8

Local Anesthetic Agents in Arthroscopy

Joseph Baker
Cappagh National Orthopaedic Hospital
Ireland

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 Table2). 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 that bupivacaine infiltrated around the portal sites(Townshend 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 studies in a very limited capacity and a clear conclusion in 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-articulat 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 doe more effectuve. The intra-articular route was more effective than the intravenous route.
(Batra et al., 2008)	RCT	60	Intra-articular **midazolam** (50 or 75μg/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 intraarticuular **bupivacaine** (20ml 0.5%) were compared with noraml saline placebo. Single dose morphine by either route provided superior pain conrol 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 thos 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 thos receiving either agent in isolation or placebo.
(Eren et al., 2008)	RCT	90	Patients receving either 8mg **lornoxicam** or 50mg **bupivacaine** had less analgesic consumption after surgery than those receiving plcebo. Pain rating were lower for those receinving the lornoxicam than thos 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-opeatively 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 onsumption 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-opertive 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 recevinign 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 incombination 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 reposrted 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 receinving 10mg **morphine** intra-articularly repoted 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-articulalry at the end of surgery.Bupivacaine with mprhine was effective at reducing pain and duration of immobilization, the addition of methylprednisolone futher reduce dpain 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 **ropivacaine** given at the time of surgery. Arthoscopy 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 anlgesia at 6- and 24-hours post-surgery. An intra-articular dose of 5mg morphine was more effective thatn 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 **morphin**e (2mg in 10ml saline) was given following surgery via an intra-articular catheter in patients with at least moderate pain. Equivalent improvements in pain intesnity 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 beneift 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	Patientes 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 effectivley than **bupivacaine** in isolation or placebo.
(Townshend et al., 2009)	RCT	137	Patients receiving 20ml of 0.5% bupivacaine either intra-articulalry or infiltrated around the portals reported equivalent pain scores at 1-hour post-surgery.
(VanNess and Gittins, 1994)	RCT	81	Patients receiving intra-artticular **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 thoe treated with intra-articular **buprenorphine** or **bupivacaine.**
(Vranken et al., 2001)	RCT	60	**Sufentanil** (5 or 10μg) given intra-articulalry 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 vloume 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 the serve as a caution.

The aim of this section is to provide an over view 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 modesl 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 bupivacine 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 bupivacine (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 respose to the local anaetshetic 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 mepivacine 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 pratice. 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 bupivaine group, but there was a greater toxic effect seen at 72 hours. Further work using the same bioreactor model demonstrated that epineprhine, 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 monlayer 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 dereases 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 chondrcytes 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 in patients underoing 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 simlar 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 suflate 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 shoulde in theory provide the best simulation of what may happen in pratcice. 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 diod note howeevr, 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 recieved 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 gourps 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 of 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 mechaisn of local anaesthetic mediated chondroctoxicity

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 bupivacine 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 bupivacine was mixed with culture medium. Acididc 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 sgents as these are the most widely used in clinical practice. Depsite 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 anaesthetc 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 anaesthetcis may have on articular chondrocytes.

Ropivacaine appears to 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 diffculties 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.

4. References

Aasbo, V., Raeder, J. C., Grogaard, B. & Roise, O. 1996. No additional analgesic effect of intra-articular morphine or bupivacaine compared with placebo after elective knee arthroscopy. *Acta Anaesthesiol Scand,* 40, 585-8.

Al-Metwalli, R. R., Mowafi, H. A., Ismail, S. A., Siddiqui, A. K., Al-Ghamdi, A. M., Shafi, M. A. & El-Saleh, A. R. 2008. Effect of intra-articular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. *Br J Anaesth,* 101, 395-9.

Alagol, A., Calpur, O. U., Kaya, G., Pamukcu, Z. & Turan, F. N. 2004. The use of intraarticular tramadol for postoperative analgesia after arthroscopic knee surgery: a comparison of different intraarticular and intravenous doses. *Knee Surg Sports Traumatol Arthrosc,* 12, 184-8.

Anz, A., Smith, M. J., Stoker, A., Linville, C., Markway, H., Branson, K. & Cook, J. L. 2009. The effect of bupivacaine and morphine in a coculture model of diarthrodial joints. *Arthroscopy,* 25, 225-31.

Baker, J. F., Byrne, D. P., Hunter, K. & Mulhall, K. J. 2011a. Post-operative opiate requirements after hip arthroscopy. *Knee Surg Sports Traumatol Arthrosc,* 19, 1399-402.

Baker, J. F., Byrne, D. P., Walsh, P. M. & Mulhall, K. J. 2011b. Human chondrocyte viability after treatment with local anesthetic and/or magnesium: results from an in vitro study. *Arthroscopy,* 27, 213-7.

Baker, J. F., McGuire, C. M., Byrne, D. P., Hunter, K., Eustace, N. & Mulhall, K. J. 2011c. Analgesic control after hip arthroscopy: a randomised, double-blinded trial comparing portal with intra-articular infiltration of bupivacaine. *Hip Int,* 21, 373-377.

Baker, J. F., Walsh, P. M., Byrne, D. P. & Mulhall, K. J. 2011d. In vitro assessment of human chondrocyte viability after treatment with local anaesthetic, magnesium sulphate or normal saline. *Knee Surg Sports Traumatol Arthrosc*.

Batra, Y. K., Mahajan, R., Kumar, S., Rajeev, S. & Singh Dhillon, M. 2008. A dose-ranging study of intraarticular midazolam for pain relief after knee arthroscopy. *Anesth Analg,* 107, 669-72.

Bogatch, M. T., Ferachi, D. G., Kyle, B., Popinchalk, S., Howell, M. H., Ge, D., You, Z. & Savoie, F. H. 2010. Is chemical incompatibility responsible for chondrocyte death induced by local anaesthetics? *Am J Sports Med,* 38, 520-6.

Buerkle, H., Huge, V., Wolfgart, M., Steinbeck, J., Mertes, N., Van Aken, H. & Prien, T. 2000. Intra-articular clonidine analgesia after knee arthroscopy. *Eur J Anaesthesiol,* 17, 295-9.

Busfield, B. T. & Romero, D. M. 2009. Pain pump use after shoulder arthroscopy as a cause of glenohumeral chondrolysis. *Arthroscopy,* 25, 647-52.

Calmet, J., Esteve, C., Boada, S. & Gine, J. 2004. Analgesic effect of intra-articular ketorolac in knee arthroscopy: comparison of morphine and bupivacaine. *Knee Surg Sports Traumatol Arthrosc,* 12, 552-5.

Cepeda, M. S., Uribe, C., Betancourt, J., Rugeles, J. & Carr, D. B. 1997. Pain relief after knee arthroscopy: intra-articular morphine, intra-articular bupivacaine, or subcutaneous morphine? *Reg Anesth,* 22, 233-8.

Chu, C. R., Coyle, C. H., Chu, C. T., Szczodry, M., Seshadri, V., Karpie, J. C., Cieslak, K. M. & Pringle, E. K. 2010. In vivo effects of single intra-articular injection of 0.5% bupivacaine on articular cartilage. *J Bone Joint Surg Am,* 92, 599-608.

Chu, C. R., Izzo, N. J., Coyle, C. H., Papas, N. E. & Logar, A. 2008. The in vitro effects of bupivacaine on articular chondrocytes. *J Bone Joint Surg Br,* 90, 814-20.

Colbert, S. T., Curran, E., O'Hanlon, D. M., Moran, R. & McCarroll, M. 1999. Intra-articular tenoxicam improves postoperative analgesia in knee arthroscopy. *Can J Anaesth,* 46, 653-7.

Convery, P. N., Milligan, K. R., Quinn, P., Scott, K. & Clarke, R. C. 1998. Low-dose intra-articular ketorolac for pain relief following arthroscopy of the knee joint. *Anaesthesia,* 53, 1125-9.

Cook, T. M., Tuckey, J. P. & Nolan, J. P. 1997. Analgesia after day-case knee arthroscopy: double-blind study of intra-articular tenoxicam, intra-articular bupivacaine and placebo. *Br J Anaesth,* 78, 163-8.

Dalsgaard, J., Felsby, S., Juelsgaard, P. & Frokjaer, J. 1993. [Analgesic effect of low-dose intra-articular morphine after ambulatory knee arthroscopy]. *Ugeskr Laeger,* 155, 4166-9.

Dogan, N., Erdem, A. F., Erman, Z. & Kizilkaya, M. 2004. The effects of bupivacaine and neostigmine on articular cartilage and synovium in the rabbit knee joint. *J Int Med Res,* 32, 513-9.

Dragoo, J. L., Korotkova, T., Kanwar, R. & Wood, B. 2008. The effect of local anesthetics administered via pain pump on chondrocyte viability. *Am J Sports Med,* 36, 1484-8.

Dragoo, J. L., Korotkova, T., Kim, H. J. & Jagadish, A. 2010. Chondrotoxicity of low pH, epinephrine, and preservatives found in local anesthetics containing epinephrine. *Am J Sports Med,* 38, 1154-9.

Drosos, G. I., Vlachonikolis, I. G., Papoutsidakis, A. N., Gavalas, N. S. & Anthopoulos, G. 2002. Intra-articular morphine and postoperative analgesia after knee arthroscopy. *Knee,* 9, 335-40.

Elhakim, M., Nafie, M., Eid, A. & Hassin, M. 1999. Combination of intra-articular tenoxicam, lidocaine, and pethidine for outpatient knee arthroscopy. *Acta Anaesthesiol Scand,* 43, 803-8.

Elsharnouby, N. M., Eid, H. E., Abou Elezz, N. F. & Moharram, A. N. 2008. Intraarticular injection of magnesium sulphate and/or bupivacaine for postoperative analgesia after arthroscopic knee surgery. *Anesth Analg,* 106, 1548-52, table of contents.

Eren, M., Koltka, K., Koknel Talu, G., Asik, M. & Ozyalcin, S. 2008. [Comparison of analgesic activity of intraarticular lornoxicam, bupivacaine and saline after knee arthroscopy]. *Agri,* 20, 17-22.

Fagan, D. J., Martin, W. & Smith, A. 2003. A randomized, double-blind trial of pre-emptive local anesthesia in day-case knee arthroscopy. *Arthroscopy,* 19, 50-3.

Farouk, S. & Aly, A. 2009. A comparison of intra-articular magnesium and/or morphine with bupivacaine for postoperative analgesia after arthroscopic knee surgery. *J Anesth,* 23, 508-12.

Franceschi, F., Rizzello, G., Cataldo, R. & Denaro, V. 2001. Comparison of morphine and ropivacaine following knee arthroscopy. *Arthroscopy,* 17, 477-80.

Gomoll, A. H., Kang, R. W., Williams, J. M., Bach, B. R. & Cole, B. J. 2006. Chondrolysis after continuous intra-articular bupivacaine infusion: an experimental model investigating chondrotoxicity in the rabbit shoulder. *Arthroscopy,* 22, 813-9.

Gomoll, A. H., Yanke, A. B., Kang, R. W., Chubinskaya, S., Williams, J. M., Bach, B. R. & Cole, B. J. 2009. Long-term effects of bupivacaine on cartilage in a rabbit shoulder model. *Am J Sports Med,* 37, 72-7.

Goodwin, R. C., Amjadi, F. & Parker, R. D. 2005. Short-term analgesic effects of intra-articular injections after knee arthroscopy. *Arthroscopy,* 21, 307-12.

Goodwin, R. C. & Parker, R. D. 2005. Comparison of the analgesic effects of intra-articular injections administered preoperatively and postoperatively in knee arthroscopy. *J Knee Surg,* 18, 17-24.

Grabowska-Gawel, A., Gawel, K., Hagner, W. & Bilinski, P. J. 2003. Morphine or bupivacaine in controlling postoperative pain in patients subjected to knee joint arthroscopy. *Ortop Traumatol Rehabil,* 5, 758-62.

Graham, N. M., Shanahan, M. D., Barry, P., Burgert, S. & Talkhani, I. 2000. Postoperative analgesia after arthroscopic knee surgery: a randomized, prospective, double-blind

study of intravenous regional analgesia versus intra-articular analgesia. *Arthroscopy,* 16, 64-6.

Grishko, V., Xu, M., Wilson, G. & Pearsall, A. W. t. 2010. Apoptosis and mitochondrial dysfunction in human chondrocytes following exposure to lidocaine, bupivacaine, and ropivacaine. *J Bone Joint Surg Am,* 92, 609-18.

Gupta, A., Axelsson, K., Allvin, R., Liszka-Hackzell, J., Rawal, N., Althoff, B. & Augustini, B. G. 1999. Postoperative pain following knee arthroscopy: the effects of intra-articular ketorolac and/or morphine. *Reg Anesth Pain Med,* 24, 225-30.

Hansen, B. P., Beck, C. L., Beck, E. P. & Townsley, R. W. 2007. Postarthroscopic glenohumeral chondrolysis. *Am J Sports Med,* 35, 1628-34.

Hege-Scheuing, G., Michaelsen, K., Buhler, A., Kustermann, J. & Seeling, W. 1995. [Analgesia with intra-articular morphine following knee joint arthroscopy? A double-blind, randomized study with patient-controlled analgesia]. *Anaesthesist,* 44, 351-8.

Hennig, G. S., Hosgood, G., Bubenik-Angapen, L. J., Lauer, S. K. & Morgan, T. W. 2010. Evaluation of chondrocyte death in canine osteochondral explants exposed to a 0.5% solution of bupivacaine. *Am J Vet Res,* 71, 875-83.

Izdes, S., Orhun, S., Turanli, S., Erkilic, E. & Kanbak, O. 2003. The effects of preoperative inflammation on the analgesic efficacy of intraarticular piroxicam for outpatient knee arthroscopy. *Anesth Analg,* 97, 1016-9, table of contents.

Jacobs, T. F., Vansintjan, P. S., Roels, N., Herregods, S. S., Verbruggen, G., Herregods, L. L. & Almqvist, K. F. 2011. The effect of Lidocaine on the viability of cultivated mature human cartilage cells: an in vitro study. *Knee Surg Sports Traumatol Arthrosc.*

Jacobson, E., Assareh, H., Cannerfelt, R., Anderson, R. E. & Jakobsson, J. G. 2006. The postoperative analgesic effects of intra-articular levobupivacaine in elective day-case arthroscopy of the knee: a prospective, randomized, double-blind clinical study. *Knee Surg Sports Traumatol Arthrosc,* 14, 120-4.

Jaureguito, J. W., Wilcox, J. F., Cohn, S. J., Thisted, R. A. & Reider, B. 1995. A comparison of intraarticular morphine and bupivacaine for pain control after outpatient knee arthroscopy. A prospective, randomized, double-blinded study. *Am J Sports Med,* 23, 350-3.

Jawish, D., Antakly, M. C., Dagher, F., Nasser, E. & Geahchan, N. 1996. [Intra-articular analgesia after arthroscopy of the knee]. *Cah Anesthesiol,* 44, 415-7.

Joshi, G. P., McCarroll, S. M., Cooney, C. M., Blunnie, W. P., O'Brien, T. M. & Lawrence, A. J. 1992. Intra-articular morphine for pain relief after knee arthroscopy. *J Bone Joint Surg Br,* 74, 749-51.

Joshi, G. P., McCarroll, S. M., O'Brien, T. M. & Lenane, P. 1993. Intraarticular analgesia following knee arthroscopy. *Anesth Analg,* 76, 333-6.

Juelsgaard, P., Dalsgaard, J., Felsby, S. & Frokjaer, J. 1993. [Analgesic effect of 2 different doses of intra-articular morphine after ambulatory knee arthroscopy. A randomized, prospective, double-blind study]. *Ugeskr Laeger,* 155, 4169-72.

Kanbak, M., Akpolat, N., Ocal, T., Doral, M. N., Ercan, M. & Erdem, K. 1997. Intraarticular morphine administration provides pain relief after knee arthroscopy. *Eur J Anaesthesiol,* 14, 153-6.

Karaman, Y., Kayali, C., Ozturk, H., Kaya, A. & Bor, C. 2009. A comparison of analgesic effect of intra-articular levobupivacaine with bupivacaine following knee arthroscopy. *Saudi Med J,* 30, 629-32.

Karpie, J. C. & Chu, C. R. 2007. Lidocaine exhibits dose- and time-dependent cytotoxic effects on bovine articular chondrocytes in vitro. *Am J Sports Med,* 35, 1621-7.

Kligman, M., Bruskin, A., Sckliamser, J., Vered, R. & Roffman, M. 2002. Intra-synovial, compared to intra-articular morphine provides better pain relief following knee arthroscopy menisectomy. *Can J Anaesth,* 49, 380-3.

Lo, I. K., Sciore, P., Chung, M., Liang, S., Boorman, R. B., Thornton, G. M., Rattner, J. B. & Muldrew, K. 2009. Local anesthetics induce chondrocyte death in bovine articular cartilage disks in a dose- and duration-dependent manner. *Arthroscopy,* 25, 707-15.

Lundin, O., Rydgren, B., Sward, L. & Karlsson, J. 1998. Analgesic effects of intra-articular morphine during and after knee arthroscopy: a comparison of two methods. *Arthroscopy,* 14, 192-6.

Middleton, F., Coakes, J., Umarji, S., Palmer, S., Venn, R. & Panayiotou, S. 2006. The efficacy of intra-articular bupivacaine for relief of pain following arthroscopy of the ankle. *J Bone Joint Surg Br,* 88, 1603-5.

Miyazaki, T., Kobayashi, S., Takeno, K., Yayama, T., Meir, A. & Baba, H. 2011. Lidocaine cytotoxicity to the bovine articular chondrocytes in vitro: changes in cell viability and proteoglycan metabolism. *Knee Surg Sports Traumatol Arthrosc.*

Niemi, L., Pitkanen, M., Tuominen, M., Bjorkenheim, J. M. & Rosenberg, P. H. 1994. Intraarticular morphine for pain relief after knee arthroscopy performed under regional anaesthesia. *Acta Anaesthesiol Scand,* 38, 402-5.

Park, J., Sutradhar, B. C., Hong, G., Choi, S. H. & Kim, G. 2011. Comparison of the cytotoxic effects of bupivacaine, lidocaine, and mepivacaine in equine articular chondrocytes. *Vet Anaesth Analg,* 38, 127-33.

Piper, S. L. & Kim, H. T. 2008. Comparison of ropivacaine and bupivacaine toxicity in human articular chondrocytes. *J Bone Joint Surg Am,* 90, 986-91.

Pooni, J. S., Hickmott, K., Mercer, D., Myles, P. & Khan, Z. 1999. Comparison of intra-articular fentanyl and intra-articular bupivacaine for post-operative pain relief after knee arthroscopy. *Eur J Anaesthesiol,* 16, 708-11.

Raj, N., Sehgal, A., Hall, J. E., Sharma, A., Murrin, K. R. & Groves, N. D. 2004. Comparison of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy. *Eur J Anaesthesiol,* 21, 932-7.

Rasmussen, S., Lorentzen, J. S., Larsen, A. S., Thomsen, S. T. & Kehlet, H. 2002. Combined intra-articular glucocorticoid, bupivacaine and morphine reduces pain and convalescence after diagnostic knee arthroscopy. *Acta Orthop Scand,* 73, 175-8.

Rautoma, P., Santanen, U., Avela, R., Luurila, H., Perhoniemi, V. & Erkola, O. 2000. Diclofenac premedication but not intra-articular ropivacaine alleviates pain following day-case knee arthroscopy. *Can J Anaesth,* 47, 220-4.

Richardson, M. D., Bjorksten, A. R., Hart, J. A. & McCullough, K. 1997. The efficacy of intra-articular morphine for postoperative knee arthroscopy analgesia. *Arthroscopy,* 13, 584-9.

Rosseland, L. A. 2005. No evidence for analgesic effect of intra-articular morphine after knee arthroscopy: a qualitative systematic review. *Reg Anesth Pain Med,* 30, 83-98.

Rosseland, L. A., Helgesen, K. G., Breivik, H. & Stubhaug, A. 2004. Moderate-to-severe pain after knee arthroscopy is relieved by intraarticular saline: a randomized controlled trial. *Anesth Analg,* 98, 1546-51, table of contents.

Rosseland, L. A., Stubhaug, A., Grevbo, F., Reikeras, O. & Breivik, H. 2003. Effective pain relief from intra-articular saline with or without morphine 2 mg in patients with moderate-to-severe pain after knee arthroscopy: a randomized, double-blind controlled clinical study. *Acta Anaesthesiol Scand,* 47, 732-8.

Rosseland, L. A., Stubhaug, A., Skoglund, A. & Breivik, H. 1999. Intra-articular morphine for pain relief after knee arthroscopy. *Acta Anaesthesiol Scand,* 43, 252-7.

Samoladas, E. P., Chalidis, B., Fotiadis, H., Terzidis, I., Ntobas, T. & Koimtzis, M. 2006. The intra-articular use of ropivacaine for the control of post knee arthroscopy pain. *J Orthop Surg Res,* 1, 17.

Santanen, U., Rautoma, P., Luurila, H. & Erkola, O. 2001. Intra-articular ropivacaine injection does not alleviate pain after day-case knee arthroscopy performed under spinal anaesthesia. *Ann Chir Gynaecol,* 90, 47-50.

Solheim, N., Rosseland, L. A. & Stubhaug, A. 2006. Intra-articular morphine 5 mg after knee arthroscopy does not produce significant pain relief when administered to patients with moderate to severe pain via an intra-articular catheter. *Reg Anesth Pain Med,* 31, 506-13.

Solomon, D. J., Navaie, M., Stedje-Larsen, E. T., Smith, J. C. & Provencher, M. T. 2009. Glenohumeral chondrolysis after arthroscopy: a systematic review of potential contributors and causal pathways. *Arthroscopy,* 25, 1329-42.

Souza, R. H., Issy, A. M. & Sakata, R. K. 2002. [Intra-articular analgesia with morphine, bupivacaine or fentanyl after knee video-arthroscopy surgery.]. *Rev Bras Anestesiol,* 52, 570-80.

Syed, H. M., Green, L., Bianski, B., Jobe, C. M. & Wongworawat, M. D. 2011. Bupivacaine and Triamcinolone May Be Toxic To Human Chondrocytes: A Pilot Study. *Clin Orthop Relat Res*.

Tamosiunas, R., Brazdzionyte, E., Tarnauskaite-Augutiene, A. & Tranauskaite-Keraitiene, G. 2005. [Postoperative analgesia with intraarticular local anesthetic bupivacaine and alpha2-agonist clonidine after arthroscopic knee surgery]. *Medicina (Kaunas),* 41, 547-52.

Townshend, D., Emmerson, K., Jones, S., Partington, P. & Muller, S. 2009. Intra-articular injection versus portal infiltration of 0.5% bupivacaine following arthroscopy of the knee: a prospective, randomised double-blinded trial. *J Bone Joint Surg Br,* 91, 601-3.

VanNess, S. A. & Gittins, M. E. 1994. Comparison of intra-articular morphine and bupivacaine following knee arthroscopy. *Orthop Rev,* 23, 743-7.

Varrassi, G., Marinangeli, F., Ciccozzi, A., Iovinelli, G., Facchetti, G. & Ciccone, A. 1999. Intra-articular buprenorphine after knee arthroscopy. A randomised, prospective, double-blind study. *Acta Anaesthesiol Scand,* 43, 51-5.

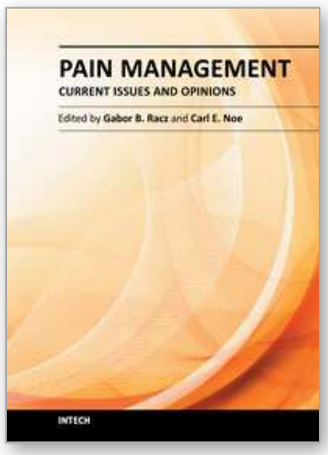
Vranken, J. H., Vissers, K. C., de Jongh, R. & Heylen, R. 2001. Intraarticular sufentanil administration facilitates recovery after day-case knee arthroscopy. *Anesth Analg,* 92, 625-8.

Webb, S. T. & Ghosh, S. 2009. Intra-articular bupivacaine: potentially chondrotoxic? *Br J Anaesth,* 102, 439-41.

White, A. P., Laurent, S. & Wilkinson, D. J. 1990. Intra-articular and subcutaneous prilocaine with adrenaline for pain relief in day case arthroscopy of the knee joint. *Ann R Coll Surg Engl,* 72, 350-2.

Yang, L. C., Chen, L. M., Wang, C. J. & Buerkle, H. 1998. Postoperative analgesia by intra-articular neostigmine in patients undergoing knee arthroscopy. *Anesthesiology,* 88, 334-9.

Zeidan, A., Kassem, R., Nahleh, N., Maaliki, H., El-Khatib, M., Struys, M. M. & Baraka, A. 2008. Intraarticular tramadol-bupivacaine combination prolongs the duration of postoperative analgesia after outpatient arthroscopic knee surgery. *Anesth Analg,* 107, 292-9.



Pain Management - Current Issues and Opinions

Edited by Dr. Gabor Racz

ISBN 978-953-307-813-7

Hard cover, 554 pages

Publisher InTech

Published online 18, January, 2012

Published in print edition January, 2012

Pain Management - Current Issues and Opinions is written by international experts who cover a number of topics about current pain management problems, and gives the reader a glimpse into the future of pain treatment. Several chapters report original research, while others summarize clinical information with specific treatment options. The international mix of authors reflects the "casting of a broad net" to recruit authors on the cutting edge of their area of interest. Pain Management - Current Issues and Opinions is a must read for the up-to-date pain clinician.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen