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"I would have everie man write what he knowes and no more."–Montaigne

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Editorial

Intra-articular bupivacaine: potentially chondrotoxic?

The management of acute postoperative pain after orthopaedic surgery is a challenge for anaesthetists and surgeons. The administration of local anaesthetic drugs into the joint space, either by single injection or by continuous infusion, has become a well-recognized technique for postoperative analgesia, in particular after arthroscopic surgery. Bupivacaine is commonly used for intra-articular analgesia because of its long duration of action. Other local anaesthetics used for intra-articular analgesia include ropivacaine and lidocaine. Intra-articular use of these drugs has been widely regarded as safe, and adverse effects of local anaesthetic agents in the joint space have been reported only rarely. Peak plasma concentrations of bupivacaine are sufficiently low after intra-articular injection such that systemic toxicity is extremely unlikely.[1] However, overdose or inadvertent intravascular injection may result in central nervous system and cardiovascular toxicity.[2 3]

Despite their widespread use, the effects of intra-articular local anaesthetic agents on joint structures have not been fully elucidated. Early evidence from animal experiments suggested that bupivacaine acutely inhibits the synthesis of articular cartilage.[4] A later study found that intra-articular bupivacaine 0.5% resulted in articular cartilage inflammation and synovial membrane changes in rabbit knee joints.[5] However, clinical reports of postoperative chondrolysis of the shoulder joint[6–9] and ankle joint[10] after arthroscopic surgery, and the possible association with the use of intra-articular bupivacaine, have brought the safety of intra-articular local anaesthetics to the fore among orthopaedic surgeons.

Chondrolysis is a condition in which extensive loss of articular cartilage occurs over a relatively short period of time. After arthroscopic shoulder surgery, the consequences of postoperative glenohumeral chondrolysis are clearly devastating. The condition typically occurs in young athletes and effective treatment options are limited. The pain and reduced mobility associated with chondrolysis tend to progress to severe osteoarthritis, which may eventually require joint arthroplasty. The largest series of cases of post-arthroscopic glenohumeral chondrolysis (PAGCL) described 12 cases.[7] The authors state that the common factor in all cases was the postoperative administration of an intra-articular infusion of bupivacaine with epinephrine. In total, 27 cases of PAGCL have been reported, with 25 of these cases having received postoperative continuous intra-articular analgesia with bupivacaine.[7–9]

Recently, a number of experimental studies have suggested that local anaesthetics may damage articular cartilage. It has been shown that bupivacaine 0.5% is toxic to both bovine articular chondrocyte cultures and bovine articular osteochondral tissue.[11] The effect of bupivacaine on human cartilage has also been analysed. The effects of bupivacaine 0.5%, bupivacaine 0.25%, bupivacaine 0.125%, and saline 0.9% on bovine and human articular chondrocyte cultures were compared.[12] Both bupivacaine 0.5% and bupivacaine 0.25% displayed dose-dependent and time-dependent chondrotoxicity. The toxicity of bupivacaine 0.5% was more marked than bupivacaine 0.25% at all time points. The toxicity of both drugs increased as the duration of exposure increased (from 15 to 60 min) and as the time after exposure increased (from 1 h to 1 week). The effect of bupivacaine 0.125% on bovine and human articular chondrocytes was no different from 0.9% saline. The effects of different concentrations of bupivacaine on bovine articular osteochondral tissue were also compared. Again, both bupivacaine 0.5% and bupivacaine 0.25% demonstrated dose-dependent chondrotoxicity. However, the effect of bupivacaine 0.125% was not different from 0.9% saline.

Although less profound than the effects of bupivacaine, lidocaine 1% and lidocaine 2% also exhibit dose-dependent and time-dependent toxic effects on bovine articular chondrocytes.[13] Ropivacaine is the third local anaesthetic to be associated with chrondrotoxicity.[14] The effects of bupivacaine 0.5% and ropivacaine 0.5% on both human articular chondrocyte cultures and human articular

cartilage explants were compared. Although ropivacaine 0.5% was toxic to chondrocyte cultures, it was significantly less toxic than bupivacaine 0.5%. On exposure of cartilage explants to both local anaesthetic agents, the effect of ropivacaine 0.5% was no different from that of 0.9% saline, whereas bupivacaine 0.5% did demonstrate chondrotoxicity.

Other studies have tested the effects of continuous administration of local anaesthetic agents on intra-articular structures. In an experimental animal model, the 48 h intra-articular infusion of bupivacaine 0.25%, both with and without epinephrine, resulted in significant histopathological and metabolic changes in rabbit shoulder joints after 1 week.[15] However, using the same model, no significant histopathological changes were found 3 months after the 48 h intra-articular infusion of bupivacaine, both with and without epinephrine.[16] Metabolic effects consistent with increased articular cartilage synthesis, which may represent a reparative process, could, however, be demonstrated.

Another study investigated the *in vitro* effects of the 72 h administration of lidocaine 1%, bupivacaine 0.25%, and bupivacaine 0.5%, each with and without epinephrine, on human articular chondrocyte cultures.[17] All of the local anaesthetic solutions containing epinephrine resulted in significant chondrocyte necrosis at 24, 48, and 72 h. None of the local anaesthetic solutions which did not contain epinephrine caused chondrocyte necrosis at 24 h. However, significant chondrocyte necrosis developed after 48 h exposure to lidocaine 1% and after 72 h exposure to bupivacaine 0.5%.

The pathogenesis and aetiology of postoperative chondrolysis are unclear and the clinical entity remains poorly understood. The condition is rare and only a small number of case series have been published. However, information about PAGCL is widely available in the public domain and a number of lawsuits have been filed in the USA against infusion device manufacturers for personal injury caused by the condition. In addition to local anaesthetics, other aetiological factors have been implicated in postoperative chondrolysis and the cause may be multifactorial. These factors include an exaggerated inflammatory response to bioabsorbable implants,[18] therapeutic use of thermal energy devices,[19] inadvertant intra-articular injection of methylmethacrylate bone cement,[20] accidental joint irrigation with chlorhexidine,[21] or pre-existing low-grade joint infection.[8] A further consideration in the aetiology of postoperative chondrolysis is the effect of intra-articular epinephrine. Local anaesthetic solutions administered into the joint space may or may not contain epinephrine. Evidence relating to the role of epinephrine in contributing to cartilage damage has yet to be elucidated. Similarly, the effect of preservative agents in local anaesthetic solutions on intra-articular surfaces needs to be defined.

Single intra-articular local anaesthetic injections are well established in clinical practice. In contrast, the technique of continuous intra-articular delivery of local anaesthetic using a 'pain pump' is a relatively new innovation that has become increasingly popular, particularly in North American practice. It is notable that adverse clinical effects appear to occur only after continuous intra-articular infusions of bupivacaine, but not after single injections.

A number of comments can be made with regard to the experimental studies when viewed in the light of the recent clinical reports and the emerging medico-legal ramifications. First, it should be noted that hyaline cartilage, which covers the articular surface of synovial joints, is an avascular tissue which is dependent on synovial fluid for its metabolic supply; intra-articular administration of any fluid may dilute, displace, or alter the composition of synovial fluid, thus compromising the nutritional supply to articular cartilage. Secondly, the potential chondrotoxic effects of intra-articular local anaesthetics in clinical practice may be quite different from the experimental effects. Clinical effects may be modified by multiple factors including the following: the protective effect of intact articular cartilage as opposed to chondrocytes or osteochondral tissue used in experimental studies, the pre-existing pathological state of the articular cartilage, local absorption of the drug into joint structures, dilution of the drug by synovial fluid and arthroscopic lavage fluid, and ongoing joint reparative processes.

In conclusion, the demonstration of dose-dependent and time-dependent human chondrotoxicity of local anaesthetics, particularly bupivacaine, suggests that prolonged, continuous intra-articular administration of higher concentrations of bupivacaine may result in adverse clinical effects, whereas a single injection of low-concentration bupivacaine appears to be safe. Further investigation should aim to elucidate the aetiology of PAGCL and provide clarity into the role, if any, of intra-articular local anaesthetics. Much larger case–control studies will be required to determine the possible causative factors involved in the condition. The putative benefits of continuous intra-articular local anaesthetic infusions, including better pain relief, improved mobilization, and shorter hospital stay, are worthy aims. However, novel techniques must not compromise patient safety. We should be prepared to modify our approach to drug usage in the light of new knowledge of adverse effects.

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References

1 Katz JA, Kaeding CS, Hill JR, Henthorn TK. The pharmacokinetics of bupivacaine when injected intra-articularly after knee arthroscopy. *Anesth Analg* 1988; **67**: 872–5

2 Sullivan SG, Abbott PJ. Cardiovascular toxicity associated with intraarticular bupivacaine. *Anesth Analg* 1994; **79**: 591–3

3 Ligouri GA, Chimento GF, Borow L, Figgie M. Possible bupivacaine toxicity after intraarticular injection for postarthroscopic analgesia of the knee: implications for the surgical procedure. *Anesth Analg* 2002; **94**: 1010–3

4 Nole R, Munson NM, Fulkerson JP. Bupivacaine and saline effects on articular cartilage. *Arthroscopy* 1985; **1**: 123–7

5 Dogan N, Erdem AF, Erman Z, Kizilkaya M. The effects of bupivacaine and neostigimine on articular cartilage and synovium in the rabbit knee joint. *J Int Med Res* 2004; **32**: 513–9

6 Petty DH, Jazrawi LM, Estrada LS, Andrews JR. Glenonhumeral chrondrolysis after shoulder arthroscopy: case reports and review of the literature. *Am J Sports Med* 2004; **32**: 509–15

7 Hansen BP, Beck CL, Beck EP, Townsley RW. Postarthroscopic glenohumeral chondrolysis. *Am J Sports Med* 2007; **35**: 1628–34

8 Levy JC, Virani NA, Frankle MA, Cuff D, Pupello DR, Hamelin JA. Young patients with shoulder chondrolysis following arthroscopic shoulder surgery treated with total shoulder arthroplasty. *J Shoulder Elbow Surg* 2008; **17**: 380–8

9 Greis PE, Legrand A, Burks RT. Bilateral shoulder chondrolysis following arthroscopy. A report of two cases. *J Bone Joint Surg Am* 2008; **90**: 1338–44

10 Bojescul JA, Wilson G, Taylor DC. Idiopathic chondrolysis of the ankle. *Arthroscopy* 2005; **21**: 224–7

11 Chu CR, Izzo NJ, Papas NE, Fu H. In vitro exposure to bupivacaine 0.5% is cytotoxic to bovine articular chondrocytes. *Arthroscopy* 2006; **22**: 693–9

12 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

13 Karpie JC, Chu CR. Lidocaine exhibits dose- and time-dependent cytotoxic effects on bovine articular chondrocytes in vitro. *Am J Sports Med* 2007; **35**: 1622–7

14 Piper SL, Kim HT. Comparison of ropivacaine and bupivacaine toxicity in human articular chondrocytes. *J Bone Joint Surg Am* 2008; **90**: 986–91

15 Gommoll AH, Kang RW, Williams JM, Bach BR, Cole BJ. Chondrolysis after continuous intra-articular bupivicaine infusion: an experimental model investigating chondrotoxicity in the rabbit shoulder. *Arthroscopy* 2006; **22**: 813–9

16 Gommoll AH, Yanke AB, Kang RW, *et al*. Long-term effects of bupivacaine on cartilage in a rabbit shoulder model. *Am J Sports Med* 2009; **37**: 72–7

17 Dragoo JL, Korotkova T, Kanwar R, Wood B. The effect of local anesthetics administered via pain pump on chondrocyte viability. *Am J Sports Med* 2008; **36**: 1484–8

18 Athwal GS, Shridharani SM, O'Driscoll SW. Osteolysis and arthropathy of the shoulder after use of bioabsorbable knotless suture anchors. A report of four cases. *J Bone Joint Surg Am* 2006; **88**: 1840–45

19 Levine WN, Clark AM Jr, D'Alessandro DF, Yamaguchi K. Chondrolysis following arthroscopic thermal capsulorrhaphy to treat shoulder instability. A report of two cases. *J Bone Joint Surg Am* 2005; **87**: 616–21

20 Leclair A, Gangi A, Lacaze F, *et al*. Rapid chondrolysis after intra-articular leak of bone cement in treatment of a benign acetabular subchondral cyst: an unusual complication of percutaneous injection of acrylic cement. *Skeletal Radiol* 2000; **29**: 275–8

21 Douw CM, Bulstra SK, Vandenbroucke J, Geesink RG, Vermeulen A. Clinical and pathological changes in the knee after accidental chlorhexidine irrigation during arthroscopy: case report and review of the literature. *J Bone Joint Surg Br* 1998; **80**: 437–40