The peri-operative use of intra-articular local anesthetics: A review

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Abstract: Acute and chronic pain are of major concern after orthopedic surgery. The increasing trend toward day case surgery induced the development of different techniques in postoperative pain control. One commonly used strategy in pain management after knee and shoulder joint surgery is the intra-articular (IA) use of local anesthetics (LA). Recent attention has been drawn to the possible toxicity on chondrocytes of local anesthetics. The aim of this manuscript is to evaluate and compare through literature review the existing evidence on the clinical use and possible adverse effects of intra-articular injection of local anesthetics peri-operatively.

Keywords: Local anesthetics; intra-articular; chondrolysis; continuous; efficacy.

INTRODUCTION

An increasing number of joint surgery procedures, mainly arthroscopic, are performed in an outpatient setting. A variety of techniques focused on decreasing postoperative pain have been developed. Pain is most severe the first two days after surgery, although persistent pain after arthroscopy may be significant (44). Multimodal analgesia, particularly essential after day case surgery, has become the gold standard for pain management (43, 47). The use of local anesthetics has gained increased attention and seems an attractive method because of simplicity, safety and low cost. Intra-articular instillation is routinely used by orthopaedic surgeons and is thought of to be a safe procedure. Pain pumps were developed for the continuous delivery of local anesthetic agents, commonly bupivacaine, into the affected joint (40, 2, 3). This infusion is generally continued for 48 hours after the procedure. However, despite widespread use, little consensus is available on if, which type, in which doses and following which surgical procedures (diagnostic, therapeutic), intra-articular local anesthetics provide clinically relevant postoperative pain relief. Furthermore, recent publications have hypothesized the use of local anesthetics as a cause of postarthroscopic chondrolysis (21, 18) and concerns have arisen about the possible chondrotoxicity of local anesthetics.

This review intends to summarize the available literature on intra-articular local anesthetics in terms of efficacy, clinical use, relative effectiveness compared to other analgesic procedures, side effects and possible toxicity.

MATERIALS AND METHODS

Reports of prospective RCT’s, reviews, case reports and overview articles were systematically sought. The search was performed using the MEDLINE database without language restriction, although only studies with abstracts in English could be retained. Search terms were “intra-articular”, “local anesthetic”, “efficacy”, “effectiveness”, “side effect”, “adverse effect”, “comparison”, “bupivacaine”, “ropivacaine”, “lidocaine”, “chondrotoxicity”, “chondrolysis”, “local toxicity”. There was no publication date limitation (last search july 2008). Additional reports were identified from reference lists of retrieved reports and review articles. Two correspondences were included in the search results. Authors were not contacted for original data. Additional drug information on...
bupivacaine was retained from the UpToDate® database.

RESULTS

Efficacy of intra-articular local anesthetics

The use of LA by single shot or continuous infusion is most extensively and almost exclusively used and studied in knee and shoulder surgery. The type of surgery is most often arthroscopic, only four trials handled open surgery (5, 26, 36, 39) and one trial studied both arthroscopy and open surgery (4). Of the discussed studies, 11 were conducted in shoulder surgery, 16 in knee surgery. The most studied local anesthetic was bupivacaine.

a. Open knee surgery

Browne et al. randomized 60 patients to receive either bupivacaine or saline IA after total knee arthroplasty. The authors found a non significant reduction in pain scores in the bupivacaine group (5). In a prospective RCT in 105 patients after knee arthroplasty, Mauerhan et al. found a modest short-term reduction in pain scores after single shot morphine and bupivacaine injection compared with saline, however with great variability in pain score data and questionable clinical significance (36). In a randomized study in 20 patients no significant improvement in pain was found with continuous IA infusion of bupivacaine versus saline after total knee arthroplasty (39). After open anterior cruciate ligament reconstruction, a significant decrease in Visual Analog Scale was found only on the day of surgery with single dose bupivacaine IA (26).

b. Single dose IA anesthetic in arthroscopy

Moniche et al. reviewed twenty double-blind randomized controlled trials of single dose IA bupivacaine compared with placebo or no treatment for the control of postoperative pain after arthroscopic knee surgery (38). In 12 studies an improved pain relief was shown; 8 studies failed to demonstrate a beneficial effect of bupivacaine. The authors concluded that there was only weak evidence for a reduction of postoperative pain with IA bupivacaine, albeit moderate and of short duration. Geutjens et al. reported a significant pain reduction with IA bupivacaine 0.5% in a RCT with 48 patients undergoing knee arthroscopy (17). This finding is consistent with that of Heard and Chirwa who demonstrated significant analgesia with IA bupivacaine 0.25% (7, 23).

When compared to prilocaine in a prospective placebo-controlled trial, IA bupivacaine resulted in lower mean pain scores after knee arthroscopy. However, there were no statistically significant differences in the oral intake of analgesics and the level of analgesia obtained between the IA anesthetics groups (1). Marret et al. found a significantly better analgesia with IA ropivacaine 0.75% compared to bupivacaine 0.5%, whereas no differences in VAS scores were documented between the bupivacaine and a control saline group (35). Levo-bupivacaine 0.5% IA was found to produce effective local analgesia during the first 24 postoperative hours in knee arthroscopy compared to lidocaine with adrenaline and lower concentrations of levo-bupivacaine (28). In this study however, the skin port sites were also infiltrated. Convery et al. evaluated three concentrations of ropivacaine (0.5%, 0.75% and 1%) and bupivacaine 0.5%. Both ropivacaine 100 mg and bupivacaine 100 mg produced effective analgesia after knee arthroscopy, and ropivacaine in a higher dose of 150 mg further reduced pain scores in the first postoperative hours (9).

Beaudet et al. found inferior immediate postoperative pain control after IA administration of bupivacaine, when compared to interscalene block after shoulder surgery. However, equal overall pain scores were noted the first 24 hours after surgery (4). Singelyn on the other hand demonstrated superior pain control with interscalene block with bupivacaine over IA bupivacaine after shoulder AS. Moreover, there was no difference between the IA LA group and the control group who received IV analgesics (48).

Goodwin suggested that LA, when given preoperatively, may provide better analgesia than when given at the end of the surgery (19).

c. Local anesthetics versus other analgesics IA

– Non steroidal anti-inflammatory agents :

In a RCT comparing bupivacaine 0.25%, tenoxicam 20 mg and placebo, no differences in pain scores were noted between the three groups. In the tenoxicam IA group a reduction in oral analgesic requirements was recorded (10).

– Morphine :

Several publications have evaluated the analgesic effects of IA morphine, compared to local anesthetics. There seems to be no consensus on
whether or not LA are more effective than morphine. 

Parker et al. found that continuous IA bupivacaine 0.25% infusion over 36 hours after ACL reconstruction compared to placebo (40). This was confirmed by Dauri and colleagues, who reported inferior analgesia with continuous IA bupivacaine compared to epidural analgesia or continuous femoral block after ACL reconstruction (11). Hoenecke et al. reported satisfactory analgesia with continuous bupivacaine infusion after ACL reconstruction (24).

In shoulder surgery, where most of the comparative studies with continuous IA LA have been published, data are conflicting. Both Savoie and Barber found bupivacaine infusion (0.25 and 0.5% respectively) to be superior to placebo during the first 48 hours after shoulder arthroscopy (45, 3). On the other hand, there was no significant difference between bupivacaine infiltration (both 0.25 and 0.5%) and placebo in a recent study after AS rotator cuff repair (2). When compared to continuous interscalene administration of LA for pain control after arthroscopic shoulder surgery, Ciccone and coworkers demonstrated superior pain control with interscalene analgesia (6), whereas Webb et al. could not find a difference in pain control between interscalene and IA analgesia (52). Klein et al. found both the interscalene infusion as well as the intra-articular infusion with ropivacaine to provide inadequate pain control for rotator cuff surgery in an ambulatory setting (31). In an inpatient population continuous interscalene block with ropivacaine was shown to result in better analgesia after rotator cuff repair than continuous subacromial infusion, but with an increased incidence of minor side effects (13). When techniques are combined (interscalene block + continuous IA infusion of ropivacaine), analgesia is improved after shoulder AS compared to single-injection IS block (32).

Side effects (other than chondrotoxicity)

Possible adverse reactions are mainly due to systemic toxicity after inadvertent intravascular injection. Most detrimental is the cardiovascular toxicity (most significant with bupivacaine) with hypotension, bradycardia and heart block and cardiac arrest. Other toxicity involves the central nervous system with dizziness, seizure, paralysis and paresthesia; the gastrointestinal system with nausea and vomitus and the respiratory system with hypoventilation (usually after subarachnoid injections). Finally, muscle weakness, blurred vision and allergic reactions are reported (51).

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In the reviewed literature the few side effects that were reported include: numbness (13), dizziness (31), paresthesia (4). However, follow-up was usually short (usually 48 hours to maximal 9 months).

Few case reports describe an adverse reaction after IA administration of LA. Sullivan and Abbott reported two cases of cardiovascular toxicity after administration of 150 mg and 75 mg of bupivacaine with epinephrine respectively. Both patients developed symptoms within minutes after injection. Symptoms were altered consciousness, EKG abnormalities, desaturation and hypertension. In one patient a serum bupivacaine level drawn 10 minutes after injection was within the toxic range (2-4 mcg/ml). Both patients were scheduled for knee AS after trauma. Liguori reported a similar case with cardiovascular toxicity after IA injection of 50 mg bupivacaine with 40 mg of methylprednisolone. In this case a microfracture technique was used to treat a full-thickness cartilage defect (33). The authors suggest that the type of surgery greatly influences the level of absorption of LA. A greater risk for absorption is expected in surgery involving more vascular structures and surgery with microfracture techniques. When fairly avascular structures, such as the meniscus, are being manipulated, risks are relatively low.

Several authors have examined the absorption of LA after IA injection. Meinig et al. (37) measured low serum levels of bupivacaine both after instillation of 75 mg and 150 mg intraarticularly without the use of a tourniquet. Katz et al. (30) examined the pharmacokinetics of an injection of 100 mg of bupivacaine intra articularly after AS, followed by tourniquet deflation 2-3 min later. Peak serum levels of bupivacaine occurred at 43 minutes post-tourniquet deflation and were less than 0.5 mcg/ml. Their results suggest that during prolonged duration of tourniquet ischemia may lead to more rapid absorption of bupivacaine due to enhanced postsischaemic reperfusion. A longer duration of tourniquet time after IA injection might allow for greater tissue binding and decreased serum peak levels. Slanki et al. (49) also found low serum levels after IA injection of 50 mg of bupivacaine. They suggested that injection after tourniquet inflation and adding epinephrine to the injectate reduce peak serum bupivacaine levels in an additive manor. Convery et al. (9) randomized patients to receive an IA injection of 100, 150 or 200 mg of ropivacaine or 100mg of bupivacaine 5 min before tourniquet deflation after knee arthroscopy. Serum levels of LA were measured up to 3 hours after injection and were found to be well below the threshold for systemic toxicity.

Hoef et al. (24) investigated serum levels of bupivacaine during continuous IA infusion of 0.25 and 0.5% bupivacaine at a rate of 4ml/h after knee arthroplasty. The study was halted because in one patient in the 0.5% group a bupivacaine concentration of 1.2 mcg/ml was registered. Although no adverse reactions occurred, previously reactions had been reported with concentrations as low as 1.1 mcg/ml.

One case report described a transient aphonia due to laryngeal nerve paralysis after IA injection of 20 ml 0.5% bupivacaine with epinephrine after shoulder arthroscopy (20), presumably because of diffusion of LA out of the articular cavity.

**Chondrotoxicity**

Hansen et al. (21) recently reported on a series of 10 patients (12 shoulders) with postarthroscopic glenohumeral chondrolysis diagnosed in a time frame of 19 months. As the authors had not experienced this complication before, specific changes in technique from prior patients treated by the surgeon were determined. Of the 177 shoulder arthroscopies performed in that time frame, 30 underwent AS stabilization. In this group, 19 shoulders had intra-articular pain catheters with bupivacaine and epinephrine. Of these, 12 had been identified with chondrolysis. The patients received a pre- and postoperative injection of 25 ml of 0.25% bupivacaine with epinephrine and 5 mg of morphine. Subsequently, a pain pump catheter was installed with 0.25% bupivacaine with epinephrine at a rate of 4.16 ml/h during 2 days. Patients developed symptoms of chondrolysis (new onset pain, stiffness, crepitus, increased pain with motion) within the first 3 to 12 months after surgery. Of the other 152 patients treated in the same time frame, another 104 patients were treated with the same pre- and postoperative injection and pain pump techniques, but with the catheter placed extra-articularly. None of these patients experienced chondrolysis.

Dragoo et al. (15) evaluated the in vitro chondrotoxicity of anesthetic formulations. They subjected freshly isolated human articular chondrocytes to a perfusion of either 1% lidocaine, 0.25% or 0.5% bupivacaine, all with or without epinephrine over a time period of 24-72 hours. A control group was perfused with growth media for comparison. Chondrocyte necrosis was assessed using fluorescent microscopy and histomorphometry. Strikingly, all cultures perfused with local anesthetics containing...
epinephrine showed a significant decrease in chondrocyte viability at all times. Cell death rates were comparable to controls in the lidocaine group at 24 hours and in the bupivacaine groups at 24 and 48 hours. The 0.5% bupivacaine group showed significant increased necrosis at 72 hours. In an animal study by Gomoll et al. (18), 30 rabbits were randomized to receive a continuous infusion in the glenohumeral joint with either saline, bupivacaine 0.25% or bupivacaine with epinephrine for 48 hours. Significant metabolic changes and reduction in cell viability was shown after infusion of bupivacaine with or without epinephrine. Also Dogan et al. (14) found significant histopathological changes with increased inflammation in rabbit knee joints after injection with bupivacaine 0.5%. Chu et al. (8) subjected bovine articular chondrocytes in alginate cultures to a bupivacaine 0.50% or a saline exposure for 15 to 60 minutes. Subsequently they treated bovine osteochondral cores with or without intact articular surface with either saline or bupivacaine and tested the cores on cell viability after 24 hours. The results showed a significant cytotoxicity of bupivacaine after only 15 to 30’ exposure. The intact articular surface had some chondroprotective effects.

The same research group did a comparable study on bovine chondrocytes and osteochondral cores, but with treatment with lidocaine 1 or 2% for 15 to 60’. The results show dose- and time-dependent cytotoxic effects of lidocaine. In this study the intact articular surface was not considered protective (29).

Piper et al. (41) evaluated the effect on cell viability of human articular cartilage harvested from the knee joint after a 30’ treatment with ropivacaine 0.5%, bupivacaine 0.5% or saline. Chondrocyte viability was significantly greater after treatment with ropivacaine as compared with bupivacaine. There was no difference between the ropivacaine and the saline groups.

**DISCUSSION**

As the technique of IA injection of local anesthetics is routinely being used in a peri-operative setting, extensive research on efficacy has been performed throughout the years. Most research has been conducted with bupivacaine as the LA for postoperative pain relief after arthroscopy. Despite years of experience and study, data on effectiveness are not uniformly conclusive.

After knee arthroplasty, single shot IA LA results in a modest improvement in analgesia in two studies. Continuous IA infusion with LA does not seem to produce acceptable pain relief. Single shot LA after anterior cruciate ligament reconstruction might be beneficial on the day of surgery only.

Concerning analgesia of a single shot LA after arthroscopy, data are conflicting. Overall, there seems to be a significant analgesic effect, but only for a short period of time (the first postoperative hours). Higher concentrations produce better analgesia. Bupivacaine seems to be more efficacious than prilocaine and is equipotent to levobupivacaine and ropivacaine. The latter products have a safer risk profile in terms of cardiovascular toxicity. When compared to IA morphine, data are again inconclusive. Both morphine and bupivacaine seem to be effective after AS. The combination of these products might be beneficial, but this is not confirmed by all groups. Morphine is believed to be more efficacious in high inflammatory surgery, while bupivacaine may be more suitable for low inflammatory surgery, as suggested by Marchal et al. This finding has yet to be confirmed and more research is warranted. Compared to peripheral nerve block (interscalene block), IA LA produces inferior analgesia, but with less side effects.

If the purpose of IA LA is to fit in a multimodal analgesia protocol mainly for an outpatient setting, one might expect that the patient has a satisfactory analgesia in the immediate postoperative period in the hospital, alleviating the need for other analgetics. However, the beneficial effects can be lost after discharge of the patient, leaving the patient with insufficient analgesia at home.

Single shot IA LA has mainly been thought of as safe with little side effects being reported. One has to bear in mind that follow up is usually limited to the first 48 postoperative hours and that to our knowledge no data exist on long term adverse effects. As discussed above, bupivacaine can be chondrotoxic after even short exposure times in vitro. The greatest known risk exists in inadvertent intravascular injection or absorption from the articular cavity of LA with systemic toxicity. The risk of systemic absorption might be dependent on the type of surgery and is highest in surgery of well vascularised articular structures. Tourniquet inflation seems to reduce absorption, however longer tourniquet ischaemia may lead to enhanced postschaemic reperfusion with enhanced systemic absorption.

When injected intramuscularly, LA have been shown to result in reversible myonecrosis. All LA seem to be myotoxic, but bupivacaine produces the most severe muscle injury. However, this is an uncommon side effect (53).
Recently, more attention has been drawn to the experimental model of continuous wound infiltration with local anesthetic in different types of surgery (e.g. abdominal surgery). This evolution has led to the development of techniques for continuous LA delivery after AS surgery. These have already been extensively used in an inpatient as well as an outpatient setting. Arthroscopic shoulder surgery seems particularly indicated for the use of continuous IA analgesia given the painful nature of the surgery. There is little evidence that continuous IA LA provides superior analgesia, when compared to placebo. Further more, other peripheral nerve block techniques such as interscalene block are superior to the IA technique for pain control. Great concern has arisen about the toxicity of prolonged exposure of joint chondral tissue to local anesthetics. Some case reports have postulated a causal relationship between the use of continuous IA pain pumps and the occurrence of postarthroscopic chondrolysis. This detrimental complication usually leads to invasive corrective surgery such as arthroplasty. Further research indeed revealed a significant in vitro chondrotoxicity of LA, even after exposures as short as 15 minutes. It is not clear whether the histopathological changes seen after these short exposures are transient in nature and whether they result in clinical significant chondropathy. There are precipitating factors for the chondrotoxicity of LA. Based on cell culture studies, the use of epinephrine in the injection may worsen the toxic effect due to vasoconstriction with ischaemia in an already marginally vascularized tissue, reduced clearance of LA or due to low pH of the injectate containing epinephrine. Higher concentrations result in higher toxicity. All cases of chondrolysis concern shoulder surgery. No case of chondrolysis after knee surgery has been linked to the use of a pain pump catheter. It is possible that the knee is less prone to chondrolysis because of a thicker cartilage or a larger intra-articular cavity with more rapid clearance of LA. In vitro, an intact articular surface has chondroprotective effects. This might imply that the risk for chondrolysis is greater in more extensive surgery (where morphine is more beneficial than bupivacaine for IA analgesia). Ropivacaine is less toxic than bupivacaine in one in vitro study, but this finding has yet to be confirmed.

CONCLUSION

The use of intra-articular local anesthetics as part of multimodal postoperative pain management has extensively been practiced and studied. However data on efficacy are inconclusive. Single shot injection is effective only for the first postoperative hours and up to date no major side effects are reported. Caution is warranted however, since local anesthetics have been shown to be chondrotoxic even after short exposure. This toxic effect may be worsened by the addition of epinephrine.

Continuous intra-articular infusion of local anesthetic has not been demonstrated to be an effective analgesic strategy after arthroscopy. Furthermore, there is a strong correlation with postoperative chondrolysis after shoulder surgery. We hence advise against the use of continuous intra-articular local anesthetics.

References