Editorial Commentary: Periarticular and Intra-Articular Injections May Do the Right Thing for Patients' Pain but May Be the Wrong Thing for Their Articular Cartilage: Be Careful

Stephen Edward Lemos, M.D., Ph.D.

Abstract: Periarticular and intra-articular injections are regularly used by orthopaedic surgeons both in the clinic and operative setting. These injections include the use of local anesthetics, nonsteroidal anti-inflammatories, steroidal anti-inflammatories, and other classes of pharmaceuticals. Local anesthetics can be injected alone or in conjunction with other pharmaceuticals to maximize pain control and to minimize narcotic use as part of a multimodal pain control algorithm. Use of intra-articular local anesthetics has been shown to improve postoperative pain scores and reduce intravenous and oral narcotic consumption and narcotic-related side effects, such as constipation, sedation, depression, respiratory depression, and long-term abuse potential. However, there have been reports of chondrolysis and other side effects from these injections. In general, it can be said that lidocaine is more chondrotoxic than bupivacaine and that methylprednisolone is more chondrotoxic when combined with either lidocaine or bupivacaine. Ropivacaine with steroid maybe less chondrotoxic, but this has yet to be established. It has been shown that ropivacaine with steroids may be toxic to chondrocytes as well as bovine tenocytes. In addition, it can be generalized that longer exposures, such as an indwelling, intra-articular catheter, are more chondrotoxic than shorter exposures, such as an intra-articular injection. Greater concentrations of lidocaine and bupivacaine (i.e., 1% vs 2% and 0.25% vs 0.5%, respectively) are more toxic to chondrocytes. Cellular morphine studies have resulted in conflicting reports of whether or not it is chondrotoxic. Both ketorolac and acetaminophen have been shown to decrease postoperative pain, but ketorolac also has been shown to be chondrotoxic in a human chondrocyte model. Doing the right thing for our patients' pain may be the wrong thing for their articular cartilage. Expansion of indications for these injections should be approached with caution.

See related article on page 1980

Intra-articular injections of analgesic drugs are regularly used for perioperative analgesia after arthroscopic and open surgery.[1,2] Local anesthetics can be injected alone or in conjunction with other pharmaceuticals to maximize pain control and to minimize narcotic use as part of a multimodal pain control algorithm. Use of intra-articular local anesthetics has been shown to improve postoperative pain scores and reduce intravenous and oral narcotic consumption and narcotic-related side effects, such as constipation, sedation, depression, respiratory depression, and long-term abuse potential.[3-6] Chondrocyte dysfunction and death are key characteristics of early osteoarthritis. Case reports and basic science research studies have demonstrated lidocaine, bupivacaine, and other local anesthetics with and without epinephrine, various exposure times, and concentrations of exposure to be chondrotoxic alone or in combination with other pharmaceuticals.[7] Early evidence of the local anesthetic chondrotoxicity produced by bupivacaine prompted further investigation into the long-term sequelae of exposure to intra-articular local anesthetics.[8,9] In general, it can be said that lidocaine is more chondrotoxic than bupivacaine and that methylprednisolone is more chondrotoxic when combined with either lidocaine or bupivacaine. Ropivacaine with steroids maybe less chondrotoxic, but this has yet to be established. It has been shown that ropivacaine with steroids may be toxic to chondrocytes as well as bovine tenocytes.[10,11] In

Wayne State University School of Medicine.

The author reports the following potential conflicts of interest or sources of funding: leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Executive Board of Directors, Michigan Orthopaedic Society; and other financial or nonfinancial interests: President/Chair, Detroit Sports Medicine Foundation, and Course Director, Detroit Sports Medicine Symposium. Full ICMJE author disclosure forms are available for this article online, as supplementary material.

0749-8063/22279/$36.00

https://doi.org/10.1016/j.arthro.2022.03.003

addition, it can be generalized that longer exposures, such as an indwelling, intra-articular catheter, are more chondrotoxic than shorter exposures, such as an intra-articular injection. Greater concentrations of lidocaine and bupivacaine (i.e., 1% vs 2% and 0.25% vs 0.5%, respectively) are more toxic to chondrocytes. It is clinically important to explore the potential toxicity of exposing healthy articular cartilage to local anesthetics. The potentiating effects of combining drugs in so-called "cocktails" are important to study. Together in various combinations, pharmaceuticals can be less toxic or more toxic to chondrocytes such as the increase toxicity seen when methylprednisolone and lidocaine are combined. In the study by Baumann, Stoker, Bozynski, Sherman, and Cook, "An Injectable Containing Morphine, Ropivacaine, Epinephrine, and Ketorolac is Not Cytotoxic to Articular Cartilage Explants from Degenerative Knees,"[12] the authors combined morphine, ropivacaine, epinephrine, and ketorolac and compared the "Orthococktail" with a saline control. They found no negative effects on chondrocytes. Practitioners should be wary of expanding this application to other indications such as continuous infusion or assuming individually these agents are safe.

Chu et al.[13] investigated the chondrotoxicity of bupivacaine with a series of studies exploring the local anesthetic effects on articular chondrocyte viability, function, and integrity in an alginate culture model. Their findings showed that normal human articular knee cartilage in alginate bead culture had dose- and time-dependent chondrotoxic responses to bupivacaine exposure. Other intra-articular anesthetics include morphine, which has been shown to contribute to decreased pain postmeniscectomy, other procedures, and in vitro.[14-17] However, cellular morphine studies have resulted in conflicting reports of whether or not it is chondrotoxic.[8,18,19] Both ketorolac and acetaminophen have been shown to decrease postoperative pain, but ketorolac also has been shown to be chondrotoxic in a human chondrocyte model.[20-22] Primary cultures of human cartilage cells were used as a cellular model to evaluate and compare the cytotoxic effects of Duramorph (preservative-free morphine; Hikma Pharmaceuticals), ketorolac, bupivacaine, and acetaminophen. Cooke et al.[23] explored the chondrotoxic potential of 4 intra-articular injections that are used in clinical and surgical practice. Their data demonstrated that Duramorph is less toxic to chondrocytes compared with the commonly used bupivacaine. Furthermore, in their study, ketorolac did not show any significant increase in cell death nor apoptotic gene expression, and thus should be safe for intra-articular use. Acetaminophen expresses a marker of apoptosis, but it did not show increased cell death. Acetaminophen should be used with caution, and further study is warranted.

Other studies have investigated bupivacaine's effect on chondrocyte viability. The authors felt in their study that it was important to compare relatively untested agents with other agents that demonstrated chondrotoxicity. Piper et al. showed that exposure to bupivacaine in vitro was significantly toxic to human articular chondrocytes both in full-thickness cartilage explants and cultured chondrocytes after a 30-minute exposure. Bupivacaine also has been shown to be toxic to cell types other than chondrocytes.[19,24] Haasters et al.[18] obtained pluripotent stem cells from hamstring tendon samples during anterior cruciate ligament reconstruction and found that exposure to local anesthetics (bupivacaine) significantly reduced cell viability and metabolism while significantly increasing the induction of apoptosis compared with morphine and saline controls. Thus, bupivacaine was included in Cooke et al.'s study. It is important for orthopaedic surgeons and others not to expand the use of this pharmaceutical blend. It could be used periarticularly, but, with epinephrine and the large volume that is often injected with "orthococktails," could pose a danger if used superficially or in contained compartments. No long term intra-articular infusion should be attempted with this mixture despite the results of the short-term exposure in this study.

References

1. Manuar MB, Majumdar S, Das A, et al. Pain relief after arthroscopic knee surgery: A comparison of intra-articular ropivacaine, fentanyl, and dexmedetomidine: A prospective, double-blinded, randomized controlled study. *Saudi J Anaesth* 2014;8:233-237.
2. Sun QB, Liu SD, Meng QJ, Qu HZ, Zhang Z. Single administration of intra-articular bupivacaine in arthroscopic knee surgery: A systematic review and meta-analysis. *BMC Musculoskelet Disord* 2015;16:21.
3. Macintyre PE, Huxtable CA, Flint SL, Dobbin MD. Costs and consequences: A review of discharge opioid prescribing for ongoing management of acute pain. *Anaesth Intensive Care* 2014;42:558-574.
4. Ayoglu H, Altunkaya H, Bayar A, Turan IO, Ozer Y, Ege A. The effect of intraarticular combinations of tramadol and ropivacaine with ketamine on postoperative pain after arthroscopic meniscectomy. *Arch Orthop Trauma Surg* 2008;130:307-312.
5. Stein CC. Analgesic effect of intraarticular morphine after arthroscopic knee surgery. *N Engl J Med* 1991;325:1123-1126.
6. Wang JJJ. Intraarticular triamcinolone acetonide for pain control after arthroscopic knee surgery. *Anesth Analg* 1998;87:1113-1116.
7. Petty DH, Jazrawi LM, Estrada LS, Andrews JR. Glenohumeral chondrolysis after shoulder arthroscopy: Case reports and review of the literature. *Am J Sports Med* 2004;32:509-515.

8. Breu AA. The cytotoxicity of bupivacaine, ropivacaine, and mepivacaine on human chondrocytes and cartilage. *Anesth Analg* 2013;117:514-522.
9. Piper SL, Kim HT. Comparison of ropivacaine and bupivacaine toxicity in human articular chondrocytes. *J Bone Joint Surg* 2008;90:986-991.
10. Seshadri V, Coyle CH, Chu CR. Lidocaine potentiates the chondrotoxicity of methylprednisolone. *Arthroscopy* 2009;25:337-347.
11. Piper SL, Laron D, Manzano G, et al. A comparison of lidocaine, ropivacaine and dexamethasone toxicity on bovine tenocytes in culture. *J Bone Joint Surg Br* 2012;94:856-862.
12. Baumann JR, Stoker AM, Bozynski CC, Sherman SL, Cook. An injectable containing morphine, ropivacaine, epinephrine, and ketorolac is not cytotoxic to articular cartilage explants from degenerative knees. *Arthroscopy* 2022;38:1980-1995.
13. Chu CR, Coyle CH, Chu CT, et al. In vivo effects of single intra-articular injection of 0.5% bupivacaine on articular cartilage. *J Bone Joint Surg Am* 2010;92:599-608.
14. Arti H, Arti S. The effects of intraarticular opioids in pain relief after arthroscopic menisectomy: A randomized clinical trial study. *Pakistan J Med Sci* 2013;29:625-628.
15. Likar R, Kapral S, Steinkellner H, Stein C, Schäfer M. Dose-dependency of intra-articular morphine analgesia. *Br J Anaesth* 1999;83:241-244.
16. Rosseland LA, Stubhaug A, Skoglund A, Breivik H. Intra-articular morphine for pain relief after knee arthroscopy. *Acta Anaesth Scand* 1999;43:252-257.
17. Gupta AA. Postoperative pain following knee arthroscopy: The effects of intra-articular ketorolac and/or morphine. *Reg Anesth Pain Med* 1999;24:225-230.
18. Haasters F, Polzer H, Prall WC, et al. Bupivacaine, ropivacaine, and morphine: Comparison of toxicity on human hamstring-derived stem/progenitor cells. *Knee Surg Sports Traumatol Arthrosc* 2011;19:2138-2144.
19. Hatsukari II. Induction of apoptosis by morphine in human tumor cell lines in vitro. *Anticancer Res* 2007;27:857-864.
20. De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: A meta-analysis of randomized trials. *Anesth Analg* 2012;114:424-433.
21. De Oliveira GS Jr, Castro-Alves LJ, McCarthy RJ. Single-dose systemic acetaminophen to prevent postoperative pain: A meta-analysis of randomized controlled trials. *Clin J Pain* 2015;31:86-93.
22. Abrams GD, Chang W, Dragoo JL. In vitro chondrotoxicity of nonsteroidal anti-inflammatory drugs and opioid medications. *Am J Sports Med* 2017;45:3345-3350.
23. Cooke C, Osborne J, Jackson N, Keating P, Flynn J, Markel D, et al. Acetaminophen, bupivacaine, Duramorph and toradol: A comparison of chondrocyte viability and gene expression changes in osteoarthritic human chondrocytes. *Knee* 2020;27:1746-1752.
24. Breu A, Eckl S, Zink W, Kujat R, Angele P. Cytotoxicity of local anesthetics on human mesenchymal stem cells in-vitro. *Arthroscopy* 2013;29:1676-1684.