CHONDROTOXICITY OF LOCAL ANESTHETIC

Sport Med 2017

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NO DISCLOSURES
Objectives

To understand the clinical presentation and pathogenesis of chondrolysis

Differentiate between the use of IA pain pumps and single-dose local anesthetics

Develop a treatment algorithm for your own practice based on the best available evidence
History

• Suture anchors for labral repair and thermal capsulorrhaphy were introduced in the early 1990s

• Use of pain pumps for the infusion of LA was introduced in the early 2000s

• The first published case of chondrolysis in a shoulder receiving an infusion of LA via a pain pump was in 2004
Media and the Law
Structure

• % by weight
  - Water (65-80%) > collagen (10-20%) > proteoglycan (10-15%) > noncollagenous protein > cells

• PG’s
  - function to provide compressive strength and attract water
  - aggregcan is most responsible for hydrophilic behavior
  - produced by chondrocytes
  - composed of GAG subunits
    - chondroitin sulfate
    - keratin sulfate
Function

- Hyaline cartilage
- Bearing Surface
- Frictionless
- Distributes loads
- Exhibits stress-shielding of the solid matrix components due to its high water content, the incompressibility of water, and the structural organization of the proteoglycan and collagen molecules
Glenohumeral Chondrolysis

- The irreversible destruction of previously healthy articular cartilage resulting from a loss of the chondrocytes that maintain the intercellular matrix.

- Once initiated, it usually progresses to the complete loss of articular cartilage.
The At-Risk Post-Operative Joint

- IA LA’s must diffuse through the intercellular matrix of the cartilage to the chondrocytes before they can exert their toxic effects, the superficial layer and an intact intercellular matrix offer protection to the embedded chondrocytes.

- When the surface layer is intact, chondrocytes primarily in the superficial layer are affected.

- When superficial layer is damaged, LA can more easily reach the chondrocytes within the matrix.

- Because lidocaine has a smaller MW, it is more prone to easily diffuse through the matrix, even with intact superficial layers.

- Suture anchors breach the integrity of all layers of articular cartilage.
Is the shoulder more prone than the knee?

- Thinner cartilage
- Smaller joint cavity and volume
- Smaller hematoma and less dilution
- Nonweightbearing joint – continuous exposure of chondrocytes to anesthetic without extrusion
Clinical Presentation

- Normal appearing cartilage at the index procedure and a period of benign recovery

- Followed in a few months by the onset of pain and stiffness associated with the global loss of cartilage from humeral and glenoid surfaces

- No prominent osteophytes

- No associated infection
Radiographs

- Radiographs of a 24 y/o male, posterior Bankart repair
  - Pre-op and 6 months post-op
Fellowship Case
Specimen Retrieval

- **Intra-operative appearance (at hemi-arthroplasty)**
Why does chondrolysis occur months later?

- Extracellular matrix of cartilage is not directly affected by local anesthetic.

- The delay in the onset of symptoms is most likely due to a combination of two factors:
  - Lack of cartilage maintenance by chondrocytes affected by LA will have a delayed effect.
  - In addition to immediate necrosis, alteration in mitochondrial DNA leading to delayed cell death through apoptosis is seen.
Chondrolysis After Continuous Intra-Articular Bupivacaine Infusion: An Experimental Model Investigating Chondrotoxicity in the Rabbit Shoulder

Long-Term Effects of Bupivacaine on Cartilage in a Rabbit Shoulder Model

Andreas H. Gomoll,* MD, Adam B. Yanke,† Richard W. Kang,‡ MD, MS, Susan Chubinskaya,‡ PhD, James M. Williams,§ PhD, Bernard R. Bach,‖ MD, and Brian J. Cole,** MD, MBA

Arthroscopy, 2006
AJSM, 2008
Chondrolysis After Continuous Intra-Articular Bupivacaine Infusion: An Experimental Model Investigating Chondrotoxicity in the Rabbit Shoulder

Andreas H. Gomoll, M.D., Richard W. Kang, B.S., James M. Williams, Ph.D., Bernard R. Bach, M.D., and Brian J. Cole, M.D., M.B.A.

- 30 rabbits divided into 3 groups (control, bupivacaine, bupivacaine + epi) treated with continuous infusions over 48 hours
- Decreased sulfate uptake (>50%), decreased cell viability (30%) with LA groups
- In this study, bupivacaine showed profound cytotoxic effects – histopathologic and metabolic changes
• 36 rabbits randomized to control, B, B+E groups
• No permanent impairment of cartilage function was detected after 3 months
• Cartilage metabolism was increased suggested a possible reparative response
• Articular cartilage may have the ability to recover from the chondrotoxic effects of bupivacaine in this rabbit model
Reports of 213 cases of chondrolysis have been identified
Mean age 30 years
79% of all cases had an IA pain pump
Other reports seen in ankle and knee
Both suture anchors and pain pumps were used in 119 cases (HR 2.6, p<0.01)
Suture anchors alone were used in 6 cases
• **Risk of glenohumeral chondrolysis in shoulders with an IA pain pump was highest with:**
  - Greater doses (esp 0.5% Marcaine, 2% lidocaine)
  - Higher flow rates (4-5 mL/hr for 48+ hours)
  - These high doses increase the amount of agent that diffuses through intact cartilage matrix to the chondrocytes embedded in the matrix
Postulated Mechanism of Action

- Disruption of the cell membrane causing acute necrosis

- Slow down mitochondrial respiration by disrupting the mitochondrial transmembrane potential

- Delayed cell death through alteration in mitochondrial DNA leading to apoptosis
Rho-kinase (ROCK) activation is required for bleb formation of the cell membrane.

Lidocaine induces ROCK-dependent membrane blebbing and therefore is cytotoxic at clinically relevant concentrations.

Cartilage in healthy young patients may be more susceptible due to neutral pH that increases the amount of non-ionic lidocaine.

Pre-treatment with ROCK inhibitors may have a protective effect.
The In Vitro Chondrotoxicity of Single-Dose Local Anesthetics

Jason L. Dragoo,*† MD, Hillary J. Braun,† BA, Hyeon Joo Kim,† PhD, Huy D. Phan,† BS, and S. Raymond Golish,† MD, PhD

Investigation performed at the Department of Orthopaedic Surgery, Stanford University, Palo Alto, California

- Evaluated administration of single dose 1% lidocaine, 0.25% bupivacaine, 0.5% ropivacaine
- In vitro culture/bioreactor study
Human chondrocytes were incubated with different concentrations of bupivacaine, s-ketamine, morphine, dexamethasone for 1 hour.

Morphine and dexamethasone did not induce chondrotoxicity.

Dose dependent chondrotoxicity was observed for bupivacaine.

Significant apoptosis observed with s-ketamine.
56 patients with frozen shoulder treated with 1.5 injections LA (1% lidocaine or 0.5% Marcaine) + 80mg depomedrol

- Mean followup 54 months
- Good clinical outcomes
- No radiographic evidence of chondrolysis
- These findings do not support the cessation of corticosteroid-analgesic injections for frozen shoulder
In Vivo Effects of Single Intra-Articular Injection of 0.5% Bupivacaine on Articular Cartilage

By Constance R. Chu, MD, Christian H. Coyle, PhD, Charleen T. Chu, MD, PhD, Michal Szczodry, MD, Venkat Seshadri, MD, John C. Karpie, MD, Kristina M. Cieslak, and Elise K. Pringle, BS

Investigation performed at the Department of Orthopaedic Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania

- **48 Sprague-dawley rats**
- **3 groups: NS, 0.5% bupivacaine, 0.6 mg/mL monoiodoacetate**
- **No difference with B on gross and histological examination**
- **No difference in superficial chondrocyte viability**
- **However, quantitative histological analysis of the bupivacaine-treated knees at six months revealed up to 50% reduction in chondrocyte density compared with that of control**
- **In the MIA group, despite severe histological damage early, no difference on gross inspection until 6 months**
- **In vivo effects of a single injection of IA B on articular cartilage are subtle**
- **Difficult to detect clinically**
Articular cartilage and local anaesthetic: A systematic review of the current literature

Abhinav Gulihar\textsuperscript{a}, Shibby Robati\textsuperscript{b,\ast}, Haider Twaij\textsuperscript{c}, Alan Salih\textsuperscript{b}, Grahame J.S. Taylor\textsuperscript{d}

\textsuperscript{a}Trauma and Orthopaedics, Dartford and Gravesham NHS Trust, UK
\textsuperscript{b}Trauma and Orthopaedics, East Sussex Hospitals, UK
\textsuperscript{c}St. Mary’s Hospital, London W2 1NY, UK
\textsuperscript{d}Leicester General Hospital, Leicester LE5 4PW, UK

Table 3 – Summary of the findings of this study.

1. Chondrolysis is a devastating complication of arthroscopic surgery especially in young patients. A large proportion requires further surgery and most will eventually undergo arthroplasty.
2. Intra-articular LA PPs have a high risk of chondrolysis and should be avoided.
3. There is minimal clinical evidence of chondrolysis resulting from a single injection of LA.
4. Laboratory studies have demonstrated that bupivacaine, lidocaine, ropivacaine and levobupivacaine are all toxic to cartilage.
5. No toxicity has been shown with mepivacaine but the effect of different concentrations has not been studied.
6. Increase in dose or exposure time increases toxicity.
7. Effect of pH combined with LA is unclear.
8. Effect of adrenaline remains inconclusive.
9. Effect of preservatives is unclear.
10. There is limited evidence on mechanism of toxicity but mitochondrial DNA damage or chemical incompatibility has been suggested.
11. Combining other compounds, such as MgSO\textsubscript{4}, may offer protection.
How will this affect my practice

- Do not use intra-articular pain pumps

- Post-operative local anesthesia only used for soft tissues (e.g. portals)

- Local anesthetic used with cortisone for frozen shoulder

- For IA cortisone injections, small volume of 0.25% bupivacaine used along with 40mg depomedrol.

- No repeat injections
So how do we manage patients with joint pain?

- Cortisone + local anesthetic
- Cortisone + normal saline
- PRP
- Other biologics?
Synovium and cartilage harvested from TKA patients and co-cultured with either PRP or HA media

- ELISA
  - TNF-a, IL-6, and IL-1b in the media

- RT-PCR
  - Synoviocytes: Hyaluronan synthase-2 (HAS2), MMP 1, MMP 13, and TNF-a gene expression
  - Cartilage: Collagen type 1, collagen type 2a1, aggrecan, MMP-13 expression
The Anti-inflammatory and Matrix Restorative Mechanisms of Platelet-Rich Plasma in Osteoarthritis

Emily A. Sundman, Brian J. Cole, Vasili Karas, Craig Della Valle, Mathew W. Tetreault, Hussni O. Mohammed and Lisa A. Fortier

DOI: 10.1177/0363546513507766

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**Enrollment**

N = 21 knees from patients undergoing TKA

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**Sample Preparation**

N = 21 PRP produced from 21 volunteers

For each sample knee:
- 13-14 cartilage explants
- 2.0 x 10^6 synoviocytes/cm² in 3 wells

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**Co-culture**

4 cartilage explants
Plated synoviocytes

4 cartilage explants
Plated synoviocytes

4 cartilage explants
Plated synoviocytes

---

**Treatment**

2.5 mL PRP
1.5 mL Media

2.5 mL HA
1.5 mL Media

4 mL Media

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**Analysis**

Cartilage RT-PCR
- 18s
- COL1A1
- COL2A1
- Aggrecan
- MMP-13

Synoviocyte RT-PCR
- 18s
- HAS-2
- MMP-1
- MMP-13
- TNF-α

ELISA
- IL-6
- IL-1β
- TNF-α
The Anti-inflammatory and Matrix Restorative Mechanisms of Platelet-Rich Plasma in Osteoarthritis

Emily A. Sundman, Brian J. Cole, Vasili Karas, Craig Della Valle, Mathew W. Tetreault, Hussni O. Mohammed and Lisa A. Fortier

DOI: 10.1177/0363546513507766

### TNF-α in “joint fluid”

- **Control**: A
- **ACP**: B
- **HA**: B

### HA in synoviocytes

- **Control**: B
- **ACP**: A
- **HA**: B

### MMP 13-in synoviocytes

- **Control**: A
- **ACP**: B
- **HA**: A
• **Media:**
  - TNF-α: decreased in PRP and HA vs controls
  - IL-6: decreased in HA vs PRP and control

• **Synoviocytes**
  - MMP-13 expression decreased in PRP vs HA and control
  - HAS-2 expression increased in PRP vs HA and control

• **No effect from platelet or WBC [ ] in PRP**
Conclusions

- Both HA and PRP decrease catabolism
  - Effect on TNFα decreases inflammation and is anti-nociceptive

- PRP also has the ability to increase endogeneous HA production and decrease MMP-13 gene expression
  - The latter suggested decreased cartilage matrix breakdown possible

- Hence, PRP has both anti-nociceptive and anti-inflammatory activities in osteoarthritis
Systematic Review


- Arthroscopy 2012
- Six level I and II studies
- N=577, mean age 56, followup 6 months

### Table 3. PRP Preparation Protocol

<table>
<thead>
<tr>
<th>Study</th>
<th>PRP System</th>
<th>No. of Centrifugations</th>
<th>Platelet (per mL)</th>
<th>WBC</th>
<th>Activator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerza et al.</td>
<td>ACP</td>
<td>Single</td>
<td>3-5 (10^6)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Filarido et al</td>
<td>Custom</td>
<td>Double</td>
<td>5× WB</td>
<td>1.2× WB</td>
<td>NR</td>
</tr>
<tr>
<td>Kon et al.</td>
<td>Custom</td>
<td>Double</td>
<td>&gt;6 (10^7)</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Spakova et al</td>
<td>Custom</td>
<td>Double</td>
<td>6.8 (10^6)</td>
<td>2.3 (10^7)</td>
<td>NR</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>Custom</td>
<td>Single</td>
<td>3.1 (10^6)</td>
<td>0</td>
<td>Yes</td>
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<tr>
<td>Li et al.</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**NOTE.** All reported activators were calcium chloride.

ACP, autologous conditioned plasma (Biocore: Arthrex, Karlsfeld, Germany); NR, not reported; WB, whole blood concentrations per injection; WBC, white blood cell.
Systematic Review


A WOMAC

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRP Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>SD</th>
<th>Total Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Cerza 2012</td>
<td>36.5</td>
<td>17.8</td>
<td>60</td>
<td>65.1</td>
<td>10.4</td>
<td>60</td>
<td>36.1%</td>
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<tr>
<td>Li 2011</td>
<td>10.7</td>
<td>9.9</td>
<td>15</td>
<td>20.6</td>
<td>8.3</td>
<td>15</td>
<td>25.1%</td>
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<tr>
<td>Patel 2013</td>
<td>30.1</td>
<td>25.9</td>
<td>50</td>
<td>53.1</td>
<td>17.9</td>
<td>46</td>
<td>22.9%</td>
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<tr>
<td>Spakova 2012</td>
<td>18.8</td>
<td>14.1</td>
<td>60</td>
<td>30.1</td>
<td>16.6</td>
<td>60</td>
<td>25.0%</td>
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<td></td>
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<td>105</td>
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</tbody>
</table>

Heterogeneity: Tau^2 = 87.37, Chi^2 = 58.33, df = 3 (P < 0.0001); I^2 = 89%

Test for overall effect: Z = 5.05 (P = 0.0001)

B IKDC

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PRP Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>SD</th>
<th>Total Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
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<tr>
<td>Pardo 2012</td>
<td>64.2</td>
<td>16.4</td>
<td>50</td>
<td>61.2</td>
<td>15.1</td>
<td>50</td>
<td>38.0%</td>
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<tr>
<td>Kong 2011</td>
<td>64.3</td>
<td>17.7</td>
<td>50</td>
<td>52.6</td>
<td>15.0</td>
<td>50</td>
<td>36.2%</td>
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<tr>
<td>Li 2011</td>
<td>78.4</td>
<td>13.5</td>
<td>15</td>
<td>63.2</td>
<td>11.9</td>
<td>15</td>
<td>25.8%</td>
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<td></td>
<td></td>
<td></td>
<td>119</td>
<td></td>
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</tbody>
</table>

Heterogeneity: Tau^2 = 11.23, Chi^2 = 5.36, df = 2 (P = 0.04)  I^2 = 84%

Test for overall effect: Z = 2.46 (P = 0.04)

Table 7. AEs After Injection

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (No. of Injections)</th>
<th>No. of AEs</th>
<th>PRP</th>
<th>Control</th>
<th>PRP</th>
<th>Control</th>
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<tr>
<td>Cerza et al.17</td>
<td>240</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Kon et al.22</td>
<td>150</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kon et al.22</td>
<td>150</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Spakova et al.33</td>
<td>180</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Patel et al.37</td>
<td>50</td>
<td>19</td>
<td>0</td>
<td>19</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Li et al.42</td>
<td>45</td>
<td>31</td>
<td>30</td>
<td>31</td>
<td>30</td>
<td>31</td>
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<tr>
<td>Total</td>
<td>66.5</td>
<td>56</td>
<td>30</td>
<td>56</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>Percent (AE rate) (%)</td>
<td>45.8</td>
<td>8.4</td>
<td>3.8</td>
<td>45.8</td>
<td>8.4</td>
<td>3.8</td>
</tr>
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</table>

*Second control cohort (LMW HA).
Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review

Carlos J. Meheux, M.D., Patrick C. McCulloch, M.D., David M. Lintner, M.D., Kevin E. Varner, M.D., and Joshua D. Harris, M.D.

- Arthroscopy, 2016
- Level 1 evidence only
- Six studies, n=817 knees
- Mean age 60, ave f/u 38 weeks
- Improved change scores in PRP vs HA groups at three, six and twelve months
Table 4. Platelet-Rich Plasma (PRP) Preparation and Characteristics and Use of Ultrasound Guidance for Verification of Injection in Knee Joint

<table>
<thead>
<tr>
<th>Article</th>
<th>PRP Spinning Approach</th>
<th>Duration of Spin (Minutes)</th>
<th>Company</th>
<th>PRP Activator</th>
<th>PRP Volume Injected (mL)/No. of Injections</th>
<th>Platelet Concentration</th>
<th>White Blood Cell Count</th>
<th>PAW Classification</th>
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<tbody>
<tr>
<td>Cerza et al.</td>
<td>Single</td>
<td>NR</td>
<td>Biocore, Arthrex Inc, Karlsfeld, Germany</td>
<td>None</td>
<td>5.5/4</td>
<td>&gt;5× baseline</td>
<td>Low</td>
<td>P4-B</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>Double</td>
<td>6 and 15(^a)</td>
<td>NR</td>
<td>NR</td>
<td>8/3</td>
<td>5× baseline</td>
<td>1.2× baseline</td>
<td>P4-A</td>
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<tr>
<td>Sanchez et al.</td>
<td>Single</td>
<td>15</td>
<td>PGIMER</td>
<td>CaCl(_2)</td>
<td>8/1 and 2(^b)</td>
<td>&lt;5× baseline</td>
<td>0</td>
<td>P2-B/P3-B</td>
</tr>
<tr>
<td>Vaquerizo et al.</td>
<td>Single</td>
<td>8</td>
<td>BTI Biotechnology Institute, Vitoria, Spain</td>
<td>CaCl(_2)</td>
<td>8/3</td>
<td>&lt;5× baseline</td>
<td>Low</td>
<td>P2-B/P3-B</td>
</tr>
<tr>
<td>Raissadat et al.</td>
<td>Double</td>
<td>15 and 7(^a)</td>
<td>Arya Mabna Tashkis Corp.</td>
<td>None</td>
<td>4-6/2</td>
<td>5.2× and 4.8× baseline(^c)</td>
<td>780 and 808 cells/µL</td>
<td>P4-B</td>
</tr>
</tbody>
</table>

NOTE. No ultrasound guidance was used in any study.

NR, not recorded; PAW classification, classification system for PRP that looks at platelet concentration, activation method, and white blood cell count\(^5\); PGIMER, Department of Transfusion Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

\(^a\)Represents times for first and second centrifugation.

\(^b\)One group received one injection, and the other group received 2 injections.

\(^c\)Averages for first and second injections, respectively.
• 6 randomized trials
• 3 prospective cohort studies
• N=1055 patients, mean age 55
• LP-PRP resulted in improved WOMAC scores vs HA
• No difference between LR-PRP and HA
• Higher incidence of adverse reactions in PRP vs HA
Bone marrow concentrate and platelet-rich plasma differ in cell distribution and interleukin 1 receptor antagonist protein concentration

Jennifer M. Cassano¹ · John G. Kennedy² · Keir A. Ross² · Ethan J. Fraser² · Margaret B. Goodale¹ · Lisa A. Fortier¹

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Table 5 Summary of the defining characteristics of BMA, BMC-A, BMC-B, WB, and PRP

<table>
<thead>
<tr>
<th></th>
<th>BMA</th>
<th>BMC-A</th>
<th>BMC-B</th>
<th>WB</th>
<th>PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1ra</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>IL-1ra/IL-1β</td>
<td>−</td>
<td>++</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>MSC</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>TGF-β1, PDGF</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Il-1β, IL-8</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>
Does BMC make sense in OA?

IL-1Ra/IRAP/Orthokine
Summary

• There is clear evidence that a dose-dependent relationship between the use of the LA pain pumps and chondrotoxicity exists.

• The effect of single dose anesthetics on articular cartilage is less clear – effects are more likely subtle and difficult to diagnose.

• Use IA local anesthetics with sparingly and with caution.

• Strong case for alternative carriers or the use of biologics that demonstrate emerging positive clinical evidence.
Thank You