<td>8.7 ± 6.9</td>
<td></td>
</tr>
<tr>
<td>Caucasian race (n=319)</td>
<td>59.1 ± 18.5</td>
<td>&lt;0.001*</td>
<td>16.1 ± 4.3</td>
<td>&lt;0.001*</td>
<td>7.7 ± 6.7</td>
<td>0.002*</td>
</tr>
<tr>
<td>Non-Caucasian race (n=33)</td>
<td>71.6 ± 16.3</td>
<td></td>
<td>18.6 ± 4.0</td>
<td></td>
<td>11.8 ± 7.2</td>
<td></td>
</tr>
<tr>
<td>Currently working (n=231)</td>
<td>59.5 ± 18.9</td>
<td>0.689</td>
<td>16.1 ± 4.4</td>
<td>0.256</td>
<td>7.9 ± 6.9</td>
<td>0.449</td>
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<tr>
<td>Currently not working (n=120)</td>
<td>61.5 ± 18.3</td>
<td></td>
<td>16.7 ± 4.3</td>
<td></td>
<td>8.4 ± 6.8</td>
<td></td>
</tr>
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<td>On workers’ compensation (n=9)</td>
<td>66.3 ± 16.7</td>
<td>0.304</td>
<td>19.6 ± 4.1</td>
<td>0.017*</td>
<td>6.4 ± 7.5</td>
<td>0.344</td>
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<td>Uses cane, walker, or wheelchair (n=21)</td>
<td>71.2 ± 17.9</td>
<td>0.005*</td>
<td>19.0 ± 2.9</td>
<td>0.002*</td>
<td>10.8 ± 8.1</td>
<td>0.110</td>
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<tr>
<td>History of prior orthopaedic surgery (n=143)</td>
<td>59.1 ± 18.2</td>
<td>0.331</td>
<td>16.4 ± 4.3</td>
<td>0.828</td>
<td>7.0 ± 6.4</td>
<td>0.002*</td>
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<td>On narcotic medication (n=17)</td>
<td>63.1 ± 10.9</td>
<td>0.520</td>
<td>19.5 ± 2.6</td>
<td>0.001*</td>
<td>4.1 ± 5.1</td>
<td>0.012*</td>
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<td>Diagnosis of hallux valgus (n=92)</td>
<td>55.5 ± 19.2</td>
<td>0.005*</td>
<td>15.0 ± 4.4</td>
<td>&lt;0.001*</td>
<td>7.7 ± 6.6</td>
<td>0.680</td>
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<td>Diagnosis of hallux rigidus (n=39)</td>
<td>56.1 ± 17.0</td>
<td>0.138</td>
<td>15.2 ± 3.9</td>
<td>0.029*</td>
<td>7.9 ± 6.5</td>
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<td>Diagnosis of pes planus (n=38)</td>
<td>62.9 ± 13.4</td>
<td>0.357</td>
<td>17.4 ± 2.7</td>
<td>0.225</td>
<td>7.1 ± 6.4</td>
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<td>Diagnosis of ankle arthritis (n=35)</td>
<td>63.0 ± 17.8</td>
<td>0.370</td>
<td>17.3 ± 4.1</td>
<td>0.157</td>
<td>7.2 ± 6.5</td>
<td>0.486</td>
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<td>Diagnosis of chronic tendon injury (n=28)</td>
<td>66.5 ± 18.5</td>
<td>0.065</td>
<td>17.8 ± 4.3</td>
<td>0.028*</td>
<td>9.5 ± 7.3</td>
<td>0.283</td>
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<td>Diagnosis of ankle instability or osteochondral lesion (n=27)</td>
<td>70.0 ± 18.6</td>
<td>0.004*</td>
<td>18.1 ± 3.8</td>
<td>0.026*</td>
<td>11.1 ± 7.3</td>
<td>0.024*</td>
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<td>Diagnosis of mid- or hindfoot arthritis (n=19)</td>
<td>48.9 ± 16.0</td>
<td>0.006*</td>
<td>15.1 ± 5.2</td>
<td>0.314</td>
<td>2.4 ± 4.0</td>
<td>&lt;0.001*</td>
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</table>
The “Safe Zone” Technique Improves Suture Placement and Accuracy During Arthroscopic Remplissage: A Cadaveric Validation of A Novel Technique

Grant H Garcia, MD; Ryan M Degen MD; Joseph N Liu, MD; Cynthia Kahlenberg, MD; Dan Hurwit, MD; Joshua S. Dines, MD

Introduction:

Recent studies have raised concern over the accuracy of suture passage into the infraspinatus tendon during remplissage. This inaccuracy has been shown to result in over-medialization and muscular penetration causing post-operative external rotation loss and posterior shoulder pain. Our purpose was to evaluate the accuracy of suture passage during remplissage and identify surface landmarks to improve accuracy. Our secondary purpose was to validate the use of these identified landmarks to improve accuracy of suture passage through the infraspinatus tendon.

Materials and Methods:

12 cadaveric specimens were used. In the first 6 specimens (control group), standard arthroscopic remplissage was performed. Specimens were dissected to quantify the location of suture passage in reference to the posterolateral acromion (PLA) and to identify the location of posterior cuff penetration. After analyzing the control group specimens a “safe zone” (SZ) was identified to improve accuracy of passage and increase infraspinatus tendon penetration.

For final 6 specimens, the safe zone technique was utilized for suture passage during arthroscopic remplissage. Specimens were again dissected to analyze the accuracy of suture passage and location of penetration. Results were compared to the control group.

Results:

For the control group, 24 sutures were passed. 25.0% (6/24) were passed through the infraspinatus tendon, and 75%(18/75) were through the teres or infraspinatus muscle or MTJ.

Sutures passage through the infraspinatus were an average of 25±5.4 mm distal to the PLA, while teres minor sutures were an average of 35.8±5.7mm distal to the PLA. If passes were less than 3 cm distal to the PLA, there was a significantly higher rate of infraspinatus tendon penetration (odds ratio[OR]=25 ,p<0.01). Sutures passing through muscle and MTJ were significantly more medial than those passing through tendon, at an average 8.1±5.1mm lateral to the PLA compared to 14.5±5.5mm (p<0.02). Passes were more likely to be in tendon, rather than muscle or MTJ if greater than 1 cm lateral to the PLA (p=0.013).

The safe zone was defined as passing all tenodesis sutures greater than 1 cm lateral and less then 3cm distal to the PLA. Utilizing this technique, 24 sutures were also passed arthroscopically in the remaining 6 specimens. 83.3% (20/24) were in the infraspinatus tendon, which was significantly improved from the control group (p<0.01). Only, 4.2% (1/24) of attempted passes in the SZ group passed through the muscle or MTJ which was also significantly improved from the control group (p<0.01).

Prevention of over-medialization significantly improved using the SZ as represented by both anchors having suture passage significantly more lateral (6-10mm) than the control group (p<0.01). There was also an improvement in the precision of suture passes with utilization of the SZ, as overall precision (SD) improved in 75% of sutures passes.
Conclusions:

We found standard remplissage suture passage was inaccurate with only 25% of sutures penetrating the infraspinatus tendon. We recommend utilization of the “safe zone” technique, which consists of passing sutures 1 cm lateral and within 3 cm distal of the PLA. Furthermore this study validates that the “safe zone” technique, demonstrating significant improvement in accuracy of suture passage into the infraspinatus tendon and prevented over-medialization with muscle penetration. The safe zone technique provides a reproducible method that may prove useful to prevent previously reported complications associated with arthroscopic remplissage.

References:


Level of Evidence: Basic Science, Cadaveric

Funding Acknowledgement: We would like to thank the HSS sports and shoulder department for their generous grant support for this study.

IRB/IACUC Approval Number: IRB Exemption Study #2015-400
Anti-Sclerostin (Scl-Ab) Increases Bone Mass and Fusion Volume in a Rat Posterolateral Spinal Fusion Model

Shaffer, AD; Shonuga, OA; Hirsch, BP; Cunningham, ME; Li, Chaoyang; Ke, HZ; Lane, JM

Introduction:

Sclerostin is a Wnt-signaling pathway inhibitor specific to bone. Monoclonal antibodies to sclerostin (a-Scl) have been shown to enhance bone mass and healing in diaphyseal fracture models in animals\(^1\),\(^2\),\(^3\). Spinal fusion is a commonly performed procedure indicated in a number of conditions including degenerative and traumatic conditions. We hypothesize that lumbar spinal fusion is enhanced by the subcutaneous aScl antibody injection.

Methods:

Sixty male 10 wk Lewis rats underwent posterolateral intertransverse process spine fusion between L4 and L5 with 0.2g of morselized bone graft from a donor rat and randomized prior to surgery into two groups. Rats were started on a twice weekly regimen of saline (n=30) or 0.25 mg/kg aScl (Amgen, Inc, Mountain View, CA) on post-op day 2 that continued until sacrifice at six wks postoperatively. At sacrifice spines were harvested en-bloc from sacrum to L1 and cleaned of soft tissue. Harvested spines were frozen and underwent microCT (uCT) imaging. Thawed spines were evaluated for gross motion by manual palpation by three blinded authors, with fusion defined as no motion and scored by consensus. uCT was evaluated for total bone mass in the spines and fusion mass in selected spines from each group (n=6).

Results:

Manual palpation revealed no statistically significant differences between the two groups, a-Scl and saline, with fusion rates by manual palpation of 61% and 60% respectively (p = 0.92). uCT imaging revealed significantly increased bone volume in the spines of animals treated with a-Scl antibody with mean bone volume of 554.74±58.71 and 362.111±34.60 in spines treated with a-Scl and saline respectively (p = 0.000). Bone volume in the fusion mass was also significantly increased in spines treated with aScl over saline (BV.aScl = 255.530±40.63, BV.saline = 137.26±18.71, p = 0.000)

Conclusions:

a-Scl is an effective adjunct for spinal fusion in a rat model, showing increased bone mineral volume and density in the fusion mass and entire spine. a-Scl is an easily administered adjunct that increased fusion mass and overall bone stock. While greater fusion rate was not seen, bone in aScl treated animals was denser and fusion mass contained more bone than in saline treated animals. Greater bone volume and density may signal greater clinical benefits, since greater bone density and growth may be associated with lower rates of instrumentation failure in spinal fusion.\(^4\),\(^5\),\(^6\),\(^7\)

References:


Level of Evidence:

IRB/IACUC Number:
Locally Applied Simvastatin as an Adjunct to Promote Spinal Fusion in Rats

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Introduction: Obtaining a solid fusion is crucial to achieving stable, long-term outcomes following surgery for a number of spinal disorders (1). In order to maximize the likelihood of fusion, surgeons typically use bone graft (autograft or allograft) as well as adjuncts such as recombinant bone morphogenetic protein-2 (BMP-2). BMP-2, however, is expensive and its use has been associated with complications like wound problems, leg pain, and retrograde ejaculation (2). There exists a need for a safe, cost-effective, anabolic molecule that can assist with fusion but avoid complications. Given their well-established safety profile, relative cost-effectiveness and proven bone-anabolic effect, we believe that statins represent an ideal candidate to address this need. There is strong in vitro and in vivo evidence to support statins’ role in bone formation (3). There are, however, no studies that have evaluated the impact of locally delivered statins on spinal fusion. Local delivery of statins is typically accomplished with the use of degradable nanoparticles; these are necessary because orally administered statins have low bioavailability. Our investigation had two specific aims: 1) develop a readily usable device to enable to local delivery of SIM to the spine and 2) determine the impact of locally delivered SIM on spine fusion in a rat model.

Methods: Nanoparticle Preparation: Blank PLGA (BlankNP) and SIM-loaded PLGA (SimNP) nanoparticles were created by adapting established techniques (4). Briefly, 120mg of PLGA was dissolved in 2.4mL of chloroform. For SimNP 12mg of SIM was added. This solution was emulsified, added to 24 mL of 2% polyvinyl alcohol solution and emulsified again. Chloroform was then evaporated and the particles were centrifuged. Sustained Release: SimNP, ranging from 217ug/mL to 883ug/mL, was placed in 15mL of PBS at 37ºC with agitation. SIM release was measured for 15d using an UV spectrophotometer at 247.2nm. In Vitro: MC3T3-E1 osteoblast precursor cells were cultured in complete (COMP) or mineralizing (MIN) media. COMP consisted of DMEM, 10% FBS and 1% 100X Antibiotic/antimycotic. MIN media was COMP with 0.5M beta-glycerol phosphate, 50mM vitamin C and 1nM dexamethasone. Alizarin staining was performed at 1 week (wk) and 3wks to assess for mineralization. Real-time PCR measurements were performed at 1 wk and 2wks to quantify expression of osteocalcin (OCN) and osteopontin (OPN). Cells were cultured in COMP, MIN, or MIN treated with SimNP or SIM drug. In Vivo: A posterior spinal fusion model was utilized in 40 male 12wk old outbred Wistar rats. The transverse processes (TP) of L4 and L5 were exposed and decorticated. Corticocancellous bone graft was harvested from each iliac wing, morselized and implanted bridging the TP with one of three treatments (BlankNP [100-200mg/kg], SimNP [100-200mg/kg] or SIM drug [10-20mg/kg]). Treatments were assigned randomly. The groups were as follows: BlankNP (15 rats), SimNP (15 rats) or SIM drug (10 rats). X-rays (XR) to assess for bone formation were obtained at 4wks and 9wks after surgery. XR were scored by three blinded observers using a 6-point scale (0: no bone, 1: < 25% bone filling, 2: 25-%<50% filling, 3: 50-<75% filling, 4: 75-99% filling, 5: clear fusion). Spines were explanted at 9wks and a manual assessment of fusion (MAF) was performed by three blinded observers checking for motion at L4-5 compared to the levels above and below. Spines were considered fused if 2 of 3 observers agreed.

Results: SimNP successfully achieved sustained release over two weeks with ~50% occurring in the first day. Release efficiency averaged 74.1%. MC3T3 cells cultured with SimNP at 200ug/mL had higher expression of OCN and OPN at 1wk and 2wks (Fig 1). Cells cultured with SimNP showed more deposition of calcium as assessed by alizarin staining at 1wk and 3wks. Three animals (one from each group) were sacrificed due to postoperative complications (paralysis x2, infection). The remaining animals were analyzed. We found no significant differences between the BlankNP and SIM drug rats in XR scores or MAF. Compared to BlankNP, SimNP treated rats had significantly higher XR scores at 4wks (3.0 vs. 1.9, p<0.010) and 9wks (3.6 vs. 1.8, p<0.001) (Fig 2a and b). Compared to SIM drug, SimNP rats had similar XR scores at 4wks but higher scores
at 9wks (3.6 vs 2.1, p=0.005). MAF showed that SimNP had a significantly higher fusion rate than BlankNP (42.9% vs. 0%, p=0.006) (Table 1).

**Discussion:** We were able to successfully validate the sustained release of SIM and were able to show that SimNP was able to induce an increase in mineralization as well as an increase in markers of bone formation (OCN and OPN). There was no clear dose-response to SIM observed in vitro. This, however, is not inconsistent with the existing literature and might relate to the fact that high local concentrations of simvastatin can be cytotoxic (4). Determining the optimal dosing of SIM and SimNP, including the minimum cytotoxic dose, is an important area of future investigation. Our dosing of SIM drug in vivo was guided by previous research on fracture healing (5) and the SimNP dose was calculated to roughly match this dose. We hypothesize that the sustained release of SIM by the nanoparticles results in lower local concentrations that provide the bone-anabolic effects of SIM while avoiding the cytotoxicity. Additionally, sustained release might be beneficial because bolused local delivery of the drug alone may be washed out before any meaningful bone healing can occur. We believe that this is why SimNP rats had higher XR scores compared to the SIM drug animals.

To our knowledge, this is the first study to demonstrate that the local delivery of simvastatin using a PLGA nanoparticle can assist in achieving spinal fusion in an animal model. Rats treated with SimNP had significantly more bone formation on XR and were significantly more likely to achieve fusion judged by MAF compared to control animals (BlankNP).

**Significance:** Our findings highlight the potential of simvastatin as a safe, cost-effective bone anabolic agent for use in spinal fusion surgery.


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**Images and Tables:**

**Fig 1:** RT-PCR at 1wk and 2wks for OCN and OPN. Conditions: MIN media (control) and MIN treated with Sim drug at 4 and 8µg/mL and SimNP at 100 and 200µg/mL.

**Fig 2a (left):** XR scores at 4wk and 5wk. **Fig 2b (right):** Example of spaces in the BlankNP and SimNP group. Note bone formation in SimNP (arrows).

**Table 1:** Fusion as assessed by MAF. P-values are compared to BlankNP.

**Level of Evidence:** N/A

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