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Local Anesthetic Agents in Arthroscopy

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1. Introduction

Arthroscopy is performed with increasing frequency on a number of joints. In the lower limb the role of knee arthroscopy is well established with procedures enabling more accurate diagnosis and treatment of a myriad of conditions including but not being limited to meniscal injury and articular surface defects. Hip and ankle arthroscopy are less widely performed. However, despite this their use can be expected to increase as indications are better developed and techniques honed.

While surgical technique often determines outcome in the long-term, analgesic control can significantly affect the patient's satisfaction following a procedure as well as the overall acceptability of a procedure. Arthroscopic procedures in particular have enabled many procedures to be performed on a day case basis where as more traditional surgical interventions may have required at least an overnight hospital stay. This trend toward day case surgery also emphasizes the importance of optimum analgesic control.

Traditionally intra-articular analgesic agents have been used following arthroscopic procedures as an augment to post-operative pain control. Classically these include the typical local anesthetic agents but also alternatives such as morphine. Recently however, the potential for deleterious effects of the intra-articular analgesics on the articular cartilage has been reported in a number of experimental studies, which has caused concern among practicing arthroscopic surgeons. The purpose of this chapter is to review the potential intra-articular analgesic agents used for pain control following lower limb arthroscopy and to also provide an up-to-date review of the evidence for the potential chondrotoxic effect of these agents.

2. Analgesic agents

Classical local anesthetic agents can be classified into the esters and amides. Amides including lignocaine and bupivacaine among others have commonly been used in arthroscopy. Local anesthetics block action potential initiation and propagation along sensory pathways by blocking the sodium channel transmembrane pores. Their activity is increased in alkaline conditions and this enables them to penetrate the nerve sheath and axonal membrane.

Other agents to have been trialed as intra-articular agents include opiates or opiate related substances (e.g. morphine, tramadol), non-steroidal anti-inflammatory medications, benzodiazepines and NMDA-receptor antagonists (e.g. magnesium sulfate) among others.

2.1 Hip and ankle arthroscopy

Numerous studies have assessed the ability of local anesthetic agents to provide pain control following arthroscopic procedures in the lower limb. A vast majority of these have focused on the knee and only a few have reported the use of local anaesthetic following hip and ankle arthroscopy (Middleton et al., 2006, Baker et al., 2011c).

Of these two studies both found that intra-articular local anaesthetic was superior to either placebo or local anesthetic infiltrated around the arthroscopic portals (Table 1). The paucity of data here reflects the relative infancy of hip and ankle arthroscopy compared to knee arthroscopy and highlights the need for further work – hip arthroscopy in particular requires significant force to overcome the intra-articular negative pressures and can result in significant post-operative pain (Baker et al., 2011a).

| Author | Setting | Number | Key findings |
|--------------------------|---------|--------|---|
| (Baker et al., 2011c) | RCT | 73 | Intra-articular bupivacaine superior to peri-portal bupivacaine at controlling pain following HIP arthroscopy |
| (Middleton et al., 2006) | RCT | 35 | Intra-articular bupivacaine was superior to saline placebo in reducing post-operative VAS pain scores and need for supplemental analgesia following ANKLE arthroscopy |

Table 1. Studies assessing the benefit of intra-articular analgesic agents following hip and ankle arthroscopy

2.2 Knee arthroscopy

Numerous studies have attempted to establish the ideal intra-articular analgesic for pain control following knee arthroscopy (for a summary of these studies see Table 2). The studies selected for inclusion here predominantly include those that use an intra-articular analgesic following surgery in a bolus dose fashion. Some studies that use it prior to surgery are also included for comparison sake particularly where comparison is later made with a bolus given following surgery. This section focuses on intra-articular analgesia given as an augment following surgery performed under general anesthesia or spinal anesthesia.

Although many studies have found that classical local anesthetic agents are of benefit following knee arthroscopy a randomized controlled trial reported by Townsend et al noted that intra-articular bupivacaine was no more effective than bupivacaine infiltrated around the portal sites (Townsend et al., 2009). This equivalence takes on even more importance with the reported potential for the toxic effect on articular cartilage of bupivacaine and other similar agents.

In general local anesthetics have been shown to be effective compared to placebo although this is not necessarily the case if the surgery is performed under spinal anesthetic when it appears the additional use of an intra-articular agent is negated by the spinal block (Santanen et al., 2001).

Non-steroidal anti-inflammatory medications have been trialed as intra-articular agents but are not in wide spread use. A single study has found that tenoxicam was superior to bupivacaine following surgery but this was only with regards analgesic consumption – the reported pain scores were still similar (Cook et al., 1997). It was similarly found that lornoxicam resulted in lower pain scores than did bupivacaine in a randomized controlled trial of 40 patients (Fagan et al., 2003). The use of an anti-inflammatory into the joint cavity may play a role in pain control particularly when a significant inflammatory component to the intra-articular pathology is found (Izdes et al., 2003).

When compared to opiate type analgesics ropivacaine was shown in one study to provide quicker onset of analgesia but was not significantly better at 24 hours after surgery (Franceschi et al., 2001). The benefit of morphine as an intra-articular analgesic is questionable however as noted later and this perhaps reflects poorly on ropivacaine.

Combinations of amide local anesthetics with other agents have been tried and this may represent the optimum way to control pain although at this point in time it is unknown. A combination of magnesium sulfate and bupivacaine was shown to be superior to either agent in isolation, which were again superior to placebo with regard pain scores following knee arthroscopy (Elsharnouby et al., 2008). These findings are supported by another study that also included morphine in the intra-articular cocktail but again found that a combination of agents was superior to any of the agents given in isolation (Farouk and Aly, 2009). A combination of bupivacaine with fentanyl was shown to be superior to bupivacaine in isolation following knee arthroscopy in a randomized trial including 33 patients (Jawish et al., 1996). Despite these promising reports in combinations of an amide local anesthetic and an opiate type agent others have failed to find this multimodal approach any better than placebo alone (Aasbo et al., 1996). While pain intensity or pain scale score is a frequent measure in these studies, the actual need for additional analgesia is a limiting factor with regard the ability to perform a procedure as a day case or not and may reflect a more practical end-point for further research.

Despite a small number of studies suggesting that morphine provides adequate analgesic control following knee a recent review of these studies has suggested that of the higher quality studies, most had a negative finding not in favor of its use as an intra-articular analgesic agent (Rosseland, 2005, Drosos et al., 2002). The key point of this review was that post-operative pain intensity was no less in the morphine treated groups than the placebo treated groups in the well-designed studies. This review is supported by a study by the same author group that found only those with intense pain after arthroscopy had any benefit from intra-articular morphine (Rosseland et al., 1999).

Other agents have been studied in with some success including midazolam (increased the time to first analgesia after surgery compared to placebo), clonidine (additive effect with bupivacaine compared to bupivacaine alone) and neostigmine (more effective when compared to morphine) (Batra et al., 2008, Tamosiunas et al., 2005, Yang et al., 1998). Unfortunately these agents have been studied in a very limited capacity and a clear conclusion is unable to be drawn as their effectiveness.

| Author | Setting | Number | Key findings |
|----------------------------|---------|--------|---|
| (Aasbo et al., 1996) | RCT | 107 | Patients randomised to receive either: bupivacaine (20ml of 2.5mg/ml) + morphine (3mg); bupivacaine (20ml of 2.5mg/ml) alone; morphine (3mg) alone; or isotonic saline - no differences between the groups with regard analgesic requirement post-surgery |
| (Al-Metwalli et al., 2008) | RCT | 60 | Intra-articular dexmedetomidine (α -2-adrenergic agonist) given via the intra-articular route resulted in less post-operative pain and analgesic requirement than either dexmedetomidine given intravenously or intra-articulate and intravenous placebo (saline) |
| (Alagol et al., 2004) | RCT | 210 | Intra-articular tramadol at doses 50-100mg provided good post-operative analgesia with the higher dose more effective. The intra-articular route was more effective than the intravenous route. |
| (Batra et al., 2008) | RCT | 60 | Intra-articular midazolam (50 or 75 μ g/kg) provided superior, albeit briefly, analgesic control compared to saline placebo. Time to first analgesic requirement was 4.7 and 4.6 hours compared to 0.7. |

| Author | Setting | Number | Key findings |
|----------------------------|---------|--------|---|
| (Buerkle et al., 2000) | RCT | 60 | Patients given morphine (1mg) and clonidine (150µg) intra-articularly in combination had lower VAS pain scores at 2 hours post-surgery and lower need for rescue analgesia compared to groups given either agent in isolation or saline placebo |
| (Calmet et al., 2004) | RCT | 80 | Following arthroscopic meniscectomy, patients receiving intra-articular ketorolac (60mg) had better post-operative pain control and less need for rescue analgesia compared to those receiving 10ml of 0.25% bupivacaine , 1mg of morphine or normal saline placebo. |
| (Cepeda et al., 1997) | RCT | 112 | Intra-articular and subcuticular morphine (10mg) and intraarticular bupivacaine (20ml 0.5%) were compared with normal saline placebo. Single dose morphine by either route provided superior pain control with lower pain scores at 6- and 3-hours post-surgery. |
| (Colbert et al., 1999) | RCT | 88 | Patients receiving intra-articular tenoxicam had lower pain scores at 30-180 minutes post-surgery and required less analgesia later than those receiving the same drug intravenously. |
| (Convery et al., 1998) | RCT | 60 | Patients given 5mg ketorolac with 20ml of 0.25% bupivacaine into the joint after surgery provided similar analgesic control to 10mg ketorolac given intravenously with 20ml of 0.25% bupivacaine given into the joint. |
| (Cook et al., 1997) | RCT | 63 | Patients received either 40ml solution containing only normal saline, 0.25% bupivacaine or 20mg tenoxicam at the end of knee arthroscopy. Less analgesia was needed by the tenoxicam group but subjective pain reporting was similar in all groups. |
| (Dalsgaard et al., 1993) | RCT | 52 | Patients receiving 1mg of morphine intrarticularly at the end of surgery had lower pain scores at 8- and 24-hours after surgery and used less paracetamol compared to those receiving saline placebo. |
| (Drosos et al., 2002) | RCT | 30 | No significant difference seen in VAS pain scores between patients receiving intra-articular saline, 5mg morphine or 15mg morphine following diagnostic arthroscopy or arthroscopic meniscectomy. |
| (Elhakim et al., 1999) | RCT | 60 | Patients randomised to receive either saline placebo; 2% lidocaine and 10mg pethidine , or; 2% lidocaine , 10mg pethidine and 20mg tenoxicam . Combination of all three agents resulted in lower VAS pain scores for longer and less need for analgesic use. |
| (Elsharnouby et al., 2008) | RCT | 108 | Patients receiving 1g magnesium sulfate and 0.25% bupivacaine (20ml total) had significantly lower VAS pain scores and longer time to first analgesic use than those receiving either agent in isolation or placebo. |
| (Eren et al., 2008) | RCT | 90 | Patients receiving either 8mg lornoxiam or 50mg bupivacaine had less analgesic consumption after surgery than those receiving placebo. Pain ratings were lower for those receiving the lornoxiam than those receiving the bupivacaine. |
| (Fagan et al., 2003) | RCT | 40 | Patients receiving pre-emptive injection of bupivacaine with adrenaline showed a trend toward needing less analgesia in the recovery room than those receiving the injection at completion of surgery. |
| (Farouk and Aly, 2009) | RCT | 80 | A combination of magnesium (150mg) and morphine (2mg) with 20 ml of 0.25% bupivacaine provided superior analgesic control (lower VAS scores and longer time to first analgesic) than either agent alone with bupivacaine or bupivacaine alone. |

| Author | Setting | Number | Key findings |
|--|---------|--------|--|
| (Franceschi et al., 2001) | RCT | 90 | Ropivacaine (75mg in 20ml saline) had quicker onset of effective analgesia post-operatively than morphine (2mg in 20ml saline) with lower VAS pain scores in the first 4 hours and equivalent control in the first 24 hours. |
| (Goodwin et al., 2005, Goodwin and Parker, 2005) | RCT | 50 | Bupivacaine with epinephrine and morphine or bupivacaine with epinephrine alone given either pre- or post-operatively resulted in lower pain scores and narcotic consumption than with epinephrine alone. There was a trend toward superior control in those receiving the injection pre-operatively. |
| (Goodwin and Parker, 2005) | RCT | | Combinations of bupivacaine , morphine and epinephrine given pre- or post-surgery resulted in similar pain control. |
| (Grabowska-Gawel et al., 2003) | | 56 | Patients received either 10ml 0.5% bupivacaine or 5mg morphine in normal saline. Mean time to rescue analgesia was shorter in the bupivacaine group but there was no difference in reported VAS pain scores. |
| (Graham et al., 2000) | RCT | 36 | Intra-articular analgesia given at completion of arthroscopy was equivalent to pre-operative intravenous regional analgesia with respect to post-operative pain control |
| (Gupta et al., 1999) | RCT | 100 | Knee arthroscopy performed under LA (prilocaine (5mg/ml). Morphine (3mg), ketorolac (30mg) or a combination of the two was given at completion of surgery. A combination of morphine and ketorolac provided significantly superior analgesia than morphine alone or placebo. |
| (Hege-Scheuing et al., 1995) | RCT | 59 | Morphine (1mg) given either intra-articularly or intravenously at the end of arthroscopy had equivalent analgesic benefit. |
| (Izdes et al., 2003) | RCT | 90 | Patients receiving intra-articular piroxicam (20mg) and 25ml of 0.25% bupivacaine had longer analgesic duration in cases where synovial inflammation was confirmed present than when not present. |
| (Jacobson et al., 2006) | RCT | 120 | Levobupivacaine (5mg/ml) significantly reduced the need for analgesia in the first 24 hours post-surgery compared to levobupivacaine (2.5mg/ml) and lidocaine (10mg/ml) with adrenaline . |
| (Jaureguito et al., 1995) | RCT | | Knee arthroscopy [performed under LA. Patients receiving intra-articular morphine (4mg) had lower VAS pain scores than those receiving 0.25% bupivacaine or saline placebo. Less supplemental pain medication was needed by the morphine group. |
| (Jawish et al., 1996) | RCT | 33 | Patients receiving a combination of 0.25% bupivacaine with 50µg of fentanyl had reduced post-operative pain for at least 9 hours post-surgery when compared to patients receiving 0.25% bupivacaine alone or saline placebo. |
| (Joshi et al., 1992) | RCT | 20 | Patients receiving intra-articular morphine (5mg) following knee arthroscopy had lower VAS pain scores and needed less rescue analgesia than those receiving saline placebo. Low serum morphine metabolites suggested that the morphine was acting locally. |
| (Joshi et al., 1993) | RCT | 40 | Intra-articular morphine (5mg) either in isolation or in combination with 25ml of 0.25% bupivacaine resulted in significantly lower pain scores and need for supplementary analgesia than bupivacaine in isolation or saline placebo. |

| Author | Setting | Number | Key findings |
|---------------------------|---------|--------|--|
| (Juelsgaard et al., 1993) | RCT | 47 | There was no difference in reported VAS pain scores or acetaminophen use in the 48 hours after knee arthroscopy in patients receiving either 2 or 4mg of intra-articular morphine after surgery |
| (Kanbak et al., 1997) | RCT | | Patients receiving 5mg morphine intra-articularly after arthroscopy had superior pain control in the 24 hours after surgery compared to those receiving 1mg morphine or saline placebo. |
| (Karaman et al., 2009) | RCT | 40 | No significant difference was found in control of post-operative pain and analgesic requirement between patients receiving 20ml of 0.5% levobupivacaine and 20ml of 0.5% bupivacaine . |
| (Kligman et al., 2002) | RCT | 60 | Infiltration of morphine (1mg) into the synovial tissue or outer third of meniscal tissue resulted in better pain control (lower VAS pain scores and less analgesic use) post-arthroscopy than if morphine (1mg) was given by the intra-articular route. |
| (Lundin et al., 1998) | RCT | 50 | Intra-articular bupivacaine 0.25% (40ml) with the addition of morphine 1mg compared to bupivacaine alone. Lower VAS pain scores noted with the addition of morphine in the 24 hours after surgery but no difference in supplementary analgesic use. |
| (Niemi et al., 1994) | RCT | 80 | Patients underwent knee arthroscopy under either spinal or LA (1% lidocaine with adrenaline) blockade. Intra-articular morphine (1mg) given at the end of the procedure resulted in reduced rescue analgesia requirement in the group that had LA block. |
| (Pooni et al., 1999) | RCT | 107 | Patients randomized to receive either intra-articular bupivacaine or fantanyl after knee arthroscopy reported similar pain scores except at 2-hours post-surgery when bupivacaine was superior |
| (Raj et al., 2004) | RCT | 40 | Patients receiving 10mg morphine intra-articularly reported lower pain scores between 4- and 24-hours post-surgery and consumed less analgesia than patients receiving 10mg morphine via the intramuscular route. |
| (Rasmussen et al., 2002) | RCT | 60 | Patients randomized to receive either saline placebo; 150mg bupivacaine and 4mg morphine , or; 150mg bupivacaine , 4mg morphine and 40mg methylprednisolone intra-articularly at the end of surgery. Bupivacaine with morphine was effective at reducing pain and duration of immobilization, the addition of methylprednisolone further reduce pain and use of analgesics. |
| (Rautoma et al., 2000) | RCT | 200 | Pre-operative per oral diclofenac reduced post-operative pain scores compared to the intra-articular bupivacaine given at the time of surgery. Arthroscopy performed under spinal anaesthesia. |
| (Richardson et al., 1997) | RCT | | Intra-articular morphine (1mg) was superior to bupivacaine (100mg) at reducing pain scores and need for supplementary analgesia at 6- and 24-hours post-surgery. An intra-articular dose of 5mg morphine was more effective than 1mg intra-articular or 5mg intravenous at reducing VAS pain scores. |
| (Rosseland et al., 2004) | RCT | 60 | Intra-articular saline (1 or 10ml) was given following surgery via an intra-articular catheter in patients with at least moderate pain. Within 1 hour VAS pain scores reduced from 50 to 27 on a 100mm scale with both volumes. |
| (Rosseland et al., 2003) | RCT | 40 | Intra-articular saline (10ml) or morphine (2mg in 10ml saline) was given following surgery via an intra-articular catheter in patients with at least moderate pain. Equivalent improvements in pain intensity were found in both groups. |

| Author | Setting | Number | Key findings |
|-----------------------------|---------|--------|--|
| (Rosseland et al., 1999) | RCT | 90 | Only patients with more intense pain after arthroscopy had benefit from intra-articular morphine (2mg) with regard reduced pain intensity and analgesia requirement. In most patients morphine (1 or 2mg) was equivalent to saline placebo. |
| (Samoladas et al., 2006) | RCT | 60 | Patients received either 10 or 20ml of 7.5mg/ml ropivacaine . Both provided excellent pain control for two hours, however after that the lower dose group reported increased pain and need for supplementary analgesia. |
| (Santanen et al., 2001) | RCT | 100 | Knee arthroscopy performed under spinal anaesthesia. 20ml of 0.5% ropivacaine failed to reduce VAS pain scores or need for rescue analgesia when compared to saline control. |
| (Solheim et al., 2006) | RCT | 40 | Patients received intra-articular morphine (5mg) or saline placebo via intra-articular catheter 1 hour post-surgery if they developed at least moderate pain. Morphine was of no greater benefit than saline. Timing of catheter removal did not influence the outcome. |
| (Souza et al., 2002) | RCT | 60 | Patients receiving either saline placebo, 10ml 0.25% bupivacaine , 2mg morphine or 100µg fentanyl intra-articularly at the end of arthroscopy did not differ significantly in reported pain intensity. |
| (Tamosiunas et al., 2005) | RCT | 48 | Patients receiving 20ml of 0.5% bupivacaine with the addition of 1µg/kg of clonidine controlled post-operative pain more effectively than bupivacaine in isolation or placebo. |
| (Townshend et al., 2009) | RCT | 137 | Patients receiving 20ml of 0.5% bupivacaine either intra-articularly or infiltrated around the portals reported equivalent pain scores at 1-hour post-surgery. |
| (VanNess and Gittins, 1994) | RCT | 81 | Patients receiving intra-articular morphine (2mg) reported significantly less pain and lower analgesic requirements in the 24-hours after surgery than those receiving 30ml of 0.25% bupivacaine with epinephrine . |
| (Varrassi et al., 1999) | RCT | 48 | Intra-articular buprenorphine (100µg) and intra-articular bupivacaine (50mg) resulted in lower VAS pain scores in the 6-hours after surgery than intra-articular saline or intra-muscular buprenorphine. Analgesic use was less in those treated with intra-articular buprenorphine or bupivacaine . |
| (Vranken et al., 2001) | RCT | 60 | Sufentanil (5 or 10µg) given intra-articularly resulted in lower VAS pain scores than in control (intravenous sufentanil). Post-operative analgesic use was also lower in the treatment group. |
| (White et al., 1990) | RCT | | Patients treated with prilocaine with adenaline reported prolonged time to first dose of oral analgesia but overall there was no difference in pain scores. |
| (Yang et al., 1998) | RCT | 60 | Patients receiving intra-articular neostigmine (500µg) had lower VAS pain scores 1-hour after surgery and had longer lasting duration of analgesia compared to those receiving intra-articular morphine (2mg) or saline placebo. No significant effects were seen with neostigmine 125 or 250µg. |
| (Zeidan et al., 2008) | RCT | 90 | Intra-articular administration of tramadol (100mg) and 0.25% bupivacaine to 20ml volume had lower VAS scores, longer time to rescue analgesia and less analgesic use in the first 24-hours compared to when either agent was given in isolation. |

Table 2. Studies assessing the benefit of intra-articular analgesic agents following knee arthroscopy. Treatments are in bold.

In summary a myriad of agents have been studied for their potential use in attenuating post-operative pain following knee arthroscopy. While the amide local anesthetic agents are the most widely studied their continuing benefit and use is questionable as portal infiltration has been shown to be as effective at providing pain control for a procedure that is generally very well tolerated. Knee arthroscopy performed under local anesthetic is a different entity although far less frequent.

Hip and ankle arthroscopy are far less studied and the ideal intra-articular agent is uncertain in these joints. A multi-model intra-articular analgesic bolus may be the best approach in these joints that require significant traction and subsequent injury to the capsule that can cause greater discomfort after surgery.

2.3 The potential for articular chondrocyte toxicity

The potential for deleterious effects of local anesthetic agents on articular chondrocytes was increasingly noted with the use of arthroscopic pain pumps following glenohumeral arthroscopy (Busfield and Romero, 2009, Hansen et al., 2007, Solomon et al., 2009). Increasingly however studies are alerting the practicing clinician to the potential for toxic effects secondary to amide local anesthetics given as a single bolus injection. Most of these are laboratory-based studies. Although some have questioned the relevance given the long use of intra-articular local anesthetic without seemingly any complication they serve as a caution.

The aim of this section is to provide an overview of the basic science evidence on the potential for local anesthetic agents to cause articular chondrocyte toxicity.

2.3.1 In vitro reports

A number of different laboratory models utilizing cell lines from a variety of animal species have been used in the study of local anaesthetic toxicity. A toxic effect in canine chondrocytes exposed to bupivacaine 0.5% using a proven in vitro model by Anz et al. They reported an almost 100% reduction in cell viability after two days exposure to bupivacaine. Bupivacaine conferred an anti-inflammatory effect in their study, evidenced by reduced nitric oxide and PGE rise in the presence of interleukin-1, but their conclusion maintained that continuous exposure to bupivacaine resulted in a clear toxic effect toward the canine chondrocytes (Anz et al., 2009). Again using a canine osteochondral model the toxic effect of bupivacaine was again confirmed, with or without the addition of methylparaben (Hennig et al., 2010). Exposure to the local anaesthetic alone for 5 or 30 minutes caused significant cell death, although this was only significant statistically at the 30 minute exposure.

Miyazaki et al demonstrated a concentration dependent reduction in bovine chondrocyte viability after treatment with lidocaine (0.125, 0.25, 0.5 or 1%) (Miyazaki et al., 2011). Glycosaminoglycan (GAG) content of the cells was also noted to be reduced as the concentration of the local anaesthetic was increased. GAG and lactate production were higher in the cells treated with 0.5 and 1% lidocaine. The authors felt that this finding conferred a reparative response by the cells.

Using bovine articular chondrocytes in alginate bead cultures Karpie et al exposed these to 1 or 2% lidocaine for 15 to 60 minutes (Karpie and Chu, 2007). A dose and time dependent increase in cell toxicity was reported. An intact surface on the osteochondral core or variation in the pH of the treatments (pH 7.4, 7.0, 5.0) failed to confer any protective effect (this is in contrast to other studies – see below). Others have also reported time and concentration dependent reductions in cell viability using a bovine disc model (Lo et al., 2009). In this case osteochondral cores were harvested from the radiocarpal joint of cows and these were treated with either lidocaine (1%), bupivacaine (0.25%) or ropivacaine (0.5%).

The toxic effects of bupivacaine (0.125, 0.25 and 0.5%) on the the articular chondrocyte from a bovine cell line were well demonstrated (Chu et al., 2008). Cells were cultured in a 3-dimensional alginate-bead culture. Specimens were exposed for 15, 30 or 60 minutes and analysis was performed at 1 and 24 hours and at 1 week. A clear time and concentration dependent response to the local anaesthetic treatments was observed. Treatment with 0.125% bupivacaine for 15 minutes was not significantly different to the saline control. Almost complete loss of cell viability was noted with 0.5% bupivacaine. Analysis of osteochondral cores with an intact superficial cell layer suggested that an the superficial layer of the articular cartilage provided some protective benefit when intact. This may be significant in deciding during surgery whether or not intra-articular analgesic agents are safe to administer.

To test the respective toxic effects on chondrocytes of lidocaine, mepivacaine and bupivacaine Park et al used an equine model (Park et al., 2011). Bupivacaine (0.5%) was the most toxic of the agents used with cell viability reduced to 29 +/- 8% after 30 minutes. Cell viability after treatment with saline was 96%. Lidocaine and mepivacaine were both less toxic with mepivacaine exerting the least toxic effect of the three.

A number of studies have used human cell lines which is arguably more useful for the extrapolation of results into clinical practice. Dragoo et al used a custom made bioreactor to mimic the metabolism of synovial fluid to simulate the use of a pain pump following arthroscopic surgery (Dragoo et al., 2008). They found that both lignocaine (1%) and bupivacaine (0.25 or 0.5%) resulted in reduced cell viability but that the rates of necrosis were noted with the presence of epinephrine. Cell viability was similar at 24 and 48 hours in the bupivacaine group, but there was a greater toxic effect seen at 72 hours. Further work using the same bioreactor model demonstrated that epinephrine, at levels of 1:100000-200000, conferred no significant increase in cell death compared to acidic media with a pH of 4.5-5.0 and local anaesthetics in combination with epinephrine (Dragoo et al., 2010). The authors suggest that local anaesthetic agents containing epinephrine should be used with caution as these are often titrated to a low pH.

Syed et al reported significant toxic effects of bupivacaine either alone or in combination with triamcinolone in a monolayer culture model using human articular chondrocytes (Syed et al., 2011). When the treatments were administered to the osteochondral plug with an intact surface however, the toxic effect of bupivacaine in isolation was no more than that of the control - again suggesting there is a benefit to an intact articular surface with regard exposure to potentially toxic agents.

Using chondrocytes harvested from osteoarthritic human knees it was demonstrated that exposure to lidocaine, bupivacaine or ropivacaine for 24 or 120 hours resulted in significant levels of cell death (Grishko et al., 2010). In the lignocaine 2% group massive necrosis was seen at 24 hours. After 120 hours exposure there were significant decreases in cell viability in all treatments groups with the exception of those cells treated with 0.2% ropivacaine. As viability decreased a concomitant rise in cell apoptosis was noted.

Jacobs et al harvested human articular chondrocytes from the knees of human tissue donors or patients undergoing total knee arthroplasty (Jacobs et al., 2011). They treated the articular chondrocytes with either 1% or 2% lidocaine with or without epinephrine and used saline as a control. Cell death between 91-99% was seen for each of the three treatments. A prolonged exposure time was also associated with higher rates of cell death.

Ropivacaine 0.5% was found to be significantly less toxic to human chondrocytes than bupivacaine 0.5% (Piper and Kim, 2008). Normal human articular cartilage was harvested

from the femoral head or tibial plateau in patients undergoing surgical procedures. Full thickness explants and cultured chondrocytes were treated with either ropivacaine or bupivacaine for 30 minutes. Cell viability in the explant cultures fell to 95% and 78% after treatment with ropivacaine and bupivacaine respectively. Viability in the cell cultures fell to 64% and 37%. The viability of the cells in the explant cultures treated with ropivacaine did not differ significantly to that in the controls treated with saline. Ropivacaine may therefore confer a much more acceptable risk than bupivacaine – an important consideration if using it as an intra-articular agent following arthroscopy.

However, others failed to find a difference between these two agents using a simple monolayer culture model. Both ropivacaine and bupivacaine conferred similar toxic effects to the articular chondrocytes either in isolation or if they were used in combination with magnesium sulfate (Baker et al., 2011b, Baker et al., 2011d). Lignocaine combined with magnesium sulfate was less toxic than either ropivacaine, bupivacaine or levobupivacaine combined with magnesium sulfate after an exposure time of only 15 minutes (Baker et al., 2011b).

A useful finding for the practicing surgeon in the studies that have assessed human cells in *in vitro* settings is the recurrent finding that ropivacaine is less toxic than bupivacaine (Baker et al., 2011b, Baker et al., 2011d, Piper and Kim, 2008). If ropivacaine confers a less toxic effect, then as long as it provides equally efficacious analgesic control, then these studies support its use. Notably, Piper et al also found ropivacaine to be less toxic in the explant culture with cells embedded in an intact matrix, potentially a better representation of the *in vivo* state.

2.3.2 *In vivo* studies

In vivo models should in theory provide the best simulation of what may happen in practice. However, consideration needs to be given to the culture model used and also the species studied. Arguably the ideal model is unknown to date and no human *in vivo* studies at the time of writing have been able to demonstrate a lasting deleterious effect of local anaesthetic on articular chondrocytes.

The effect of a single intra-articular injection of 0.5% bupivacaine into a stifle joint compared to 0.9% saline control was studied (Chu et al., 2010). Six months following injection gross and histological appearances showed that the chondral surfaces remained intact. They did note however, that there was a reduction in chondrocyte density of up to 50% in the joint treated with local anaesthetic compared to the saline control.

In an *in vivo* rabbit study three groups received continuous infusions of either saline, bupivacaine or bupivacaine with epinephrine over 48 hours (Gomoll et al., 2006). One week after treatment the animals were sacrificed and osteochondral and synovial samples analysed. Bupivacaine with or without epinephrine resulted in cell viability reduction by 20 to 32%. Histological analysis was worse in both treatment groups compared to saline control.

A similar treatment regime did not result in long term changes in articular cartilage (Gomoll et al., 2009). When the rabbits were sacrificed three months after the infusion of the saline or local anaesthetic there was no significant difference found between treatment and control groups. An increase in cartilage metabolism in the treatment groups was noted suggesting that the cartilage was undergoing a reparative process. This study provides conflicting information to the earlier one noted by Chu et al creating more difficulty in ascertaining the true chronic effect of intra-articular local anaesthetic use.

In another, histological changes in rabbit knee joint articular cartilage have been reported (Dogan et al., 2004). Knees were injected with either 0.9% saline, bupivacaine or

neostigmine. Histological analysis performed at 1, 2 and 10 days confirmed more toxic changes in both treatment groups compared to saline control.

2.3.3 The mechanism of local anaesthetic mediated chondrotoxicity

Despite a number of studies reporting the potential toxic effects the mechanism by which these agents exert their effect is uncertain. Mitochondrial dysfunction is thought to be a key factor in articular chondrocyte death (Grishko et al., 2010). Grishko et al demonstrated mitochondrial DNA damage and a reduction in ATP and mitochondrial protein levels in response to treatment with a variety of local anaesthetics at varying concentrations.

In another study cells exposed to lidocaine or bupivacaine in isolation had rates of cell death just over 10% (Bogatch et al., 2010). When the local anaesthetics were mixed with the cell culture medium this rate rose to over 96% in each instance. Crystal formation was seen when the bupivacaine was mixed with culture medium. Acidic phosphate buffered saline resulted in increased cell death only when the acidity was increased to a pH less than 3.4. Based on these results the authors propose an incompatibility between the synovial fluid and the local anaesthetic is responsible for the majority of chondrocyte death rather than the local anaesthetic agent itself.

3. Summary

A number of different agents have been trialed as intra-articular analgesic agents following arthroscopy in the lower limb. Many of the reported trials have focussed on the use of amide local anaesthetic agents as these are the most widely used in clinical practice. Despite multiple studies there is no agent that appears clearly superior to the rest. Bupivacaine or ropivacaine appear the most likely to offer the greatest analgesic control by this route and a small number of studies are supportive of a multi-modal infiltration. Magnesium sulfate for one may be an ideal synergist.

Although Townsend et al have offered evidence that intra-articular local anaesthetic can be avoided in knee arthroscopy without compromising analgesic control, the ideal mode of analgesic control in hip and ankle arthroscopy is still uncertain. Recent reports of chondrolysis in shoulder arthroscopy prompted a number of investigations in the potential toxic effect that amide local anaesthetics may have on articular chondrocytes.

Ropivacaine appears to be less toxic than bupivacaine and a combination of ropivacaine and magnesium has also been suggested as a more acceptable alternative approach to intra-articular local anaesthesia (Baker et al., 2011b, Webb and Ghosh, 2009). The potential difficulties in applying laboratory findings to the clinical setting has been noted (Webb and Ghosh, 2009). In the arthroscopic setting, a number of variables including the articular surface disease state, the dilutional effect of the arthroscopic fluid and absorbance of injected agents into surrounding synovium and adjacent soft tissues could all modify the effect the local anaesthetic has on the articular chondrocyte. The potential for toxic effects on articular chondrocytes by local anaesthetic needs to be further investigated.

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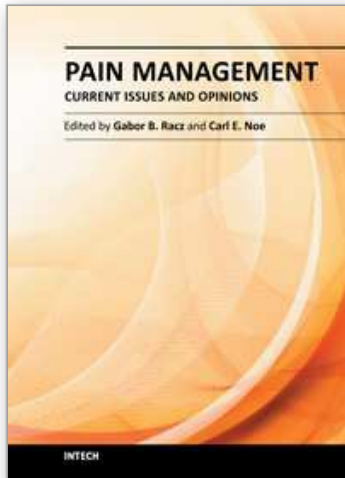
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