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Anesthetic Risks
FactFinder

Committed to providing helpful information to our members about key patient safety issues, the International Spine Intervention Society's Patient Safety Committee has developed a FactFinder series. FactFinders will explore and debunk myths surrounding patient safety issues. The intent of this FactFinder is to discuss allergy, systemic toxicity, and chondrotoxicity related to use of local anesthetics in interventional spine procedures.

Myth #1: Allergy to local anesthetics precludes their use for spinal procedures.

Fact: There are two classes of local anesthetics, amides and esters. Amides are primarily metabolized in the liver and excreted in urine. Common examples of amides are: lidocaine ropivacaine, bupivacaine, mepivacaine, and prilocaine. Esters are extensively and rapidly metabolized by plasma pseudocholinesterase and hydrolysis leads to para-aminobenzoic acid (PABA), which may cause allergic reaction specific to this class of anesthetics. Common examples of esters include: novocain, tenzocaine, tetracaine, and piperocaine. If a person has had an allergy to an ester anesthetic it does not necessarily correlate to their likelihood to react to an amide anesthetic. [1]

Myth #2: All anesthetics have the same systemic toxicity.

Fact: All anesthetics have known central nervous system (CNS) and cardiac toxicity. In the CNS, they initially cause uneasiness, metallic taste, tremors, tinnitus, and shivering. Higher doses may result in convulsions. Cardiac effects are even more life threatening. All anesthetics cause depressed cardiac conduction (AV block) and contractility. Bupivacaine is particularly cardiotoxic. Compared to lidocaine, it is 16 times more arrythmogenic due to QRS prolongation. Its cardiac effects usually precede neurologic signs and cardiovascular resuscitation is difficult due to its sustained effect. A recommended maximum dosage for bupivacaine is 150mg (or 2mg/kg body weight);[2] however, inadvertent intravascular injection and patient factors could reduce the accepted threshold for toxicity. The s-enantiomer of bupivacaine, ropivacaine, is less cardiotoxic.[3,4]

Myth #3: Anesthetics have minimal side effects other than their potential for systemic toxicity.

Fact: Anesthetics have hematologic, neural, and chondrocyte effects. More recently, the evidence of anesthetic chondrotoxicity has been more widely published.

Anesthetics are also myotoxic and inhibit fibroblasts.[5] Even in the epidural space,

anesthetics can inhibit platelets, fibrinolysis, and leukocyte function. Evidence has shown that they decrease granulocyte migration and metabolic activation at surgical sites.[6] Important to interventional pain physicians, neural toxicity of anesthetics is well documented, and is known to be dose-dependent. Although large scale surveys attest to the overall safety of spinal anesthetics,[7] direct neural or thecal injection of anesthetics can result in serious injury.

Chondrotoxicity has been more recently studied, especially in the orthopedic literature. Case reports of postarthroscopic glenohumeral chondrolysis ignited interest in chondrotoxicity of anesthetics. The clinical cases of chondrolysis have been described after pain pump infusion with bupivacaine. One case demonstrated unilateral chondrolysis after two identical shoulder arthroscopic surgeries in the same patient. Both shoulders were treated with pain pump infusion, but one pump had failed. Only the shoulder with the functioning pump resulted in chondrolysis 9 months post-operatively.[8] Though current clinical evidence suggests that there is greater risk of chondrolysis with longer exposures to higher concentrations of local anesthetics, such as with an intra-articular pain pump, the majority of clinical studies are case reports or retrospective reviews and a causal relationship has not been proven.

There is a paucity of clinical literature investigating long-term clinical outcomes after intra-articular injection in humans. Several groups, however, have found that local anesthetics are cytotoxic to animal and human articular chondrocytes *in vitro* and in animals *in vivo*.[9, 10]

In vitro animal studies have shown chondrocyte changes after a single anesthetic injection. Dogan *et al.* studied the effects of a single injection of 0.5% bupivacaine *in vivo* in rabbit knee joints at 24 hours, 48 hours, and 10 days after injection.[11] They included outcomes on inflammatory changes in articular cartilage, synovial membrane cell hyperplasia and hypertrophy, and inflammatory cell infiltration. They found that the knee joints exposed to bupivacaine had significantly worse outcomes at all time points compared to a normal saline control. This study suggests bupivacaine may be deleterious with intra-articular injection.

Chu *et al.* also studied the effect of injecting 0.5% bupivacaine into the stifle joints of rats *in vivo* and evaluated articular cartilage at longer follow-up of 1 week, 4 weeks, 12 weeks, and 6 months after injection.[10] There was a significant difference in cell density between the saline- and the bupivacaine-treated knees. There was not chondrolysis at 6 months after exposure, but the authors suggested that it could occur with longer follow-up.

In vitro studies have examined human cartilage exposed to various anesthetics. Study of cell viability 24 hours after 30-minute exposure to 0.5% ropivacaine showed that it was significantly less chondrotoxic than 0.5% bupivacaine in both the monolayer culture and intact cartilage explants.[12] In intact cartilage explants, there was no difference in chondrocyte viability between exposure to normal saline

control and 0.5% ropivacaine.

A more recent study evaluated 1% lidocaine in comparison to 0.25% bupivacaine and 0.5% ropivacaine in an *in vitro* human cartilage model. En bloc cartilage samples were exposed for the expected duration of anesthetic action (3, 6 and 12 hours respectively). Both 0.5% ropivacaine and 0.25% bupivacaine showed no significant change compared to control, while 1% lidocaine showed a significant decrease in chondrocyte viability.[9]

Based on *in vivo* and *in vitro* studies, local anesthetics have significant chondrotoxic effects even after a short exposure. Bupivacaine is the most widely studied and its s-enantiomer, ropivacaine, shows less evidence of chondrotoxicity. Though evidence is limited, lidocaine also shows significant chondrotoxicity. Overall, ropivacaine seems to be favored over other anesthetics for intra-articular injection; however, the long-term effects of local anesthetic chondrotoxicity on articular cartilage and the risk of development of osteoarthritis remain unclear. Clinicians should weigh the risk versus benefit of intra-articular anesthetic injection, and consider the choice of ropivacaine versus lower concentrations of other anesthetics.

References:

1. Eggleston ST, Lush LW. Understanding allergic reactions to local anesthetics. Ann. Pharmacother. 1996; 30:851-7.

2. Cox B, Durieux M, Marcus M. Toxicity of local anesthetics. Best Practice & Research Clinical Anaesthesiology. 2003;17:111-136.

3. Brown DL, Ransom DM, Hall JA, Leicht CH, Schroeder DR, Offord KP. Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. Anesth. Analg. 1995; 81:321-8.

4. Knudsen K, Beckman Suurkl JA, Leicht CH, Schroeder DR, Offord KP. Regional anesthesia and local anesthetic-cts of i.v infusions of ropivacaine, bupivacaine and placebo in volunteers. Br. J. Anaesth. 1997; 78:507-514.

5. Zink W, Graf BM. Local anesthetic myotoxicity. Reg. Anesth. Pain Med. 2004; 29:333-40.

6. Naguib M, Magboul MM, Samarkandi AH, Attia M. Adverse effects and drug interactions associated with local and regional anaesthesia. Drug Saf. Int. J. Med. Toxicol. Drug Exp. 1998; 18:221-250.

7. Hodgson PS, Neal JM, Pollock JE, Liu SS. The neurotoxicity of drugs given intrathecally (spinal). Anesth. Analg. 1999; 88:797-809.

8. Saltzman M, Mercer D, Bertelsen A, Warme W, Matsen F. Postsurgical chondrolysis of the shoulder. Orthopedics 2009; 32:215.

9. 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.

10. Chu CR, Coyle CH, Chu CT, *et al*. In vivo effects of single intra-articular injection of 05% bupivacaine on articular cartilage. J. Bone Joint Surg. Am. 2010; 92:599-608.

11. Dogan N, Erdem AF, Erman Z, Kizilkaya M. The effects of bupivacaine and neostigmine on articular cartilage and synovium in the rabbit knee joint. J. Int. Med. Res. 2004; 32:513–519.

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