Bupivacaine vs. Ropivacaine:
Looking at the Chondrotoxic Effects of Intraarticular Anesthetics in Osteoarthritic Joints

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Introduction

Intraarticular injections of corticosteroids used in combination with local anesthetics are a commonly practiced therapy for osteoarthritis. Injections of corticosteroids and local anesthetics can alleviate pain and inflammation in an osteoarthritic joint. Bupivacaine is currently the most commonly used intraarticular local anesthetic due to its long duration of action. Recent experimental studies have suggested that bupivacaine may be toxic to articular cartilage. Ropivacaine, a newer local anesthetic agent, may be a promising alternative to bupivacaine for intraarticular injections.

Due to a current lack of definitive data, this review aims to compare experimental studies on the toxic effects of bupivacaine and ropivacaine on chondrocytes. Studies compared these two drugs in order to determine the best local anesthetic agent, the dose of that agent, and duration that would be least harmful to articular cartilage.

CLINICAL SCENARIO:

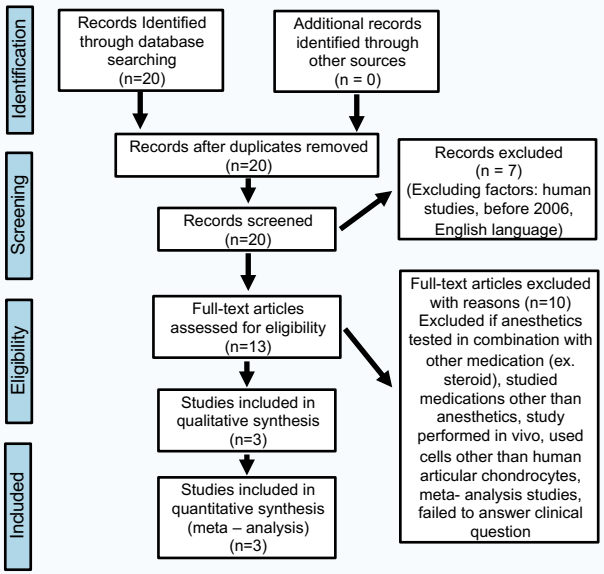
Mrs. OA is a 52 year old woman suffering from osteoarthritis of her right knee. The pain is described as constant and worsening. She has attempted weight loss, activity modifications, nonsteroidal anti-inflammatory drugs, acetaminophen, and topical analgesics but has experienced no relief of symptoms. The orthopedist discusses combined corticosteroid and anesthetic intraarticular injections with Mrs. OA as a next step option. The orthopedist recently heard about potential toxic effects of local anesthetics on chondrocytes. He wants to know which anesthetic and concentration has the least chondrotoxic effects in order to prevent further damage to Mrs. OA's knee.

Clinical Question

In 40 to 65 year olds with osteoarthritic joint pain, what are the toxic effects of bupivacaine as compared to ropivacaine on chondrocytes?

Methods

Prisma Flow Diagram



Results

Study 1. The Cytotoxicity of Bupivcaine, Ropivacaine, and Mepivacaine on Human Chondrocytes and Cartilage. *Breu et al.*
Objective: To assess the chondrotoxic effects of mepivacaine, ropivacaine, and bupivacaine.
Conclusion: Local anesthetic chondrotoxicity increases with drug type and concentration from ropivacaine to bupivacaine.
Study Critique: In vitro study performed with a small non specified sample size, location of articular cartilage used is not identified.

Study 2. Apoptosis and Mitochondrial Dysfunction in Human Chondrocytes Following Exposure to Lidocaine, Bupivacaine, and Ropivacaine. *Grishko, PhD et al.*
Objective: To investigate the effects of lidocaine, bupivacaine, and ropivacaine on human chondrocyte viability and mitochondrial function in vitro and to characterize the type of cell death elicited following exposure.
Conclusion: Bupivacaine and ropivacaine are chondrotoxic to human cartilage through the induction of cell apoptosis.
Study Critique: In vitro study performed with a small non specified sample size.

Study 3. Comparison of Ropivacaine and Bupivacaine Toxicity in Human Articular Cartilage. *Piper et al.*
Objective: To determine whether 0.5% bupivacaine is chondrotoxic to human articular cartilage and whether 0.5% ropivacaine is a less toxic alternative.
Conclusion: 0.5% bupivacaine is more chondrotoxic than 0.5% ropivacaine.
Study Critique: In vitro study performed with a small non specified sample size, intact cartilage samples were used, only measured the effects of one concentration and at only one time interval, and used obscured data in tables.

Table 1. Comparison of Subjects, Methods, and Significant Findings

	Breu, et al. (Study 1)	Grishko, et al. (Study 2)	Piper, et al. (Study 3)
In vivo or in vitro	In vitro	In vitro	In vitro
Number of patients	4	N/A	5
Patient population	42-62 year olds	53 +/- 16 years old	N/A
OA or intact cartilage	OA	OA	Intact
Bone used	N/A	Femoral condyles and tibial plateaus	3 from femoral head 2 from tibial plateau
Drug concentrations	1 mL Bupivacaine 0.03125%, 0.0625%, 0.125%, 0.25%, 0.5% 1 mL Ropivacaine 0.03125%, 0.0625%, 0.125%, 0.25%, 0.5%, 0.75%	Bupivacaine 0.5%, 0.25% Ropivacaine 0.5%, 0.2%	200 µL 0.5% Bupivacaine 200 µL 0.5% Ropivacaine
Exposure Time	1 hour	1 hour	30 minutes
Control	Saline	Saline	Saline
Statistical Significance	P < 0.01	P < 0.05	P < 0.05
Flow Cytometry	At 24 hours and 96 hours: • Concentrations < 0.75% ropivacaine and 0.25% bupivacaine showed no cytotoxic effects • 0.75% ropivacaine > 0.5% bupivacaine in cell viability • Significant cytotoxicity seen after 24 and 96 hours with bupivacaine and 96 hours with ropivacaine	At 24 hours: • Detectable but not significant decrease in cell viability with 0.5% bupivacaine • No decrease with 0.25% bupivacaine and 0.5% and 0.2% ropivacaine At 120 hours: • Only 0.2% ropivacaine did not have significant decrease in cell viability	N/A
LIVE/DEAD cell staining	At 24 hours: • Bupivacaine > ropivacaine in chondrotoxicity • Cell viability was higher in equipotent concentrations of ropivacaine vs. bupivacaine	N/A	At 24 hours: • 0.5% ropivacaine > 0.5% bupivacaine in cell viability • No significant difference in viability b/w ropivacaine and normal saline
Caspase activity	0.5% bupivacaine > 0.75% ropivacaine in cell apoptotic fragments	Increase in caspase 3 and caspase 9 cleavage demonstrated apoptosis	N/A
Cell Titer-Glo Luminescent Cell Viability Assay	N/A	N/A	At 24 hours: • 0.5% ropivacaine > 0.5% bupicacaine in cell viability • Normal saline > bupivacaine and ropivacaine in cell viability

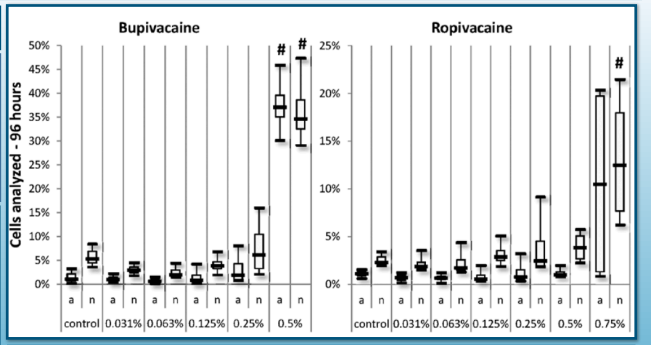


Figure 1. Dose-response curves of different concentrations of bupivacaine and ropivacaine. Chondrocyte apoptosis (A) and necrosis (N) were measured using flow cytometry at a time interval of 96 hours after a 1-hour exposure. Significant chondrotoxicity is seen with 0.5% bupivacaine and 0.75% ropivacaine, increasing from ropivacaine to bupivacaine.

Conclusion

In conclusion, all three studies revealed that both ropivacaine and bupivacaine are toxic to chondrocytes in a time dependent, drug dependent, and concentration dependent manner. The collective results show that concentrations less than 0.75% ropivacaine and concentrations of 0.25% bupivacaine or less have fewer chondrotoxic effects on osteoarthritic cartilage. These results further indicate that chondrotoxicity increases from ropivacaine to bupivacaine.

FUTURE STUDIES:

In order to further define the clinical relevance of these findings, an in vivo experiment would be necessary in order to observe the toxic effects of bupivacaine and ropivacaine on human articular cartilage directly and to better represent the pharmacokinetics of the agents. Future studies should also focus on comparing several equipotent concentrations of ropivacaine and bupivacaine and measuring the effects for longer durations.

CLINICAL APPLICATION:

The clinical impact of these results remains unclear. In regards to our clinical scenario, the results of these studies have failed to answer the question: which local anesthetic agent and concentration is the least toxic to chondrocytes? The results did however demonstrate that certain thresholds of both ropivacaine and bupivacaine show statistically significant toxic effects to chondrocytes. This is an important revelation that clinicians should be wary of when choosing an anesthetic and which concentration to use. We recommend that orthopedists should use the lowest possible concentration of bupivacaine or ropivacaine to reach therapeutic levels until further studies are performed.

References

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3. Samantha L. Piper, Hubert T. Kim. Comparison of Ropivacaine and Bupivacaine Toxicity in Human Articular Chondrocytes. J Bone Joint Surg Am. 2008; 90 (5) 986-991. Accessed Oct 26, 2016. DOI: 10.2106/JBJS.G.01033

We would like to acknowledge Dr. Erika Kancler, Ryan Chico PA-C, Carolyn Schubert, and the JMU Communication Center for their time and assistance with this research project.