Evaluation of Arthroscopic Meniscal Root Repair Constructs

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Disclosures

Eric Branch
• No Financial Disclosures

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• Consultant – Ceterix Orthopaedics
Background

- The menisci play key roles in knee stability, proprioception and load distribution.

- Central to these functions is the ability of the menisci to transfer compressive forces into hoop stresses.

- In the case of medial root injury, study has illustrated contact pressures to approximate those seen with a total menisectomy.¹

- Left untreated, these injuries have been shown to result in progressive knee arthritis and degeneration.²

Background

- Prior studies have evaluated constructs placed ex vivo without method to place the strongest constructs in an in vivo surgical setting.\(^3\)\(^,\)\(^4\)

- Many of these previously described suture patterns have remained difficult if not impossible to recreate in the surgical setting via reasonable open or arthroscopic technique.

Study Goals

● Evaluate:
  ● Feasibility of all-inside arthroscopic technique for repairing the meniscus root
  ● Construct pullout strength
  ● Surgical repair time.

● Aid the clinician in determining the best method for meniscal root repair and help in developing appropriate postoperative rehabilitation plans.
Materials & Methods

- 20 cadaveric knees (40 Menisci)
  - Mounted in a simulated surgical position
- Sutures placed arthroscopically into medial and lateral meniscal roots
- Four repair constructs were tested:
  - 2 Simple Stitches
  - 1 Inverted Mattress Stitch
  - 1 Double Locking Loop Stitch
  - 2 Double Locking Loop Stitches
Materials & Methods

• Execution of each repair was timed.

• Specimens were dissected, and the medial and lateral menisci harvested.

• Individual specimens were then tested to failure
  • Instron mechanical load frame w/ custom baseplate mimicking the transosseous suture tunnel.
  • Preconditioning: 20 cycles from 50-100 (N) at 0.5 mm/s
  • Load to failure at 0.5 mm/s until failure.

• The Kruskal-Wallis Test was used to evaluate for statistical significance between groups.
Repair Device

NovoStitch, Ceterix Orthopaedics, Melo Park, CA, USA)
Meniscus Repair Constructs

2 Simple Sutures

1 Horizontal Suture

1 Double Locking Loop

2 Double Locking Loop
Instron Mechanical Load Frame
Loading Profile

![Diagram showing a loading profile with tension on the y-axis and time in seconds on the x-axis. The graph displays a steady increase followed by a series of cyclic loads and a final sharp increase.]
Tension vs Extension

![Graph showing the relationship between tension and extension. The graph has two axes: Tension (N) on the y-axis and Extension (mm) on the x-axis. The graph shows a curve that increases with extension, peaks, and then decreases.]
Results

<table>
<thead>
<tr>
<th>Stitch</th>
<th>Failure Load</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 simple stitches (2SS)</td>
<td>137±49 N</td>
<td>1.78 ± 0.87 minutes</td>
</tr>
<tr>
<td>1 inverted mattress stitch (1MS)</td>
<td>126±44 N</td>
<td>2.40 ± 1.90 minutes</td>
</tr>
<tr>
<td>1 double loop locking stitch (1DLS)</td>
<td>201±44 N</td>
<td>4.67 ± 2.01 minutes</td>
</tr>
<tr>
<td>2 double loop locking stitches (2DLS)</td>
<td>396±69 N</td>
<td>5.38 ± 0.62 minutes</td>
</tr>
</tbody>
</table>

Note: Native meniscal roots have been shown to have substantial strength, with maximum failure loads averaging 594 +/- 241N in one study.*

Inter-construct comparison revealed statistical difference between 2DLS (p < 0.01) and all three remaining constructs (< 0.01), and 1DLS when compared to 2SS and 1MS (p <0.01, <0.01). Statistical significance was not found between 2SS and 1MS (p=0.8).
Conclusion

- All-inside arthroscopically placed double locking loop stitch repair constructs are surgically feasible and come closer to restoring the strength of the native root than previously published techniques.

- As complexity of the repair construct increases so does surgical time for fixation and pullout strength.

- Clinical Relevance: The double locking loop stitch can be feasibly placed via an all-inside arthroscopic technique delivering improved pull out strength for meniscal root repair with little relative increase in surgical time.
Future

- Radial Tear Study (Completed)
- Longitudinal Tear Study (Proposed, 12/2013)
- Publications
  - Conference Abstract (Submitted)
  - Journal Article (In Preparation)
Thank You

- FSU College of Medicine
- FSU-CoM Division of Research
- Andrews Institute for Orthopaedics & Sports Medicine
- Andrews Research and Education Institute
- Adam W. Anz M.D.
**METHODS**

- Prospective cohort study
- Selected by nurse interviewers from hospital discharges over 12 months
- Screened 3 weeks after discharge
- Physicians reviewed the records provided and determined AEs independently and which AEs resulted from drugs (ADEs) versus other causes.
Identify Adverse Events age 65 years old and older

Review History & Physical Discharge Summary

Review Discharge Medication List

Apply STOPP and Beers Criteria
DATA

TOP TWENTY PRESCRIBED MEDICATIONS OF AE INDIVIDUALS AGED 65 AND OLDER (n=57)

NUMBER OF OCCURRENCES

CLASS OF MEDICATION

- Nutrients (herbs, vitamins, supplements)
- STATINS
- BETA BLOCKER 1
- Anti-coagulants
- SALICYLATES
- ACE INHIBITOR
- DIURETIC 1, LOOP
- CORTICOSTEROIDS
- Opioids
- INSPRINES
- INSULINS
- INHIBITORS
- QUINOLONES
- ANTIEPILEPTIC/ANTICONVULSANT
- BETA BLOCKER NON-BETA-2 AGONIST
- CORTICOSTEROID/BETA-2 AGONIST
- HYPOTHYROIDISM
- NSAID
- SULFONYLUREAS
- ARB
<table>
<thead>
<tr>
<th>Characteristics Of AE Individuals 65 Years and Older (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>65-74 (n=26)</td>
</tr>
<tr>
<td>Mean No. Of Meds</td>
</tr>
<tr>
<td>Median No. Of Meds</td>
</tr>
<tr>
<td>Mean No. Of Beers Meds</td>
</tr>
<tr>
<td>Mean No. Of STOPP Meds</td>
</tr>
<tr>
<td><strong>Males</strong></td>
</tr>
<tr>
<td>13 (50%)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
</tr>
<tr>
<td>13 (50%)</td>
</tr>
<tr>
<td><strong>Urban</strong></td>
</tr>
<tr>
<td>20 (77%)</td>
</tr>
<tr>
<td><strong>Rural</strong></td>
</tr>
<tr>
<td>6 (23%)</td>
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<tr>
<td></td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Mean No. of Meds</td>
</tr>
<tr>
<td>Mean No. of Beers Meds</td>
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<tr>
<td>Mean No. Of STOFP Meds</td>
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<tr>
<td>Males</td>
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<tr>
<td>Females</td>
</tr>
<tr>
<td>Urban</td>
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<tr>
<td>Rural</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>65-74</td>
</tr>
<tr>
<td>75+</td>
</tr>
</tbody>
</table>
CONCLUSIONS

1.) Of the age groups, 65-74 and 75 and older who have experienced an AE:
Aside from nutrients, statin medications had the highest number of occurrences.
Mean number of medications was 10 to 11 medications.
Median number of medications was 10 medications.
Rural patients were on slightly more medications than urban patients.
On average, patients were on at least 1 STOPP and/or Beers.
Females tended to be on more Beers medications than males.

2.) The relative frequencies of prescribed Beers and STOPP medications within elderly age groups who have experienced an ADE were:
65-74 Age Group
Beers: NSAIDs had the highest number of occurrences.
STOPP: PPI had the highest number of occurrences.
75+ Age Group
Beers: Salicylates, vasodilators, and anti-infectives had the highest number of occurrences.
STOPP: PPI had the highest number of occurrences.
CONCLUSION

- The frequency of the implicated drug for the ADE that met the Beer’s and STOPP criteria are as follows:
REFERENCES


The Human Oral and Nasal Microbiome—A Meta-analysis
My study abroad summer in Colorado
Human Microbiome Research

- Examine bacterial composition of samples (fecal, oral, skin swab, etc) in health and disease to guide treatment
- High throughput technologies compare many 16S ribosomal RNA (rRNA) gene sequences at once
- Compare samples from different diseases, geographic locations, substances, etc.
Qiime determines bacterial composition operational taxonomic units (OTUs): roughly species classification
Abundance, taxonomy, diversity, compare samples or populations
My goal: examine differences the oral and nostril microbiota between healthy and diseased individuals.
The dataset

- **22 Studies**
- **7,540 Samples**
- Metadata includes: body site, sequencing platform, variable region,
- Clinical metadata: age, sex, body mass index, smoker, HIV status, atherosclerosis, hypertension, antibiotic usage
- Lots of missing metadata
Questions

- To what extent does the microbiota of the oral cavity and nostril differ?
- To what extent does methodology affect bacterial OTU clustering?
- Do age, disease status, personal characteristics, etc. contribute to differences in the oral microbiota?
Samples cluster by body habitat

- **Platforms:** Illumina, FLX, Titanium, Fasta
- **Regions:** V1-3, V3-5, V2, V4, V6
- 7,540 samples
- Nostril Samples
- Oral Cavity
Oral Cavity samples cluster by different methodologies

- **Platforms:**
  - Titanium,
  - Illumina, FLX
- **Regions:** V1-3, V3-5, V2, V4, V6
- 6,539 samples
Oral cavity samples cluster by age

- **Platform:** Illumina
- **Region:** V4
- **800 samples**
- **Infant Days Old**
- **Child/Adult Years Old**
Vast differences in microbiota cluster separately regardless of methodology
More specific factors will require standardized methodologies to evaluate
Bacterial colonization of infants’ oral cavity may mimic gut colonization
Future Directions

- Standardize methodologies
- Expand clinical metadata: Role of Clinicians & Translational Research
  - Language barrier ‘studying abroad’
- Bedside to bench and back again
Thank you

- Howard Hughes Medical Institute
  - Summer Medical Fellows Program

HHMI

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  - Rob Knight, Ph. D.
  - Antonio Gonzalez, Ph. D.
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  - Gail Ackermann
  - Doug Wendel
  - Tim Vigers
  - Kathy Holt
  - Yoshiki Vazquez-Baeza
  - Ulla Westermann

- Drs. Hurt and Foster
Identifying Novel Chemotherapeutic Combinations: An Effort to Override Resistance

Mark R. Rohaus, Thomas J. Morgan, Cathy W. Levenson
Florida State University, College of Medicine, Department of Biomedical Sciences
Glioblastoma

• Most common and aggressive brain cancer
• Median overall survival of only 15 months
• Current therapy:
  – tumor resection
  – radiation
  – Chemotherapy/Resistance
    • Temozolomide
    • Carmustine (BCNU)
    • bevacizumab
Project Question

Can resistance to chemotherapy be altered by manipulating central pathways vital for cellular growth and survival?

…and can therapy efficacy be improved using this targeted approach?
Signaling Pathways

- cellular growth and survival
- commonly altered in cancer
Selected Pathways

- **Ras/Raf/MEK/ERK**
- **PI3K/Akt/mTOR**
Selected Pathways

- **LKB1/AMPK**
- **Glycolysis/PDC/Mit.oxd.**
Cross Talk Between Pathways
Pathway Manipulation and Drug Selection

- Based on literature
- downstream mediators
- convergence point
- previous efficacy – clinicaltrials.gov

<table>
<thead>
<tr>
<th>Intracellular Pathway</th>
<th>Target</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ras/Raf/MEK/ERK</td>
<td>MEK</td>
<td>Selumentinb (SEM)</td>
</tr>
<tr>
<td>LKB1/AMPK</td>
<td>AMPK</td>
<td>Metformin (Met)</td>
</tr>
<tr>
<td>Glycolytic/PDC/Mit.oxd</td>
<td>PDK</td>
<td>Dichloroacetate (DCA)</td>
</tr>
<tr>
<td>PI3K/PTEN/Akt/mTOR</td>
<td>mTor</td>
<td>Temsirolimus (Tem)</td>
</tr>
<tr>
<td>DNA Damage</td>
<td>DNA Alkylation</td>
<td>Carmustine (BCNU)</td>
</tr>
</tbody>
</table>
Methodology: Human Glioblastoma Culture

Human Glioblastoma LN18 and U87

96 well plate

24hr Incubation

Human Mesenchymal Stem Cells HMSC

Drug Dosing
Methodology: Treatment Design

Allowed for testing combinations of 4 to 5 drugs at multiple concentrations
Methodology: Drug Efficacy

- 72hr Incubation
- Cell Viability Assay (Resazurin)
  - Analysis
  - Background
  - Percent Change using negative control.
  - Combination Index Values
- Cell Proliferation Assay (SRB)
Methodology: Additive vs. Synergistic
### Results: Heat Mapping

Identifying Optimal Chemotherapy Combinations

Over 2,000 combinations evaluated
DCA + Met: Synergistic Combination

LN18

U87

HMSC

Control
DCA + Met: Synergistic Combination
Selumentinib and Dichloroacetate increase Glioblastoma response to previously resistant Carmustine chemotherapy
Glioblastoma more susceptible to combinations than HMSC

![Graph showing cell viability comparison between HMSC and different concentrations of BCNU, SEM, DCA, and DCA+SEM](image)
Conclusions

• Combining Selumentinib and Dichloroacetate with Carmustine increased the response of chemoresistant glioblastoma cells

• Combinatorial administration of Dichloroacetate with Metformin acts via a synergistic relationship

• Targeting multiple central pathways involved in cellular growth and survival shows potential as a therapy for the management of resistant cancers
Acknowledgments

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Dr. Thomas Morgan
And all members of the Levenson Lab

...thanks for a great summer!