Chondrotoxicity: Which Local Anesthetics are Safest for Intraarticular Injection?

Eric K. Holder, MD[1]; George Christolias, MD[2]; Mathew Saffarian, DO[3]; Jaymin Patel, MD[4]; and Zachary L. McCormick, MD[5] on behalf of the Spine Intervention Society's Patient Safety Committee

[1]Yale University School of Medicine, Department of Orthopedics and Rehabilitation, New Haven, Connecticut, U.S.;
[2]Columbia University Medical Center, Rehabilitation and Regenerative Medicine, New York, New York, U.S.;
[3]Michigan State University, Department of Physical Medicine and Rehabilitation, East Lansing, Michigan, U.S.;
[4]Emory University, Department of Orthopaedics, Atlanta, Georgia, U.S.;
[5]University of Utah School of Medicine, Department of Physical Medicine & Rehabilitation, Salt Lake City, Utah, U.S.

Myth: All local anesthetics are equally chondrotoxic to joints.

Fact: There are drug-, concentration-, and time-dependent chondrotoxic effects that vary between local anesthetics. Current evidence related to commonly used local anesthetics indicates that with exposure to equivalent volumes, bupivacaine, at concentrations of 0.5% or higher, is the most chondrotoxic agent, while ropivacaine, at concentrations equal to or less than 0.5%, is the least chondrotoxic *in vitro*. There is minimal published evidence that confirms these findings *in vivo*.

Background

Intraarticular injection(s) of amide-type local anesthetics are performed in clinical practice without or with corticosteroids for potential diagnostic and/or therapeutic purposes. Presently, there are many local anesthetic agents available, each of which varies with regard to onset of action, half-life, duration of action, and potential cytotoxic effects on articular chondrocytes [1-3]. *In vitro* studies demonstrate similar findings regarding the chondrotoxic profiles of local amide-type anesthetics; however, *in vivo* analysis of the effects of single-dose, non-continuous administration of amide-type local anesthetics without corticosteroid on human chondrocytes remains limited [1-14]. While there are several *in vitro* studies that have found single-dose, non-continuous administration of local anesthetics to be chondrotoxic, these injections remain quite common in clinical practice without a comparable quantity of available literature confirming these effects in vivo. Consequently, there are no consensus guidelines recommending an anesthetic of choice for intraarticular use.

Uniformly, *in vitro* studies addressing the potential chondrotoxic effects of single dose, non-continuous injections of amide-type local anesthetics indicate a spectrum of chondrotoxic effects that are drug-, concentration- and time-dependent [1-14]. Time dependence refers to the duration of exposure and/or time after exposure, whereby longer timeframes are associated with decreased cellular viability. The proposed underlying mechanisms for anesthetic chondrotoxicity include increased cellular apoptosis, cartilage necrosis, mitochondrial dysfunction, extracellular matrix damage and decreased DNA-normalized glycosaminoglycan expression [5,7,9,10]. Macrophages lack access to articular cartilage; thus, the remnants of necrotic and apoptotic destruction remain and can predispose to further tissue degeneration [2]. Likewise, it has been demonstrated *in vitro* that chondrocyte death occurs more rapidly in osteoarthritic cartilage compared to intact, healthy cartilage after local anesthetic exposure [2].

Chondrotoxicity of Commonly Used Local Anesthetics

There are several papers that link chondrolysis in both human and animal joints to continuous pain pump infusion of local amide-type anesthetics [15-20]. Literature was evaluated with a specific focus on studies assessing the potential chondrotoxic effects of intraarticular injection of local amide-type anesthetics on human articular chondrocytes. Studies demonstrate a time- and concentration-dependent chondrotoxic effect with all local anesthetics; however, the threshold concentration associated with a cytotoxic effect is variable. Numerous *in vitro* studies have demonstrated that administration of equipotent dosages of local anesthetics have differing deleterious effects on chondrocyte viability [1-14].

Bupivacaine
Based on the collective literature, bupivacaine appears to be the most chondrotoxic local anesthetic in clinical use [1-4,6,8-10]. Studies consistently demonstrate that bupivacaine at concentrations of 0.5% or higher results in the greatest degree of chondrocyte death when compared to equipotent doses of alternative amide-type local anesthetics. At concentrations less than 0.5% bupivacaine, the literature is conflicting. Two studies both found that in vitro, bupivacaine at a concentration of 0.25% did not result in a significant difference in cartilage cell death when compared with a control media (P>0.01; P=0.856 respectively) [2, 5]. While alternatively other *in vitro* studies found that chondrocytes exposed to 0.25% bupivacaine show increased cell death when compared to control agents [4,6,7].

Studies assessing bupivacaine consistently demonstrate a time-dependent decrease in human chondrocyte viability after 0.5% bupivacaine exposure. One study exposed chondrocytes *in vitro* to 0.5% bupivacaine for 1 hour. Compared with saline controls, at 24 hours after exposure, viability declined to 63% +/- 8% (P<0.0001) and to 26% +/- 9% at 96 hours post exposure (P<0.0001) [2]. With the use *in vitro* time-lapsed chondrocyte imaging other investigators found that exposure to 0.5% bupivacaine resulted in cell viability of 41% after 15 minutes, 4% after 30 minutes and no living chondrocytes after 60 minutes (P<0.05) [4]. Similarly, two additional studies determined *in vitro* that there is a significant time-dependent marked decline in chondrocyte viability with exposure to 0.5% bupivacaine [6,10].

Lidocaine
There are concentration and time-dependent chondrotoxic effects of lidocaine when evaluating concentrations ranging from 0.5% to 2% [5,7, 9-12]. Investigators in one study determined that a single dose administration of 1% lidocaine resulted in significantly more *in vitro* chondrotoxicity when compared with control media (7.9% +/-0.7% vs. 2.9% +/-0.4% respectively; P<0.001) [5]. Another study performed an *in vitro* analysis of chondrocyte culture viability after a single dose 1-hour exposure to varying concentrations of lidocaine, ranging from 0.5% to 2%. The authors demonstrated that 2% lidocaine caused "massive" chondrocyte necrosis 24 hours after exposure, while 1% lidocaine caused a detectable but insignificant (P>0.05) decrease in cell viability at 24 hours. At 120 hours post treatment, all concentrations of lidocaine, 0.5% to 2%, resulted in significantly decreased cell viability (P<0.05), overall demonstrating a dose- and time-dependent decrease in cell viability [7].

Separate analysis of chondrocytes exposed *in vitro* to 1% and 2% lidocaine with and without epinephrine for 15, 30 and 60 minutes illustrated that the longer the duration of exposure to any of the lidocaine containing solutions, the greater the number of non-viable cells at 7 days after exposure [12]. Regardless of the time frame of exposure, at 7 days nearly all of the cells were dead after exposure to 2% lidocaine and all values were statistically lower than the saline group (P=0.019, 0.028, 0.032). Fifteen, thirty- and sixty-minute exposure to 1% lidocaine without epinephrine resulted in 49%, 60% and 94% non-viable cells at day 7 respectively. In this study 1% lidocaine with epinephrine appeared to be the least toxic, however, there is conflicting literature regarding the effects of epinephrine on chondrocyte viability [12,14].

Ropivacaine (as Compared to Bupivacaine & Lidocaine)
In vitro assessment found ropivacaine significantly less chondrotoxic than bupivacaine (P=0.0006), and that exposure to ropivacaine at concentrations less than 0.75% did not result in significant toxic effects on human cartilage explants [2]. This is consistent with another *in vitro* study that found only 0.75% ropivacaine resulted in a reduced cell viability while lower doses did not significantly influence cell viability [6]. Furthermore, both studies demonstrated that 0.5% bupivacaine appeared to be more toxic than 0.75% ropivacaine [2,6].

A separate study found that 0.2% and 0.5% ropivacaine did not result in significant chondrotoxic effects at 24 or 72 hours after exposure. At 120 hours post exposure, 0.5% ropivacaine did result in a significant reduction in cell viability (P<0.05). However, although not directly compared, 0.5% bupivacaine and 1% lidocaine appeared to result in a greater loss of viable chondrocytes [7].

Other investigations reported no effect of 0.5% ropivacaine on human cartilage explants compared with saline (94.4% +/-9.0% vs. 95.8% +/- 5.7%; P=0.06). However, they did observe a reduction in viability of cultured chondrocytes. Chondrocyte viability after 0.5% ropivacaine exposure was significantly greater than after exposure to 0.5% bupivacaine for both cartilage explants (94.4% +/-9.0% vs. 78% +/-12.6%; p=0.0004) and cultured chondrocytes (63.9% +/-19% vs. 37.4% +/-12%; p<0.0001) [8].

SIS APRIL 2022
DOWNLOADED FROM SPINEINTERVENTION.ORG/FACTFINDERS

Other studies demonstrate a similar pattern of findings when comparing ropivacaine to bupivacaine or lidocaine. One such study found that human chondrocytes exposed to 0.5% ropivacaine were more likely to undergo cell death compared to exposure to normal saline but less than with 0.5% bupivacaine [10]. Another found that 0.75% ropivacaine exposure resulted in greater chondrocyte death compared to saline control as well as 1% lidocaine, but less cell death than 0.5 % bupivacaine exposure [9]. Other investigators determined that when compared with controls, 0.5% ropivacaine showed no significant (P>0.05) chondrotoxic effects after a 12-hour exposure to monolayer cultured chondrocytes (P=.084), as opposed to 3-hour exposure to 1% lidocaine (P<0.001), which resulted in significant chondrotoxicity [5].

Thus, based on collective literature, in vitro, ropivacaine demonstrates concentration- and time-dependent chondrotoxicity, most pronounced at concentrations equal to or greater than 0.75% [1,2,6]. Ropivacaine at concentrations of 0.5% or less demonstrates less chondrotoxicity than bupivacaine or lidocaine [1,2,5-10].

Chondrotoxicity of Less Commonly Utilized Local Anesthetics

Mepivacaine
Assessment of mepivacaine on cultured human chondrocytes, determined that there are significant dose-dependent toxic effects [2]. Specifically, a significant reduction (P<0.01) in cell viability was noted at concentrations of 1% or greater, while lower concentrations did not demonstrate significant toxic effects. The authors determined that in an escalating order, chondrotoxicity worsened from ropivacaine to mepivacaine to bupivacaine [2].

Levobupivacaine
One study found that *in vitro* that after 1 hour of exposure, 0.5% levobupivacaine is significantly more chondrotoxic than saline controls (25.9%+/-14.1 vs. 9.6%+/-5.4; P=0.04) [13]. Furthermore, 0.5% levobupivacaine was found to be more chondrotoxic than 0.5% bupivacaine.

There does not appear to be any substantive literature regarding the potential chondrotoxic implications of the remaining less commonly utilized amide type local anesthetics (see Table 1 below).

Local Anesthetic with Corticosteroid

In clinical practice, local anesthetics are commonly mixed with corticosteroid. Rapid onset of relief from the anesthetic may provide immediate diagnostic feedback. Corticosteroid may be added to provide therapeutic benefit. Notably, *in vitro* studies have demonstrated that the combination of corticosteroid with either bupivacaine, lidocaine or ropivacaine results in a greater trend towards cellular apoptosis and necrosis than when compared to saline controls or local anesthetic alone [9,11]. Furthermore, the utility of intraarticular corticosteroid injections has been called into question as there is mounting evidence that serial injections have deleterious effects on the course of cartilage deterioration, and there is conflicting evidence regarding their benefit [21-23]. To our knowledge, there are no studies that have analyzed the chondrotoxic effects of combining corticosteroid with mepivacaine or levobupivacaine [1].

Effects of Epinephrine, Preservatives, and pH on Local Anesthetic Chondrotoxicity

Due to the potent vasoconstrictive property of epinephrine, it increases the local duration of action of the anesthetic and thus is favored by some practitioners. The preservative sodium metabisulfite is often included in epinephrine-containing local anesthetics to prevent loss of bioactivity while in storage, instead of the more commonly used preservative methylparaben [14]. One study demonstrated that local anesthetics with epinephrine at low pH results in a significant loss of cell viability (P<0.001). Additionally, while their study did not demonstrate any significant decrease in chondrocyte viability with methylparaben after 24 hours of perfusion (P>0.05), it was determined that 0.5 mg/mL sodium metabisulfite is chondrotoxic (P<.034) [14]. Thus, the authors suggest the chondrotoxicity of local anesthetics containing epinephrine appears to be a result of the combined effects of the preservative sodium metabisulfite and low pH [14]. Other investigators also determined that epinephrine was toxic to chondrocytes and synovial cells [10.] However, there is conflicting literature regarding the chondrotoxic effects of epinephrine, with other study suggesting negligible or potential protective effects [1, 12]. Further research is needed.

SIS APRIL 2022

Discussion

It is important to note that most of the studies evaluating the chondrotoxicity of amide-type local anesthetics on human articular cartilage have been performed in vitro, and thus, the effects *in vivo* may not be directly translatable. The clearance ratio of the anesthetic and the specific time that the drug is acting at a fixed concentration within the joint is not known [2,13]. Furthermore, the variance in joint synovial fluid volume based on joint size and pathological state may result in dilutional effects that limit the applicability of studies assessing chondrotoxicity in vitro. However, based on current study observations, ropivacaine at concentrations equal to or less than 0.5% is preferred over lidocaine or bupivacaine for intraarticular use. *In vivo* studies are necessary to confirm these findings.

Ultimately, the utility and safety of any intraarticular injection of corticosteroid with or without local anesthetic is currently in question due to potential for accelerated osteoarthritis progression, subchondral insufficiency fracture, complications of osteonecrosis, and rapid joint destruction with bone loss [23]. Investigation is ongoing.

Conclusions

- Decrease in cartilage cellular viability with amide-type local anesthetic exposure is drug-, concentration-, and time-dependent in vitro.
- Ropivacaine at concentrations of 0.5% or less appears to be the least chondrotoxic in vitro.
- Bupivacaine at concentrations of 0.5% or higher appears to be the most chondrotoxic in vitro.
- Lidocaine has demonstrated significant chondrotoxicity, particularly at doses 1% or greater in vitro.
- The administration of corticosteroids in conjunction with local anesthetics appears to be more chondrotoxic than local anesthetic in isolation in vitro.
- There is conflicting literature regarding the potential chondrotoxic effects of epinephrine combined with local anesthetics on human chondrocytes in vitro; further investigation is needed.
- The evidence surrounding amide-type local anesthetic toxicity is primarily based on *in vitro* investigation and additional *in vivo* studies are necessary to confirm applicability to clinical medicine.

Table 1. [24]

Amide Type Local Anesthetics
Commonly Utilized
• Bupivacaine (Marcaine, Sensorcaine)
• Lidocaine (Xylocaine)
• Ropivacaine (Naropin)
Less Commonly Utilized
• Mepivacaine (Carbocaine)
• Levobupivacaine
• Dibucaine (Nupercainal)
• Articaine (Septocaine, Zorcaine)
• Etidocaine (Duranest)
• Prilocaine (Citanest)

References

1. Jayaram P, Kennedy DJ, Yeh P, Dragoo J. Chondrotoxic effects of local anesthetics on human knee articular cartilage: a systematic review. PM&R 2019;11:379-400.
2. Breu A, Rosenmeier K, Kujat R, Angele P, Zink W. The cytotoxicity of bupivacaine, ropivacaine, and mepivacaine on human chondrocytes and cartilage. Anesth Analg 2013;117:514-22.
3. Kreuz PC, Steinwachs M, Angele P. Single-dose local anesthetics exhibit a type-, dose-, and time-dependent chondrotoxic effect on chondrocytes and cartilage: a systematic review of the current literature. Knee Surg Sports Traumatol Arthrosc 2018;26:819-830.
4. Chu CR, Izzo NJ, Coyle CH, Papas NE, Logar A. The in vitro effects of bupivacaine on articular chondrocytes. J Bone Joint Surg Br 2008;90:814-20.
5. Dragoo JL, Braun HJ, Kim HJ, Phan HD, Golish SR. The in vitro chondrotoxicity of single-dose local anesthetics. Am J Sports Med 2012;40:794-9.
6. Ickert I, Herten M, Vogl M, Ziskoven C, Zilkens C, Krauspe R, Kircher J. Opioids as an alternative to amide-type local anaesthetics for intra-articular application. Knee Surg Sports Traumatol Arthrosc 2015;23:2674-81.
7. Grishko V, Xu M, Wilson G, Pearsall AW 4th. Apoptosis and mitochondrial dysfunction in human chondrocytes following exposure to lidocaine, bupivacaine, and ropivacaine. J Bone Joint Surg Am 2010;92:609-18.
8. Piper SL, Kim HT. Comparison of ropivacaine and bupivacaine toxicity in human articular chondrocytes. J Bone Joint Surg Am 2008;90:986-91.
9. Farkas B, Kvell K, Czömpöly T, Illés T, Bárdos T. Increased chondrocyte death after steroid and local anesthetic combination. Clin Orthop Relat Res 2010;468:3112-20.
10. Rao AJ, Johnston TR, Harris AH, Smith RL, Costouros JG. Inhibition of chondrocyte and synovial cell death after exposure to commonly used anesthetics: chondrocyte apoptosis after anesthetics. Am J Sports Med 2014;42:50-8.
11. Braun HJ, Wilcox-Fogel N, Kim HJ, Pouliot MA, Harris AH, Dragoo JL. The effect of local anesthetic and corticosteroid combinations on chondrocyte viability. Knee Surg Sports Traumatol Arthrosc 2012;20:1689-95.
12. Jacobs TF, Vansintjan PS, Roels N, Herregods SS, Verbruggen G, Herregods LL, Almqvist KF. The effect of lidocaine on the viability of cultivated mature human cartilage cells: an in vitro study. Knee Surg Sports Traumatol Arthrosc 2011;19:1206-13.
13. Cobo-Molinos J, Poncela-Garcia M, Marchal-Corrales JA, Delgado-Martinez AD. Effect of levobupivacaine on articular chondrocytes: an in-vitro investigation. Eur J Anaesthesiol 2014;31:635-9.
14. Dragoo JL, Korotkova T, Kim HJ, Jagadish A. Chondrotoxicity of low pH, epinephrine, and preservatives found in local anesthetics containing epinephrine. Am J Sports Med 2010;38:1154-9.
15. Anakwenze OA, Hosalkar H, Huffman GR. Case reports: two cases of glenohumeral chondrolysis after intraarticular pain pumps. Clin Orthop Relat Res 2010;468:2545-9.
16. Anderson SL, Buchko JZ, Taillon MR, Ernst MA. Chondrolysis of the glenohumeral joint after infusion of bupivacaine through an intra-articular pain pump catheter: a report of 18 cases. Arthroscopy 2010;26:451-61.
17. Bailie DS, Ellenbecker TS. Severe chondrolysis after shoulder arthroscopy: a case series. J Shoulder Elbow Surg 2009;18:742-7.
18. Gomoll AH, Kang RW, Williams JM, Bach BR, Cole BJ. Chondrolysis after continuous intra-articular bupivacaine infusion: an experimental model investigating chondrotoxicity in the rabbit shoulder. Arthroscopy 2006;22:813-9.
19. McNickle AG, L'Heureux DR, Provencher MT, Romeo AA, Cole BJ. Postsurgical glenohumeral arthritis in young adults. Am J Sports Med 2009;37:1784-91.
20. Noyes FR, Fleckenstein CM, Barber-Westin SD. The development of postoperative knee chondrolysis after intra-articular pain pump infusion of an anesthetic medication: a series of twenty-one cases. J Bone Joint Surg Am 2012;94:1448-57.
21. McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, Ward RJ. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA 2017;317:1967-1975.
22. Zeng C, Lane NE, Hunter DJ, Wei J, Choi HK, McAlindon TE, Li H, Lu N, Lei G, Zhang Y. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2019;27:855-862.
23. Kompel AJ, Roemer FW, Murakami AM, Diaz LE, Crema MD, Guermazi A. Intra-articular corticosteroid injections in the hip and knee: perhaps not as safe as we thought? Radiology 2019;293:656-663.
24. Hsu D. Subcutaneous Infiltration of Local Anesthetics. In: Post TW, ed. UpToDate. 2022. https://www.uptodate.com/contents/subcutaneous-infiltration-of-local-anesthetics (Accessed February 16, 2022)