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Original Article

Articular cartilage and local anaesthetic: A systematic review of the current literature

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ARTICLE INFO

Article history:

Received 24 June 2015

Accepted 4 October 2015

Available online 31 October 2015

Keywords:

Chondrolysis

Cartilage

Arthroscopy

Review

Local anaesthetic

ABSTRACT

Background: Chondrolysis involves the breakdown of cartilage following arthroscopic surgery, most commonly affecting the glenohumeral joint.

Methods: This review summarises all clinical and laboratory studies regarding local anaesthetic (LA) and its association with chondrolysis. We identified 289 papers, 41 of which met our inclusion criteria and were included in the final review.

Results: Bupivacaine, lidocaine, ropivacaine and levobupivacaine are all toxic to cartilage. Intra-articular infusions confer a greater toxicity to cartilage than single injections.

Conclusions: Intra-articular LA pain pumps carry a high risk of chondrolysis and should be avoided. Further studies are indicated to assess long-term single exposure LA implications.

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1. Background

Chondrolysis is a rare, devastating complication of arthroscopic surgery. Clinically, this is manifested by a progressive increase in pain and stiffness in the affected joint. It is characterised by progressive breakdown of cartilage and a reduction of joint space on radiographs.

Prior to the widespread use of arthroscopy, only four cases of glenohumeral chondrolysis were documented and were related to the use of gentian violet leakage when identifying rotator cuff tears.^{1,2} Post-arthroscopic chondrolysis has since been described most often in the glenohumeral joint, followed by the knee joint. While the exact cause of chondrolysis is unknown, many possible causes have been suggested, including the use of thermal probes,

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Abbreviations: LA, local anaesthetic; RCT, randomised controlled trial; PP, pain pump; PAGCL, post-arthroscopic glenohumeral chondrolysis; TKA, total knee arthroplasty; PBS, phosphate buffered saline; MgSO₄, magnesium sulphate; GAG, glycosaminoglycan; PG, proteoglycan; LDH, lactate dehydrogenase; IL-6, interleukin-6.

<http://dx.doi.org/10.1016/j.jor.2015.10.005>

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bio-absorbable suture anchors and the infusion of local anaesthetic (LA).

This review aims to summarise all clinical and laboratory studies related to LA and its effect on articular cartilage.

2. Methods

This review was conducted in line with PRISMA guidelines. It included all human and animal laboratory and clinical studies investigating the use of LAs on articular cartilage. Clinical studies describing chondrolysis or adverse effects associated with LA use were included.

Letters to the editor, review articles and foreign language studies were excluded. Reference lists of all systematic and literature reviews were reviewed.

A MEDLINE search of articles from 1966 to February 2012 was used to identify all relevant studies. EMBASE was searched from 1980 to February 2012. References of all identified papers and systematic reviews were manually searched. The controlled trials register was searched for any randomised controlled trials (RCT) assessing the safety of different LAs.

Abstracts of the remaining studies were reviewed for pre-defined inclusion and exclusion criteria. Full texts of the remaining articles were examined and the final study selection was performed. Clinical studies were assessed and data including demographics, index procedure, pre-existing risk factors for chondrolysis, treatment received and outcomes were extracted. Laboratory studies were assessed and data on study design, study population, results and conclusions were recorded.

3. Results

A total of 289 studies were identified using the two databases. Manual searching of references revealed three further studies (Fig. 1). Only one foreign language study satisfied the inclusion criteria, but a translated copy was not available. After study selection, 41 studies (18 case series, 23 laboratory studies) were included. No RCTs were found.

3.1. Clinical cases

We found 167 cases of chondrolysis in 163 patients associated with intra-articular LA infusion or infiltration. Of these, 149 (89.3%) involved the glenohumeral joint. The knee was involved in 16 cases and one case each involved the ankle and elbow joints. A total of 163 (97.7%) cases involved continuous intra-articular infusion via pain pump (PP).

There were only four cases of chondrolysis following a single intra-articular injection of bupivacaine not delivered via pump. Bailie et al.³ described 23 cases of glenohumeral chondrolysis following a variety of arthroscopic procedures. While 19 of these cases had documented use of intra-articular PPs, suture anchors or radiofrequency probes, four patients did not have any treatment. All 23 patients had received an intra-articular injection of 20 ml of 0.25% bupivacaine with 1:200,000 adrenaline.

Fig. 1 – Flow chart demonstrating the study selection process used for the systematic review.

The infusate was known in 105 cases and bupivacaine was infiltrated via pump in 103 of these cases, the concentration of which varied from 0.25% to 0.5%. The rate of infiltration varied from 2 ml/h to 4.16 ml/h. Lidocaine 2% use was documented in one case, at a rate of 2 ml/h and ropivacaine 0.2% was used in one further case. Wiater et al.⁴ documented the use of lidocaine or bupivacaine in 49 cases. The anaesthetic was not specified in nine cases. Adrenaline was used in the pump in 37 cases.

In some ways, chondrolysis following exposure of articular cartilage to LA appears to be a rare occurrence; however, four individual case series have reported alarmingly high rates: 3 out of 29,⁵ 18 out of 45,⁶ 49 out of 109³ and 12 out of 19⁷ patients treated with pain catheters where the total number of cases was known. Combining data from these four studies revealed that the incidence of chondrolysis was 82 out of 202 (40.6%) where a LA PP was used. There were no cases of chondrolysis in 337 patients where no PP was used or in 141 patients where the pump was placed in the sub-acromial space. When the latter two groups were pooled together and compared to the intra-articular group, the difference was significant ($p < 0.001$, chi-squared test).

Other studies looked at the dosage of anaesthetic given and found there may be a dose-response element. Anderson⁶ found that chondrolysis developed in 16 of 32 patients who received high-flow (5 ml/h) intra-articular bupivacaine injection but only in two of 12 who received low-flow (2 ml/h) infusion. Rapley et al.⁵ found that chondrolysis did not develop in 13 cases where 100 ml of 0.5% bupivacaine was infused at 2.08 ml/h but developed in 3 out of 16 cases where 270 ml of 0.5% bupivacaine was infused at 4.1 ml/h.

The age was available in 91 cases. Mean age was 29.1 years (range 14–60). Gender was discernible in 69 patients (25F:44M). The time from the index procedure to the symptom onset was available in 85 cases. The mean time from exposure to symptomatic re-presentation was 11 months (range 0–73 months).

The outcome of chondrolysis is catastrophic. Of the 112 patients (116 shoulders) for whom the outcome was determinable, 109 (113 shoulders) underwent 148 procedures including 58 arthroplasty procedures (hemiarthroplasty, resurfacing, total or revision arthroplasty).

This chondrolysis has been termed post-arthroscopic glenohumeral chondrolysis⁷ (PAGCL). However, Serrato⁸ in 2011 reported chondrolysis in four cases of women (52–60 years) who underwent manipulation under anaesthesia for frozen shoulder with infiltration of bupivacaine. Arthroscopy itself no longer seems to be a criterion sine qua non for the evolution of the condition. The continuous intra-articular infiltration of LA may alone be sufficient.

There is no direct causal link between LA infusions and chondrolysis; however, some studies provide a compelling argument. Wiater et al.⁴ observed chondrolysis only in patients receiving a postoperative LA PP out of a consecutive series of 375 procedures. Hansen et al.⁷ found that 12 of 19 patients undergoing arthroscopic shoulder stabilisation developed PAGCL. The only change to the senior author's practice in all patients was the infusion of 0.25% bupivacaine with adrenaline for 48 h. In addition, all patients received preoperative and postoperative intra-articular injections of 25 ml of 0.25% bupivacaine with adrenaline and 5 mg of morphine sulphate. PAGCL was not seen in 13 patients who had arthroscopic stabilisation without PP, or in another 102 patients who had the same pre- and postoperative protocol but with extra-articular PP catheter (sub-acromial). Saltzman⁹ gave an account of a patient who underwent identical shoulder procedures bilaterally. The only difference in the postoperative regimen was placement of lidocaine PP in the left shoulder but not the right. Chondrolysis developed in the left only.

In a number of cases there were potential confounders. There was documented use of suture anchors in 32 cases, radiofrequency probes in 8 cases, thermal devices in 7 cases and bio-absorbable devices in 17 cases. Wiater et al.⁴ documented a case series of 375 surgical procedures in 322 patients. They found that chondrolysis only occurred in 49 procedures, all of whom had intra-articular LA PPs (109 cases in total used intra-articular LA PP). No chondrolysis was observed in the remaining 273 cases with other risk factors, which notably included 137 cases using extra-articular LA PPs. They concluded that PPs were the single most important risk factor for chondrolysis in their series.

Table 1 summarises all the case series included in the review.

3.2. Laboratory studies

The first of the laboratory studies was conducted by Nole et al.¹⁰ who recognised the increasing use of bupivacaine following arthroscopy and assessed its effect on articular cartilage. They investigated 0.5% bupivacaine solution (diluted in isotonic saline) on articular cartilage of six-week old pigs and adult dogs. They found that ³⁵SO₄ incorporation was inhibited acutely compared to in vitro controls but was not significantly different when tested three days after injection on an in vivo model. They concluded that the acute inhibition caused by bupivacaine is normalised by day three

following injection, and hence could be used safely for intra-articular analgesia.

The potentially harmful effects of bupivacaine on articular cartilage were first reported by Dogan et al.,¹¹ who injected saline or 0.5% bupivacaine into rabbit knee joints and examined cartilage specimens histopathologically after 24 h, 48 h or 10 days. They found that the specimens from animals receiving bupivacaine showed significantly more inflammatory changes in the form of inflammatory cell infiltration and synovial membrane cell hyperplasia and hypertrophy compared to saline control.

Anz et al.¹² analysed cartilage and synovium in a canine in vitro model wherein the specimens were exposed to a saline control, 0.5% bupivacaine or morphine. They found that bupivacaine reduced cell viability by 100% compared to saline but did not reduce the tissue concentration of water, collagen or glycosaminoglycans (GAGs). Morphine did not cause any appreciable reduction in cell viability.

Piper and Kim¹³ harvested cartilage explants and chondrocyte cultures from the femoral heads or tibial plateaus of five patients and exposed them to 0.9% saline control, 0.5% bupivacaine or 0.5% ropivacaine for 30 min. The explants and chondrocytes were analysed using live/dead cell viability analysis after 24 h. They found bupivacaine had significantly lower cell viability at 78% in the explants and 37% in the cell cultures compared to 94% and 64% for ropivacaine. They found no significant difference between ropivacaine and saline control in the explants. However, we believe that saline was a poor control because it has been shown to inhibit proteoglycan (PG) metabolism in in vitro studies.^{14,15} The use of a cartilage culture medium instead is likely to have shown more toxicity with ropivacaine.

Farkas et al.¹⁶ found that even ropivacaine can be harmful to articular cartilage when used at a higher concentration. They assessed the effect of 1% lidocaine, 0.5% bupivacaine or 0.75% ropivacaine with or without glucocorticoids on human chondrocyte cultures or osteochondral explants obtained from four human femoral heads using cell viability and flow cytometry analysis. They found significantly increased number of necrotic cells with all anaesthetics and this toxicity worsened with betamethasone. Toxicity increased when the duration of exposure was increased from two to six or 24 h.

Miyazaki et al.¹⁷ assessed the effect of increasing concentrations of lidocaine from 0.125% to 1% on bovine articular cartilage after 1 h, 12 h and 24 h exposure. They found that the number of viable cells using confocal microscopy reduced as the concentration and duration of exposure to lidocaine increased.

Two studies have assessed the effect of mepivacaine, which appears to be less toxic to cartilage. Park et al.¹⁸ compared the effects of 0.5% bupivacaine, 2% lidocaine or 2% mepivacaine on equine articular cartilage using cell viability and flow cytometry assays. They found that cell viability was 29% after 30 min of bupivacaine exposure, 67% after lidocaine and 87% after mepivacaine. They suggested that mepivacaine would be a safer alternative to lidocaine or bupivacaine. Bolt et al.¹⁹ assessed the effect of mepivacaine hydrochloride on articular cartilage explants obtained from four patella-femoral joints of two adult horses. On histological assessment, they found increased number of pyknotic nuclei and empty lacunae

Table 1 – Summary of all clinical case series of chondrolysis associated with LA use.

Author	Patients	Diagnosis	Surgery	Agent	Additional injections	Onset of symptoms	Further surgery
Petty, 2004	18 years, Female	Rotator cuff tear	Arthroscopic cuff repair	0.5% bupivacaine + adrenaline		3 months	
Bojescul, 2005	21 years, Male	Ankle instability	Ankle arthroscopy and lateral ligament reconstruction	Bupivacaine		11 months	
Hansen, 2007	12 shoulders in 10 patients, mean age 28.9 years (range 16–47)	Instability	7 capsular shift, 3 posterior Bankart repairs, 2 anterior Bankart	0.25% bupivacaine with adrenaline 4.16 ml/h 48 h	All had pre- and postoperative 25 ml 0.25% bupivacaine with adrenaline and 5 mg morphine sulphate without preservative	Mean 4.3 months (range 3–13 months)	8 patients needed 21 further procedures. 7 Arthroplasty procedures
Levy, 2008	9 patients, mean age 41.1 years		2 SLAP repairs, 5 Bankart repair, 2 capsular release	LA pump		16 months	All 9 had total shoulder arthroplasty
Gries, 2008	14 and 18 years, both bilateral, both female	Instability	Arthroscopic plication	Bupivacaine infusion 0.5%, 4 ml/h for 48 h	1 shoulder had 20 ml 0.5% bupivacaine with adrenaline pre-injection	Mean 9 months (range 4–24 months)	Both patients had 4 further procedures, 2 arthroplasty
Bailie, 2009	17 patients, mean age 32 years (range 15–47), Male	SLAP lesion, rotator cuff tear, frozen shoulder, Bankart lesion	Rotator cuff repair, Bankart/labral repair, arthrolysis	250–300 ml 0.25% bupivacaine – 48 h		9 months	17 procedures – 8 arthroplasty, 9 debridement
	4 patients		Arthroscopy	20–30 ml 0.25% bupivacaine with 1:200,000 adrenaline after the procedure			
Fester, 2009	3 female patients, 17–21 years	ACL rupture	ACL repair, meniscectomy	Bupivacaine pump for 48 h		Mean 12.6 months (range 7–21)	One patient had visco-supplementation
McNickle, 2009	16 cases, mean age 20.4 years (range 13–37.4)		3 SLAP, 4 capsulorrhaphy, 4 Bankart repairs, 5 labral or capsular repairs	0.25% bupivacaine	15 ml 0.5% bupivacaine	Mean 26 months (range 3–73)	16 procedures, 8 arthroplasty
Saltzman, 2009	37 years, Female		SLAP repair, Bankart repair, capsulorrhaphy, acromioplasty	2% lidocaine at a rate of 2 ml/h		Pain never improved	Hemiarthroplasty
Rapley, 2009	3 patients	Instability	Posterior Bankart, Anterior Bankart, Capsular plication	270 ml of 0.5% bupivacaine	30 ml of 0.25% bupivacaine pre- and post-procedure	3.5–12 months	2 procedures – 1 arthroplasty
Rey, 2009	9 cases, Mean age 37 years (range 26–47)	Instability, cuff tear	Anterior stabilisation, SLAP repair, Cuff repair	Bupivacaine infusion 0.5%, 2 patients had adrenaline			All 9 had arthroplasty

Table 1 (Continued)

Author	Patients	Diagnosis	Surgery	Agent	Additional injections	Onset of symptoms	Further surgery
Anderson, 2010	18 cases, 15 males, mean age 28 years (range 18–30)	Instability	18 Bankart repair	15 at 0.5% bupivacaine + adrenaline at 5 ml/h and 3 at 2 ml/h	Most patients received 15–60 ml bupivacaine at 0.25–0.5%.	Mean 9.5 months (range 2–27.5)	19 procedures – 5 resurfacing
Anakwanze, 2010	2 female patients, 19 and 26 years	Instability, labral tear	Arthroscopic capsular plication, labral repair	Bupivacaine infusion		Pain never improved	4 further procedures, both had arthroplasty
Serrato, 2011	4 female patients, 52–60 years	Frozen shoulder	Manipulation under anaesthetic	0.5% bupivacaine + adrenaline at 2 ml/h	3 patients received 2 ml of Betamethasone and 8 ml of 0.5% bupivacaine	Mean 10.3 months (range 3–17)	5 arthroplasty procedures
Slabaugh, 2010	17 years, Female	ACL rupture	ACL reconstruction, meniscal repair	48 h bupivacaine pump		4 months	Valgus producing high tibial osteotomy with osteoarticular allograft
Wiater, 2011	49 cases		Shoulder arthroscopy, cuff repair, labral repair	Bupivacaine or lidocaine			
Kinkartz, 2012	29 years, Male	Elbow arthro-fibrosis	Osteophyte debridement and capsular release	0.20% ropivacaine for 48 h		3.5 months	
Noyes, 2012	21 patients, mean age 23 years (range 14–42), Male		18 ACL reconstruction, 1 meniscal repair, 1 arthroscopy, 1 tibial tubercle, osteotomy	High-flow pump – 10, Low flow – 10, 0.5% bupivacaine – 20 0.25% bupivacaine – 1 adrenaline – 11		9 ± 7 months	19 patients had 41 operations, one arthroplasty

but found no difference in GAG content compared to control explants.

Chu et al.²⁰ isolated bovine articular chondrocyte into alginate bead cultures and exposed them to 0.5% bupivacaine or 0.9% saline for 15, 30 or 60 min. Flow cytometry was used to analyse chondrocytes for apoptotic and dead cells one hour, one day and one week after bupivacaine exposure and found 99% cell death with bupivacaine specimens compared to 20% for saline. In a second study, Karpie et al.²¹ exposed bovine chondrocytes in alginate bead cultures to 1% lidocaine, 2% lidocaine or 0.9% saline (pH 5.0, 7.0 and 7.4) for 15, 30 or 60 min and assessed cell viability/dead/apoptotic cells using flow cytometry after one hour, 24 h or one week. They also exposed 8 mm osteochondral cores to 1% or 2% lidocaine, or 0.9% saline at pH 7.4 for 30 min and assessed chondrocyte viability after 24 h. After 15-min exposure to lidocaine, in both assays, they found a significant reduction of live cells, worsening after 30 and 60 min exposures. The cell viability was worse with 2% than 1% lidocaine. Altering the pH of saline solution had no effect on the cell viability.

In another study, they evaluated the effect of 0.125%, 0.25% and 0.5% bupivacaine on human and bovine articular chondrocytes in both alginate bead cultures and chondral explants.²² Compared to a saline control, there was no difference in chondrocyte death or apoptosis after exposure to 0.125% bupivacaine. Bupivacaine 0.5% had a drastic effect on chondrocytes with less than 5% viable cells remaining after exposure for 15, 30 or 60 min. Cell viability was found to be 52% one hour following a 30-min exposure to 0.25% bupivacaine, hence the effect observed was dose-dependent i.e. the cell viability decreased as the concentration and duration of bupivacaine increased. Furthermore, no recovery was seen a week after exposure, rather, cell viability had decreased further.

In their final study, Chu et al.²³ used an in vivo technique, injecting rat knee joints with 100 µl 0.9% saline control or 0.5% bupivacaine. They then analysed the cartilage at one week, four weeks, 12 weeks and six months using confocal live/dead cell microscopy, histological analysis and quantitative cell density analysis. They found no significant differences between bupivacaine and saline in terms of cell viability and histological appearance but cell density reduced by up to 50% six months after injection of bupivacaine.

Gomoll et al.²⁴ looked at the medium-term effects of LA exposure by infusing rabbit shoulder joints with saline, 0.25% bupivacaine or 0.25% bupivacaine with adrenaline for 48 h. Three months after infusion, the articular cartilage was analysed for four parameters, radiological/macroscopic changes, PG synthesis using ³⁵SO₄ uptake, PG content and cell viability using confocal microscopy. They found ³⁵SO₄ uptake increased to 166% in cartilage exposed to bupivacaine and to 210% when combined with adrenaline. An increase in PG content was found in both groups. They did not find any macroscopic or radiological differences in any of the specimens or any differences in percentage of live/dead cells. Based on their results, they concluded that bupivacaine did not cause any long-term harmful effects on articular cartilage. However, an increase in uptake represents an increase in metabolic activity, which the authors of this paper believed was a sign that cartilage had fully recovered; however, increased

metabolism can be a sign of degenerative disease as PG metabolism is increased in osteoarthritic cartilage.²⁵

Some of the laboratory studies have not found significant toxicity with LAs alone and have tested the effect of adrenaline or preservatives used in LA solutions. Dragoo et al.²⁶ cultured chondrocytes from the articular cartilage of two patients undergoing total knee arthroplasty (TKA) and exposed them to one of seven solutions: growth medium (control), 1% lidocaine, 0.25% bupivacaine or 0.5% bupivacaine or these solutions combined with adrenaline. They were infused using a standard PP but with continuous inflow and outflow of medication and culture medium to simulate normal synovial fluid turnover. They measured live:dead cell ratio after infusion for 24, 48 or 72 h using a fluorescent microscope. They found that, consistently, solutions containing adrenaline were more toxic than control, of which, 1% lidocaine with adrenaline was the most toxic. None of the LA solutions without adrenaline were toxic at 24 h; 1% lidocaine produced reduced cell viability at 48 h while 0.5% bupivacaine produced reduced viability at 72 h. The authors questioned whether the reduced pH (<4.5) of solutions containing adrenaline contributed to the toxicity or whether it was due to the preservatives in these solutions. They suggested that single injections of any of the solutions without adrenaline should be safe. In a follow-up study, Dragoo et al.²⁷ cultured human chondrocytes from three TKA patients to assess the toxicity of low pH, adrenaline and preservatives found in commonly used LAs. They infused culture media at pH ranging from 4.5 to 6.5 or 1% lidocaine or 0.25% bupivacaine with or without adrenaline or two different preservatives for 24 h and identified the dead cell percentage. They found that culture media at pH ≤ 5.0 (70% necrosis) and LAs containing adrenaline at pH 4.0–5.5 (30–40% necrosis) had high cell death rates. The preservative 5 mg/ml sodium metabisulphite caused 30% cell death whilst the preservative methylparaben had no significant effect. The authors felt that toxicity was seen only with LAs containing adrenaline and this was due to a combined effect of acidity and the preservative sodium metabisulphite. Hennig et al.²⁸ assessed the effect of 0.5% bupivacaine with or without the methylparaben on osteochondral cores obtained from 20 glenohumeral joints of 10 cadaveric canines. They observed more than 50% cell death with bupivacaine and bupivacaine with methylparaben. Methylparaben did not significantly increase cell death.

Syed et al.²⁹ suggested that the low pH of LAs was unlikely to be a contributor to toxicity. They tested the effect of 0.25% bupivacaine on human femoral cartilage (explants and monolayer cultures) and the effects of buffering the pH to that of synovial fluid (pH 7.4). Bupivacaine 0.25% reduced cell viability to 72% in the monolayer cultures but buffering the pH resulted in worsening of cell viability to 22%.

Jacobs et al.³⁰ suggested that adrenaline may even have a protective effect on articular cartilage. They harvested articular cartilage from the knees of four human donors and three patients undergoing TKA and cultured the chondrocytes in alginate bead cultures. They tested the effects of 1% and 2% lidocaine with or without adrenaline on chondrocytes using lactate dehydrogenase (LDH) activity, interleukin 6 (IL-6) production and live/dead cell assay after 24 h, 48 h and 7 days. They found that LDH activity increased for all solutions at 24 h but normalised for all except 2% lidocaine at 7 days. IL-6

concentration was reduced for all solutions at all durations except for 1% lidocaine with adrenaline. This was also seen in the live/dead cell assay where more than 90% dead cells were seen for all solutions except 1% lidocaine with adrenaline. The toxicity of lidocaine was dose- and time-dependent.

Not all studies blame low pH or adrenaline for this toxicity and have suggested alternative hypotheses. Bogatch et al.³¹ cultured bovine articular chondrocytes and exposed them to several different solutions: (i) phosphate buffered saline (PBS) (pH 7.1); (ii) 1% lidocaine, 0.25% or 0.5% bupivacaine with or without adrenaline; (iii) PBS at pH 4.5, 3.8, 3.4 and 2.4 or (iv) mixture of different LAs and culture medium or synovial fluid. They analysed these cultured chondrocytes using flow cytometry to determine dead/live cell ratio. They found that lidocaine and bupivacaine with or without adrenaline produced about 5% reduced cell viability compared to PBS (pH 7.1). Reducing the pH of PBS caused cell death only at pH $\leq$ 3.4. Mixing 0.5% bupivacaine or 1% lidocaine with culture medium or synovial fluid caused the formation of crystals and led to more than 90% cell death. Surprisingly, this was not seen with 2% lidocaine. The authors felt that LAs, low pH or adrenaline alone do not cause significant toxicity. The chemical incompatibility between the anaesthetic solution and human synovial fluid was suggested as a possible mechanism of toxicity.

The mechanism of chondrocyte toxicity at a molecular level has been studied by Grishko et al.,³² who used chondrocyte cultures from patients undergoing TKA and exposed them to 0.9% saline solution or different concentrations of lidocaine, bupivacaine or ropivacaine for one hour. They assessed the number of dead and apoptotic cells by flow cytometry after 24, 72 and 120 h. They also assessed the cultures for mitochondrial DNA damage, changes in adenosine triphosphate production and mitochondrial protein levels. They found that 2% lidocaine caused almost 100% cell necrosis at 24 h while 1% lidocaine and 0.5% bupivacaine caused reduction in cell viability. At this stage, 0.25% bupivacaine, 0.5% ropivacaine and 0.2% ropivacaine did not cause a reduction in cell viability. Five days after exposure, all concentrations of lidocaine, bupivacaine, and ropivacaine except 0.2% ropivacaine caused a significant reduction in cell viability with an increase in the number of apoptotic cells. Mitochondrial dysfunction in the form of mitochondrial DNA damage, decrease in adenosine triphosphate and mitochondrial protein levels was seen with all LAs. Blockade of sodium channels was not thought to be responsible for this toxicity. The authors concluded that mitochondrial DNA damage induced by the LA solutions led to the development of apoptosis in these cells. They further plan to test whether the addition of DNA repair enzymes can help reduce this toxicity in chondrocytes.

Magnesium sulphate (MgSO_4) has previously been suggested as an intra-articular analgesic. Baker et al.³³ assessed cell viability in human chondrocytes using light spectroscopy after exposure to bupivacaine (0.13, 0.25, 0.5%), levobupivacaine (0.13, 0.25, 0.5%), ropivacaine (0.19, 0.38, 0.75%), 10% MgSO_4 or normal saline. They found reduced cell viability with all LAs except 0.13% bupivacaine. MgSO_4 and normal saline did not cause a significant reduction in cell viability. They suggested that MgSO_4 could be used as an alternative intra-articular analgesia. Another study³⁴ conducted by the

same authors looked at the effect of the addition of MgSO_4 to different LAs. They found that 0.5% bupivacaine, 0.5% levobupivacaine, 0.75% ropivacaine and 2% lidocaine all reduced cell viability. When MgSO_4 was added in varying concentrations (10%, 20% and 50%), the cell viability of all anaesthetics improved.

All the laboratory studies assessing the effect of different LAs on articular cartilage are summarised in Table 2.

4. Discussion

It is possible that LA chondrotoxicity is under-reported, as clinicians may not link the two. The onset of symptoms is frequently months or years following an uncomplicated procedure. The single case of ankle chondrolysis reported in 2005³⁵ is notable for the fact that the authors are at a loss to determine the cause or risk factors of chondrolysis; however, a PP was used, which in light of recent literature may be significant. There may also be a reporting bias towards younger patients. It is possible that the development of chondrolysis in older patients is presumed to be osteoarthritis secondary to the original condition for which the arthroscopy was performed.

Grishko et al.³² found that LAs caused mitochondrial DNA damage in chondrocytes leading to cell death. While this may explain the molecular mechanism of toxicity, the effect of added adrenaline, preservatives or low pH on toxicity is unclear and needs further investigation. Although Dragoo et al.²⁷ suggested that toxicity could be due to adrenaline, the preservative sodium metabisulphite and the low pH of such solutions, Bogatch et al.³¹ did not find toxicity due to adrenaline or low pH. They suggested an alternative hypothesis of an incompatibility between the synovial fluid and the LA causing intra-articular crystal formation. We believe that this is certainly possible and further studies are warranted.

In clinical practice, the toxicity of LAs has mainly been seen with continuous infusions via PPs, but in laboratory studies, even a single exposure to LAs has been found to be potentially harmful to cartilage. Chu et al.²⁰ found that exposure to 0.5% bupivacaine for 30 min caused 42% chondrocyte death in bovine cartilage. Reduced chondrocyte viability has since been found with different concentrations of lidocaine, bupivacaine and ropivacaine in a dose- and duration-dependent manner.²¹

Chu et al.²³ conducted an in vivo study on rat cartilage and found reduced chondrocyte density six months after a single exposure to 0.5% bupivacaine, indicating that this toxic effect is maintained at least in the medium term. However, there are currently only four reported cases indicating damage to articular cartilage following a single exposure to LA, suggesting a single injection may have subclinical effects. Osteoarthritis years later may be attributed to the underlying pathology. Repetitive injections may cause cumulative damage but this has not been studied either in vivo or in vitro. An in vivo study similar to that of Gomoll et al.²⁴ but with repetitive injections and a longer recovery period (>12 months) may provide more convincing results.

Intra-articular bupivacaine has been shown to be a more effective analgesic than placebo after arthroscopic surgery^{36,37} but with so much evidence that LAs may not be safe; questions

Table 2 – Effect of LAs on articular cartilage – summary of current literature.

Author	LA/additive	Study design	Salient findings
Nole, 1985	Bupivacaine 0.5%	³⁵ SO ₄ uptake – in vitro study in pigs	Reduced uptake but normalised by 3 days
Dogan, 2004	Bupivacaine 0.5%	Histopathological examination – rabbits	Histopathological changes at 10 days
Chu, 2006	Bupivacaine 0.5%	Flow cytometry – bovine alginate bead cultures and cell viability – osteochondral cores	99% cell death or apoptosis after 60 min exposure in alginate bead cultures and 42% cell death in osteochondral cores
Karpie and Chu, 2007	1% and 2% lidocaine	Flow cytometry – bovine alginate bead cultures and cell viability – osteochondral cores	Both concentrations caused chondrocyte death, 2% more than 1%
Bolt, 2008	Mepivacaine	Chondral explants from equine patello-femoral joints. Histological assessment and GAG content	Increased number of pyknotic nuclei and empty lacunae with mepivacaine exposure. No difference in GAG content after mepivacaine
Chu, 2008	Bupivacaine 0.125%, 0.25% and 0.5%	Cell viability using confocal microscopy – human and bovine bead cultures and chondral explants	Bupivacaine 0.125% not toxic compared to saline 5% viability with 0.5% bupivacaine and 52% with 0.25%
Dragoo, 2008	Lidocaine/bupivacaine with adrenaline	Cell viability using confocal microscopy – human chondrocytes – continuous in vitro infusion	No toxicity with 1% lidocaine, 0.25% bupivacaine, 0.5% bupivacaine at 24 h but all three solutions toxic with adrenaline
Piper and Kim, 2008	0.5% Bupivacaine and 0.5% ropivacaine	Cell viability using fluorescence microscopy – human explants	78% viability with bupivacaine and 94% with ropivacaine. No difference between ropivacaine and saline
Anz, 2009	Bupivacaine 0.5%	Cell viability using confocal microscopy – canine model	100% reduction in cell viability
Gomoll, 2009	0.25% Bupivacaine with/without adrenaline	In vivo–rabbits – radiology, ³⁵ SO ₄ uptake, PG content, cell viability at 3 months	Increased PG content in the bupivacaine groups. Metabolism 166% of saline in bupivacaine only group, 210% in adrenaline group
Bogatch, 2010	Lidocaine/bupivacaine with adrenaline Combination of synovial fluid and LA	Cell viability – bovine chondrocytes	No toxicity with 1% lidocaine, 0.25% bupivacaine, 0.5% bupivacaine with or without adrenaline. Crystallisation when synovial fluid mixed with 0.5% bupivacaine or 1% lidocaine
Chu, 2010	Bupivacaine 0.5%	In vivo – rat knees – cell viability, density and histology at 1,4,12 weeks and 6 months	Reduced cell density with bupivacaine at 6 months, no other differences with saline
Dragoo, 2010	Effect of pH, 1% lidocaine/0.25% bupivacaine with adrenaline, preservatives	Cell viability using confocal microscopy – human chondrocytes – continuous in vitro infusion	Culture medium pH <5.0–70% cell death. LA with adrenaline – 40% cell death. Sodium metabisulphite – 30% cell death. Methylparaben – no toxicity
Farkas, 2010	1% lidocaine, 0.5% bupivacaine or 0.75% ropivacaine with or without glucocorticoids 2,6, 24 h exposure	Human chondrocyte cultures or osteochondral explants – human femoral heads using cell viability and flow cytometry analysis	Increased cell death with all anaesthetics. Cell viability reduced due to addition of betamethasone. Cell death increased with increasing duration of exposure
Grishko, 2010	Lidocaine, bupivacaine, ropivacaine. Mechanism of toxicity	Human chondrocytes – cell viability, mitochondrial function using DNA damage, ATP and mitochondrial protein levels	2% lidocaine the only one toxic at 24 h. At 5 days, 1% and 2% lidocaine, 0.25% and 0.5% bupivacaine and 0.5% ropivacaine were toxic. Damage to mitochondrial DNA seen with all concentrations
Henning, 2010	Bupivacaine 0.5% with/without methylparaben	Osteochondral explants from glenohumeral joints of canine cadavers	>50% cell with bupivacaine with/without preservative. No increase in toxicity due to preservative
Baker, 2011	0.5% bupivacaine, 0.5% Levobupivacaine, 0.75% ropivacaine and 2% lidocaine. Addition of MgSO ₄ to all solutions above	Human chondrocytes – cell viability using light spectroscopy	All anaesthetics reduced cell viability. Addition of MgSO ₄ to all solutions increased the number of live cells i.e. reduced toxicity
Baker, 2011	Bupivacaine (0.13, 0.25, 0.5%), levobupivacaine (0.13, 0.25, 0.5%), ropivacaine (0.19, 0.38, 0.75%), 10% magnesium sulphate	Human chondrocytes–cell viability using light spectroscopy	All solutions except 0.13% bupivacaine significantly reduced cell viability. No difference between control and MgSO ₄

Table 2 (Continued)

Author	LA/additive	Study design	Salient findings
Jacobs, 2011	1% and 2% lidocaine with or without adrenaline	Chondrocytes in alginate bead cultures – from TKA patients LDH activity, IL-6 concentration and cell viability	LDH activity increased for all solutions. IL-6 concentration reduced and increased cell death for all except 1% lidocaine with adrenaline
Miyazaki, 2011	Lidocaine 0.125–1% 1, 12 and 24 h	Bovine articular cartilage – cell viability using confocal microscopy	Cell viability worsened with increasing concentration and time of exposure of lidocaine
Park, 2011	0.5% bupivacaine, 2% lidocaine or 2% mepivacaine	Equine articular cartilage – cell viability and flow cytometry	Cell viability – 29% with bupivacaine, 67% with lidocaine and 87% with mepivacaine
Syed, 2011	Bupivacaine 0.25%, effect of buffering pH to 7.5	Human femoral condyles – chondral explants and monolayer cultures	Bupivacaine reduced cell viability to 72%. Buffering worsened viability to 22%

have been asked whether they are at all necessary. Townshend et al.³⁸ found no difference between visual analogue pain scores of patients with bupivacaine injection around the arthroscopic portals only and those with intra-articular injections. However, they assessed scores one hour after arthroscopy only and did not calculate the amount of oral opiate and non-opiate analgesia consumed. Campo et al.³⁹ injected knee joints with 10 ml of saline, 0.5% bupivacaine or 0.75% ropivacaine after arthroscopy and found a small improvement in analgesia by the addition of LAs. They felt that systemic analgesia should be preferred to LA intra-articular injection in view of the published reports of chondrotoxicity. In light of recent studies, alternative analgesia, such as intra-articular injection or parenteral administration of morphine, may need to be considered as it has been found to have no adverse effects on articular cartilage.^{11,12}

An ideal study assessing adverse effects of LA administration would involve a RCT comparing outcomes of arthroscopy in patients matched by age, gender and diagnosis who have an injection of LA into the joint with or without an injection of placebo. The differences between the three groups may not be evident at short-term follow-up because a single injection of LA is unlikely to cause severe articular cartilage damage or chondrolysis. Therefore, long-term follow-up will be required

with the development of osteoarthritis as an end-point to conclude causality. Such a trial is unlikely due the ethics of deliberately injecting a potentially toxic agent. Even with ethical approval, patients may not agree to being recruited once they see current evidence. One practical way would be to conduct a retrospective review of patients who have received LA into their joints for non-arthritic conditions, such as knee arthroscopy in young patients where no arthritis was identified. This can be compared to a similar group who have had arthroscopy but no LA.

It is difficult to explain why the shoulder is particularly vulnerable—it may be due to the fact that PPs are commonly used. Secondly, as the shoulder joint is non-weight bearing, the LA bathes the cartilage for protracted periods without extrusion. In 2010, Slabaugh⁴⁰ and Fester⁴¹ separately suggested that the shoulder may be vulnerable due to its small size. The authors both described cases of knee chondrolysis following the administration of intra-articular bupivacaine in young female sports women. It is suggested that the knee may be more tolerant due to its size, within which there is relative ease of fluid egress. In addition, the postoperative haematoma would dilute the LA and the shoulder also has thinner cartilage,⁴² which may further explain its susceptibility.

5. Conclusions

Current evidence suggests that intra-articular LA PP infusions carry high risk of chondrolysis and should not be used. While there is limited evidence that a single injection can cause chondrolysis, large doses are best avoided, especially in the glenohumeral joint. Further studies are required to assess whether a single exposure of LA to articular cartilage has long-term implications (Table 3).

Conflicts of interest

The authors have none to declare.

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Table 3 – Summary of the findings of this study.

- Chondrolysis is a devastating complication of arthroscopic surgery especially in young patients. A large proportion requires further surgery and most will eventually undergo arthroplasty
- Intra-articular LA PPs have a high risk of chondrolysis and should be avoided
- There is minimal clinical evidence of chondrolysis resulting from a single injection of LA
- Laboratory studies have demonstrated that bupivacaine, lidocaine, ropivacaine and levobupivacaine are all toxic to cartilage
- No toxicity has been shown with mepivacaine but the effect of different concentrations has not been studied
- Increase in dose or exposure time increases toxicity
- Effect of pH combined with LA is unclear
- Effect of adrenaline remains inconclusive
- Effect of preservatives is unclear
- There is limited evidence on mechanism of toxicity but mitochondrial DNA damage or chemical incompatibility has been suggested
- Combining other compounds, such as MgSO₄, may offer protection

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