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NARRATIVE REVIEW

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Review of intra-articular local anaesthetic administration in horses: Clinical indications, cytotoxicity, and outcomes

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Abstract

Equine practitioners frequently inject local anaesthetics (LA) intra-articularly in both diagnosis of lameness and for pain management intra- or post-operatively with synovial endoscopy. Recent reviews of the human and veterinary literature support the concept that chondrotoxicity of LA on joint tissues depends on the type of drug, dose administered, and duration of exposure. The purpose of this review is to summarise the current literature describing intra-articular local anaesthetic use, including both in vitro and in vivo studies, and to draw some comparisons to literature from other species where potential toxicity and duration of effect have been evaluated with the goal of advancing the field's understanding of intra-articular local anaesthetic use in horses, and indicating future directions for the field. The aggregate data available from all species, while generally sparse for horses, indicate that LA are rapidly cleared from the synovial fluid after injection, often within 30 min. In vitro data strongly suggest that lidocaine and bupivacaine are likely more chondrotoxic than other LA, although to what extent is still unknown, and cytotoxicity of LA may be mitigated through concurrent injection with HA, PRP, and drug combinations including nonsteroidal anti-inflammatories and opioids. The current body of in vitro research is not reflective of the in vivo environment, and further in vitro work, if performed, should focus on mimicking the native joint environment, utilising PK data and joint/injection volumes to replicate the native environment more accurately within the joint and the expected exposures to LA.

KEYWORDS
analgesia, horse, intra-articular, intra-synovial, lameness, local anaesthetic

1 | INTRODUCTION: HISTORICAL RATIONALE FOR INTRA-ARTICULAR LOCAL ANAESTHETIC USE

Local anaesthetics (LA) represent the only drug class able to provide anti-nociception while also having minimal systemic side effects when appropriately administered. In their day-to-day practice, intra-articular and intra-synovial injections of local anaesthetics are often performed by equine practitioners in the diagnosis of lameness, management of pain involving joints or other synovial structures, and peri-operatively to facilitate standing surgical procedures or recovery from general anaesthesia. Localisation of lameness in equine patients is commonly performed through sequential and specific injection of local anaesthetic solutions intra-articularly, perineurally, or through subcutaneous infiltration over a site, followed by observation for reduction in sensation or gait abnormalities.[1,2] Although interpretation of blocking patterns is increasingly understood to be less specific than once believed, diagnostic analgesia remains the most definitive method to localise

lameness in horses as well as to provide transient relief from pain arising from intra-synovial structures without causing central depression and with low risk of systemic side effects.[2] In human healthcare (and occasionally in veterinary settings), LA have also been administered as continuous infusions intra-articularly (IA) via pumps or wound infiltration catheters for enhanced pain management in the early post-operative period in both hospital and outpatient/in-home settings, the goal being to also reduce patient dependence on systemic analgesics such as opioids.[3]

Use of IA LA solutions to facilitate procedures using standing sedation or as part of a balanced anaesthetic protocol have been described with the goal to reduce requirements for systemic analgesics or general anaesthetics and reduce complications associated with recovery from general anaesthesia.[2,4] In humans the evidence generally supports the use of pre-operative IA administration of LA and/or opioids,[5–7] although other reports provide conflicting evidence of efficacy.[8] Due to the limited body of literature and slow pace of change in practice, equine clinical perspectives remain mixed regarding use of LA in the early post-operative period with concern by many for LA administration to cause reduced proprioception resulting in catastrophic injury in recovery from general anaesthesia as well as the possibility of chondrotoxicity and cartilage damage. This was examined specifically in horses by Gaesser et al. in 2020,[9] where horses that received IA mepivacaine were described as maintaining a more even plane of anaesthetic depth during surgical stimulation and the quality of recovery was not found to be affected. However, further evidence is needed prior to more widespread use of LA in this setting in horses, despite the almost universal adoption in human healthcare.

This review will discuss published reports of IA LA use in horses and other species, including available products, mechanisms of action, evidence for toxicity and other clinical considerations, and the use of additive therapies injected concurrently with LA. The objectives are to summarise the current, and often conflicting, literature on use of this drug class in synovial structures of horses as well as to identify remaining knowledge gaps towards the goal of assisting veterinarians with making evidence-based decisions in clinical practice as well as informing future research.

A brief summary of the relevant manuscripts cited throughout is available in Tables S1 and S2.

2 | CURRENT OPTIONS FOR LOCAL ANAESTHETICS

Local anaesthetic selection: Selection of LA is generally based upon a number of salient factors, including commercial availability, desired duration of action, location of injection, and potential to induce chondrotoxicity or local tissue reaction. LA commonly found in equine practice include lidocaine, mepivacaine, ropivacaine, and bupivacaine, as well as liposomal encapsulated bupivacaine. In the United States and European countries, lidocaine (2%) and mepivacaine (2%) are most commonly used for diagnostic analgesia in horses, while in other regions bupivacaine (0.5%) or ropivacaine (0.5% or 0.75%) may be more readily available.[2] All of the available LA can be sourced commercially in multiple concentrations for use under varying circumstances (e.g., bupivacaine 0.25%, 0.5%, 0.75%, ropivacaine 0.2%, 0.5%, 0.75%, etc.). Liposomal bupivacaine suspension (under the trade name Exparel® [Pacira Pharmaceuticals]) has become popular in human surgery for post-operative tissue infiltration for abdominal procedures, hip, knee, and shoulder surgery, as well as various nerve blocks,[3,10–15] and is currently licensed in veterinary medicine (under the trade name Nocita® [Elanco US]) for tissue infiltration in dogs for post-operative analgesia after stifle surgery and in cats as nerve blocks for onychectomy. Reports in horses to date have evaluated the use of liposomal bupivacaine IA,[16] perineurally,[17–19] and intra-abdominally,[20] with variable results regarding analgesia.

Mechanism of action: All LA act by blocking sodium influx through the voltage gated sodium channels on the cell membrane. They do this on the inside of the channel, and so must cross the cell membrane first to get to their site of action. Because LA are a mixture of the ionised (water soluble) and unionised (able to cross cell membranes) forms, the local pH effects the intracellular availability of the drug. In a low pH (acidic) environment, less of the LA will be available to cross the membrane to the site of the majority of its action as there will be a larger protonated (therefore ionised) fraction extracellularlly.[21,22] In addition, decrease in local pH has an effect on the rigidity of cell membranes, which decreases the ability of LA to cross into the cytoplasm of the cell.[23] The increase in intracellular H+ ions will also increase the amount available for Na + channel blockade[22] and will also lead to trapping of the LA within the cell and make it unable to diffuse out to be removed, increasing the risk of cellular toxicity. Therefore, it is expected that LA will have a decreased efficacy in the presence of significant inflammation, but this complex interplay can cause the effects of LA to be unpredictable in this environment.

In addition, the magnitude of neural blockade achieved also relates to the type and diameter of nerve fibres and degree of nerve myelination,[24] and may vary between LA, location of injection and species. In general, the larger fast conducting nerve fibres (A α and β) that subserve motor and touch are more difficult to block due to their thicker myelin sheath and heavier peri- and epineurium, while the smaller diameter and less or non-myelinated B and C fibres are subject to more dense and rapid blockade by LA. As joint innervation can vary depending on its location (proximity to significant motor nerves, contribution to proprioception, etc.), generalisations across different joints regarding magnitude and duration of the effects are difficult to make, although there is little variation within species regarding innervation of the same articular structures.

Duration of action: Duration of action of LA varies between drugs and may be affected by whether the agent is administered into inflamed tissue or joints (due to local pH and cell membrane changes as noted above) as well as the chronicity or degree of pain associated with the underlying condition.[23,25] While specific studies evaluating the duration of action of LA when injected IA are lacking, their relative onset and duration times are presumed to be similar to those found after injection in other scenarios. Lidocaine has the quickest onset of action, within 3–5 min, as well as the shortest duration of anti-

nociception, anywhere from 30 min to 3 h, while mepivacaine make take 5–10 min for effect and reportedly lasts 90 min to 3 h.[26–31] For this reason, mepivacaine is commonly used for diagnostic analgesia as its duration of action is longer than that of lidocaine and typically sufficient time for clinicians to perform subsequent blocks towards localisation of lameness. While not evaluated in horses, bupivacaine and ropivacaine have similar onset to each other (15–30 min) and duration of action from 3 to 8 h after tissue infiltration and nerve blockade and have been demonstrated to perform similarly in humans.[25] The long duration of action of these 2 LA makes them more attractive for pain management purposes. Finally, liposomal encapsulated bupivacaine has demonstrated anticonception for up to 72 h, but similarly to the other LA, the onset, duration of action and efficacy after intra-articular administration has not been fully evaluated.

3 | PREVIOUS SUMMARIES OF INTRA-ARTICULAR LOCAL ANAESTHETIC USE IN HUMAN HEALTHCARE

There have been a number of review articles published to date that summarise previous literature related to potential chondrotoxicity of LA in humans.[32–36] These reviews, taken together, indicate that exposure to high concentrations of LA for extended periods of time is detrimental to articular cartilage, bupivacaine and lidocaine are particularly prone to causing chondrotoxicity, and continuous infusion IA via pain pumps is likely contraindicated except in the setting of total joint arthroplasty. In addition, if LA are to be used IA, other factors that have been shown to be detrimental to cartilage should be avoided such as the use of concurrent corticosteroids and use of normal saline for arthroscopic lavage fluid.

One of the earliest reviews was published in 2011 by Piper et al.[34] and compares the effects of bupivacaine and lidocaine in varying concentrations as they had been studied to that point in time. Conclusions drawn from that paper included the concept that lidocaine and bupivacaine were inherently chondrotoxic to human articular cartilage, that increased concentration and time of exposure resulted in increased risk of chondrolysis, and that compromised cartilage is more susceptible to LA induced chondrotoxicity. A scoping review was undertaken by Gulihar et al.[32] and published in 2015 that integrated 41 papers deemed appropriate for inclusion and comprised available literature from all species, with 18 case series and 23 laboratory studies; notably, no randomised controlled trials were identified for inclusion. Their main findings were that intra-articular LA pain pump infusions carry a high risk of chondrolysis and should not be used, there is limited evidence that a single injection can cause chondrolysis, large doses of LA should be avoided (especially in the glenohumeral joint), and further studies are required to assess whether a single exposure to LA has long-term implications on articular cartilage. It is unknown why the glenohumeral joint in particular would be more susceptible to the negative effects of LA, but it is possible that a temporal change in practice (addition of continuous infusion catheters after shoulder surgery) caused a secondary mechanical insult in addition to the LA effects in this particular surgery rather than the joint being particularly prone to chondrolysis after injection with LA.

An updated summary of available literature was published in 2017 by Kreuz et al.,[35] which examined available data comparing the effects of bupivacaine (0.5%, 0.25%, 0.125%), lidocaine (2%, 1%, 0.5%), mepivacaine (2%, 1%, <1%) and ropivacaine (0.5%, 0.2%, 0.1%). Findings included that bupivacaine and lidocaine demonstrate a greater degree of chondrotoxicity compared to mepivacaine and ropivacaine and were in agreement with previous findings that increased concentration and time of local anaesthetic exposure correlated with an increased risk of chondrotoxicity. Findings of Kreuz et al.[35] further supported the concept that compromised cartilage is more susceptible to chondrotoxicity which could put patients with preexisting osteoarthritis at an increased risk for disease progression following intra-articular injection and prompts clinicians to consider the toxicity of LA on cartilage metabolism when selecting doses used.

When evaluating the literature concerning risk factors for chondrolysis in the specific setting of arthroscopic surgery, Kohli et al.[36] concluded in 2020 that 'injecting local anaesthetics into joints needs careful consideration of risks and benefits and should not be routine practice post-arthroscopy and pain pumps must be avoided. More clinical studies are required …'. The majority of the clinical cases that were evaluated were in the glenohumeral joint (in humans), and 97.7%–100% of these cases involved the use of a pain pump for continuous intra-articular infusion of LA. Interestingly, the lower the dose of LA infused, the less likely the studies were to see chondrolysis. They also noted that most of the documented cases of chondrolysis had multiple risk factors and the individual effects on any one of those studies was difficult to define. A 2019 systematic review by Jayaram et al.,[33] focused specifically on the effects of IA LA on human knee cartilage, identified and summarised 16 studies that were published as of the date of submission. They also concluded that the chondrotoxic effects of the commonly used LA (lidocaine, bupivacaine, ropivacaine, levobupivacaine, and mepivacaine) were in part dose-dependent, duration-dependent, and specifically in their findings the chondrotoxicity could be exacerbated by concurrent corticosteroid use. Ropivacaine at concentrations of <0.75% appeared to be the least toxic of the LA studied, while bupivacaine at >0.5% demonstrated the most toxic effects.

4 | PHARMACOKINETICS OF INTRA-ARTICULARLY ADMINISTERED LOCAL ANAESTHETICS

In equine models: While there is only one peer-reviewed study in horses, and that one evaluated the pharmacokinetics (PK) of liposomal bupivacaine alone, multiple studies using in vitro tissues in multiple mammalian species have demonstrated LA induced toxicity to be related to duration of exposure (in addition to drug and dose), highlighting the importance of determining how long LA remain in the joints and surrounding tissues into which they are injected. The IA PK of bupivacaine when injected as the liposomal encapsulated form were studied by Knych et al.[16] in which 16 horses each received

one 0.12 mg/kg dose of liposomal bupivacaine in the right antebrachiocarpal joint. Intra-articular and plasma bupivacaine concentrations were determined over time, and the bupivacaine plasma terminal half-life was determined to be 17.8 ± 5.42 h in horses who had synovial fluid sampled daily and 11.9 ± 5.17 h for horses who were only sampled once at 96 h from injection. The synovial fluid terminal half-life was found to be similar to the former at 16.4 ± 5.38 h. Bupivacaine was still detected in the synovial fluid of horses in both groups tested at 96 h from injection with concentrations ranging from an average of 1.17 ng/mL in the multiple-sampling group to 4.27 ng/mL in the single sample group. While the continued presence of bupivacaine in the joint over a period of 96 h suggested efficacy as a longer-term local analgesic compared to conventionally available options, the longer duration of exposure to chondrocytes indicated increased potential for chondrotoxicity, although measured concentrations were well below those that have been shown in vitro to have no detrimental effects on chondrocytes. Notably, liposomal bupivacaine was not compared to other IA administered LA in this study.

Pharmacokinetics in other species: A study by Barry et al.[37] demonstrated that bupivacaine concentrations decreased rapidly in the synovial fluid of both osteoarthritic and non-osteoarthritic canine stifles after injection of 0.2 mL/kg of 0.5%. Initial concentrations after injection were approximately 1/2 as high in the osteoarthritic stifles, attributed to a significant increase in synovial fluid volume from 0.08 to 0.2 mL/kg, but synovial fluid concentrations were decreased to <25% of the initial concentration in both groups after 30 min. Several studies have also evaluated the plasma pharmacokinetics of LA in dogs and humans after IA injection. When 0.3 mL/kg of 0.5% bupivacaine was injected into the stifle joint of normal dogs, the time to peak plasma concentrations (T_{max}) was 11.37 min when injected alone and 10.37 min when followed by an 8-h continuous infusion of bupivacaine, indicating rapid uptake and distribution away from the joint.[38] All of those subjects had a normal orthopaedic exam at 4 weeks after injection. A short plasma T_{max} (between 5 and 15 min) was also noted when bupivacaine was added to the arthroscopy fluid for human knee surgeries.[39] Following arthroscopic knee surgery with tourniquet placement in human patients, a longer T_{max} was found after a single IA injection of 40 mL of 0.25% bupivacaine (43.4 min),[40] but this was deemed likely due to the use of a tourniquet and extensive local tissue binding of the drug prior to tourniquet removal by the authors.

Summary of the pharmacokinetics of intra-articularly administered local anaesthetics: Based on the sparse data available, it would appear that bupivacaine is rapidly redistributed out of the synovial fluid after injection, with the majority of the drug being cleared by 30 min post-injection. Synovial fluid concentrations of bupivacaine are also persistent but remain low after IA injection with liposomal encapsulated bupivacaine. Unfortunately, there are no studies evaluating the correlation between synovial fluid concentrations and analgesia, and the sparse data available indicate a disconnect between measurable concentrations and efficacy when used intra-articularly,[41–43] nor are there any studies evaluating other LA. Further investigations should focus on tissue and nerve distribution of LA in the periarticular region in addition to synovial and plasma concentrations in order to shed light on these data.

5 | IN VITRO STUDIES OF TOXICITY

In equine models: Park et al.[44] investigated the chondrotoxic effects of various LA on equine cartilage. Equine cultured chondrocytes were exposed to bupivacaine (0.5%–0.125%), lidocaine (2%–0.5%) and mepivacaine (2%–0.5%) for up to 60 min and cell viability was assessed via trypan blue exclusion assay, MTT assay, fluorescence microscopy and flow cytometry. After 30 min of exposure, cell viability was the lowest in the group exposed to 0.5% bupivacaine (28.73% ± 8.44%) while the saline control group maintained 95.95 ± 2.75% viability. Mepivacaine (2%) and lidocaine (2%) induced intermediate effects relative to bupivacaine and saline. Other assays produced similar findings in regard to relative ranking of induced toxicity, with bupivacaine being most toxic, followed by lidocaine, then mepivacaine. A separate study by Adler et al.[45] produced similar results, with higher concentrations of LA being more cytotoxic and bupivacaine and lidocaine demonstrating more cytotoxicity after 30 and 60 min of exposure than mepivacaine and ropivacaine when assessed by MTT and LDH assays. Mepivacaine and ropivacaine were noted to be more cytotoxic to fibroblast-like synoviocytes in this study, although different assays produced different conclusions, highlighting the complex interplay between the various tissues in vivo as well as the difficulty in interpreting the results of any one particular assay.

In another synoviocyte/chondrocyte coculture model, both bupivacaine (0.22%) and mepivacaine (0.44%) were noted to decrease cell viability after 2 h of exposure followed by 2 days of culture as compared to control, and although not compared to each other the mean cell viability appeared to be higher in the bupivacaine group.[46] In this study, levels of pro-inflammatory cytokines were also increased in the LA groups as compared to control.

Interestingly, another investigation performed in 2021 by Hussein et al.[47] did not show any significant detrimental effects to donkey chondrocytes after exposure to 5% bupivacaine for 30 min as evaluated by a MTT and live/dead assay.

In other species: Breu et al.[48] evaluated the effects of multiple concentrations of bupivacaine (0.031%–0.5%), ropivacaine (0.031%–0.75%) and mepivacaine (0.031%–2%) on human cultured chondrocytes as well as cartilage cores. Cells were evaluated over 96 h for cell death and apoptosis and/or necrosis and it was found that only the highest concentrations of these agents demonstrated significant cell death via either pathway at 96 h, with bupivacaine 0.5% having a significantly higher percentage cell death at the final time point. At lower concentrations there was no difference noted between any groups and saline control at 96 h. There was, however, a noticeably higher concentration of dead cells at 24 h than there was at 96 h in the lower concentration exposure groups in this study. Cartilage from osteoarthritic joints demonstrated higher percentages of dead cells as well as significantly worse cell morphology as compared to healthy cartilage as well. Chu et al.[49,50] also evaluated the effects of bupivacaine at concentrations ranging from 0.125% to 0.5% in both bovine and human chondrocytes via live/dead assays and time lapse chondrocyte imaging and noted no difference from control in the lowest concentration group (0.125%) with progressive increases

in the number of dead cells as the concentration of bupivacaine increased. They also noted that removing the top 1 mm of cartilage of the cores (to simulate cartilage damage) increased the percentage of dead cells. The concentration dependent inhibition of articular cartilage synthesis by bupivacaine was also noted by Nole et al.[51] based on $^{35}SO_4$ incorporation after 2 h of exposure to various concentrations from 0.06% to 0.5% followed by 18–24 h of culture.

The detrimental effects of high concentrations of bupivacaine (0.5%) on healthy cartilage was further corroborated by Hennig et al.[52] where osteochondral cores from dogs were exposed to bupivacaine 0.5% for up to 30 min both with and without the preservative methylparaben. When viability was compared at 5, 15, and 30 min, the bupivacaine treated groups demonstrated significantly decreased cell viability in the superficial chondrocyte layer, but no change in cell viability in middle or deep layers.

Anz et al.[53] investigated the effect of continuous exposure of cartilage to bupivacaine 0.133% in a 48-h cartilage/synovium coculture model using the pro-inflammatory cytokine IL-1β to simulate osteoarthritic joints and reported that, while bupivacaine inhibited an increase in inflammatory biomarkers, this was likely due to a significant decrease in cell viability in the bupivacaine treated groups as compared to controls.

In 2009, Lo et al.[54] published a study investigating the impact of either bupivacaine (0.25%), lidocaine (1%), or ropivacaine (0.5%) on the cell viability of bovine articular cartilage discs using fluorescence microscopy and manual counting of live/dead cells. The authors cultured the discs in decreasing concentrations of each LA for up to 12 h and demonstrated a dose- and duration-dependent detrimental effect of all LA evaluated. At 1 h, both bupivacaine 0.25% and ropivacaine 0.5% were similar to the control, while lidocaine 1% demonstrated significantly decreased viability at this time point. In addition, concentrations of all LA tested at <0.05% were similar to the control, with higher concentrations demonstrating decreased cell viability in a linear fashion. The detrimental effects of high concentrations of lidocaine on cultured bovine chondrocytes were also noted by Karpie and Chu,[55] where a significant decrease in cell viability at 7 days was noted after exposure to as little as 15 min of 2% lidocaine. Bianchini et al.[56] also demonstrated a decrease in cell viability of canine articular cartilage exposed to either 1% or 1.8% lidocaine but reported a potential protective effect when platelet rich plasma was coadministered.

A number of studies have noted significantly higher cell viability in cultured human chondrocytes after exposure to ropivacaine 1%, similar to control levels, than what was seen after exposure to either bupivacaine 0.25% or lidocaine 1% for 1 h.[57] Shaw et al.[58] compared the chondrotoxicity of bupivacaine (0.5%), ropivacaine (0.5%), and 1.3% liposomal bupivacaine on bovine chondrocyte derived cells. Cells were plated and exposed to each solution without dilution for 1 h, then were washed and allowed to incubate in medium for an additional 23 h. Liposomal bupivacaine had the highest cell viability (as assessed by flow cytometry) of all treatment groups, followed by ropivacaine and bupivacaine, which had the lowest chondrocyte viability of the anaesthetic solutions tested. Finally, more recent evidence evaluating the effect of bupivacaine (0.05%–0.5%) versus liposomal bupivacaine (0.67% and 1.33%) on canine chondrocytes demonstrated a concentration dependent toxicity with the bupivacaine but concluded that at clinically relevant doses a single IA administration may not be detrimental, as the concentrations expected IA after injection demonstrated no difference from saline controls.[59] However, the clonogenicity assay demonstrated lower cell survival in both liposomal bupivacaine treated cultures and the authors cautioned that release of bupivacaine from liposomal encapsulated products may have a time-dependent effect resulting in chondrotoxicity and further investigation was warranted prior to use in vivo.

The further effects of pH changes in combination with local anaesthetics (as well as epinephrine and preservatives) was evaluated by Dragoo et al.[60] using human chondrocytes in a model designed to mimic IA catheter pain pumps. They found that cell death (evaluated with calcein AM live/dead staining) was significantly higher than controls at a pH of 4.5–5.0, with the lowest pH being associated with a cell death rate of >70%. There was also a significant increase in the numbers of dead cells when epinephrine was added to both lidocaine 1% and bupivacaine 0.25%, but this was likely due to the decreased pH of these solutions, as the two LA alone did not demonstrate any difference from the control group.

Summary of in vitro data: While these studies support potential toxicity of various local anaesthetics, selection and dose of local anaesthetic have a significant effect on the extent of damage induced. Many studies have used concentrations that are impossible to achieve within the joint in normal clinical scenarios and for durations that are physiological implausible, making the interpretation of the aggregate data difficult and the applicability to the in vivo environment questionable. In any case, lidocaine and bupivacaine are likely more chondrotoxic than other LA studied, and the concentration of LA used for IA injections should be the lowest possible while maintaining the desired analgesia.

6 | IN VIVO STUDIES OF TOXICITY

In equine models: Piat et al.[61] examined the effects of 2% lidocaine and 0.5% bupivacaine in the tarsocrural and intercarpal joints of six healthy mares by measuring biomarkers of cartilage matrix synthesis (CS846-aggrecan and CPII-type II collagen) and collagen degradation (C2C and C1,2C). Both local anaesthetics resulted in increased production of CS846-aggrecan and CPII-type II collagen, indicating synthesis of aggrecan cartilage and type II collagen, respectively. Bupivacaine (0.5%) was also associated with a decrease of type II collagen biomarkers C2C and C1,2C. The authors postulated the increase of anabolic markers could be an indication of a healing response after cartilage injury, although this was not supported by the lack of increase in cartilage degradation markers in either group.

Adler et al.[62] further compared the effects of lidocaine (2%) and mepivacaine (2%) in the middle carpal joints of 12 horses. They compared synovial fluid parameters including total nucleated cell count, neutrophil percentage, and total protein in synovial fluid, as well as neutrophil myeloperoxidase, neutrophil elastase, and Coll2-1.

They observed that lidocaine and mepivacaine induced synovial fluid changes that were indicative of inflammation and a catabolic collagen response, with lidocaine inducing more significant changes within synovial fluid than mepivacaine. Knych et al.[16] evaluated the intra-articular inflammatory effects of liposomal bupivacaine (1.33%) in 16 horses, each of which received one 0.12 mg/kg dose in the right antebrachiocarpal joint. Intra-articular bupivacaine concentrations were determined in the joint over time, and biomarkers of collagen degradation (C2C, C12C) and cartilage matrix synthesis (CPII, CS846) were assessed at multiple time points out to 96 h. Synovial fluid of horses who were only sampled once at 96 h had significant increases in C12C and C2C present indicating some degree of collagen degradation, while the remaining horses who were sampled daily had an increase in CPII at 48 h and an increase in CS846 at 24 and 48 h, demonstrating an increase in cartilage matrix synthesis in this group. Finally, in 2021, Hussein et al.[47] examined the effects of injecting 5 mL of 5% bupivacaine in the middle carpal joint of 10 donkeys and evaluated the joints via radiography, CT imaging, histological evaluation, biochemical evaluation of serum and synovium, and qPCR evaluation of catabolic marker expression following injection. Despite the high concentration of bupivacaine administered there were no significant pathological changes found through any modality in this study.

In other species: The effects of LA on animal cartilage in vivo were studied in 1985 by Nole et al.[51] who evaluated the impact of 0.5% and 0.25% bupivacaine on the metabolism and ultrastructural integrity of canine and swine cartilage in situ. They determined that cartilage synthesis was significantly inhibited by injection of either bupivacaine or normal saline, but sulfate incorporation returned to normal by 72 h following bupivacaine treatment and no ultrastructural changes were appreciated via light or electron microscopy, a finding that was also noted by Fulkerson and Winters[63] at 6 days post-injection. Gomoll et al.[64,65] further studied the effects of 0.25% bupivacaine in the glenohumeral joint of rabbits. Local anaesthetic treated tissues were assessed using live/dead assays via confocal microscopy, for metabolic sulfate uptake, proteoglycan synthesis and content, radiographic changes, and via histology. Cell viability decreased by 20% and 30% and sulfate uptake decreased 50% and 56% in the presence of bupivacaine and bupivacaine/epinephrine, respectively. Histologic scores were significantly worse in tissues treated with bupivacaine as well as bupivacaine with epinephrine compared to controls. No macroscopic or radiographic changes were observed; however, PG content and sulfate uptake were both increased in shoulders treated with bupivacaine and bupivacaine with epinephrine. No significant differences were found among groups in cell counts, percentage of living cells, or histological grade.

In 2010, Chu et al.[66] investigated the delayed effects of 0.5% bupivacaine in the stifle joint of rats. They examined cell viability, cell density, and histology grade via a modified Mankin score. No differences were seen in viability via live/dead assay or histology grading score, but 50% reduction in chondrocyte density was observed in the bupivacaine treated groups 6 months following administration. Yazdi et al.[67] noted similarly that injection of 2 mL of 2% lidocaine into the stifle joint of rabbits reduced the viability of chondrocytes and increased gene expression of collagen type II and aggrecan, markers of collagen synthesis, at 8 weeks after injection. In 2015, Sherman et al.[68] investigated the effects of 0.0625% bupivacaine or 1% lidocaine in combination with methylprednisolone or triamcinolone on the cartilage of canine glenohumeral joints. The viability of synoviocytes and chondrocytes was determined through Calcien AM and Sytox Blue live/dead fluorescent stains, and cell metabolism was evaluated via the alamar blue additive test. Only the groups treated with lidocaine showed a decrease in cell metabolism and viability scores after 24 h in vivo followed by 7 days of culture.

Shaw et al.[69] evaluated bupivacaine 0.5% versus liposomal bupivacaine 1.3% injections in a swine stifle model (5 mL each) and found significantly more non-viable cells (via calcein AM live/dead assay and confocal microscopy) after 7 days in the bupivacaine group (33% non-viable) versus the liposomal bupivacaine group (6.2%) and the non-treated control (5.8%), but no visible histologic changes were noted in any group. They theorised that the low concentrations of bupivacaine eluted from the liposomal bupivacaine over time were not high enough to cause significant chondrocyte death. This lack of significant histologic changes caused by a low dose of bupivacaine was also noted by Pek et al.[70] after placing bupivacaine loaded microspheres into the stifle joint of goats. While the stifle (and plasma) bupivacaine concentrations remained at 10–15 μg/mL for at least 10 days, no changes were noted in proteoglycan content or microscopic histology at 28 days post-implantation.

Summary of in vivo studies of cytotoxicity: Taken together, these studies suggest that the cytotoxic effects observed in vitro with many LA may be mitigated in the in vivo joint environment, but it is noteworthy that these studies investigated intact cartilage and their findings may not be representative of effects seen with compromised osteoarthritic cartilage. These findings further support consideration of local anaesthetic selection, dose, and especially concentration prior to administration, particularly in osteoarthritic synovial structures.

7 | EVALUATION OF EFFICACY

In equine models: LA have long been valued for their efficacy in the diagnosis and treatment of pain and their rapid onset of action render them useful in a variety of clinical scenarios. An early study by Andreen et al.[26] demonstrated that an IA injection of 10 mL of mepivacaine 2% into the middle carpal joint completely ameliorated the lameness associated with an induced synovitis (via prior injection of 1.5 μg of LPS) for 60 min without any noted complications.

To evaluate analgesia in the peri-operative period, Gaesser et al.[9] evaluated anaesthesia and recovery characteristics in 22 horses undergoing carpal arthroscopy and receiving an intra-articular injection of either saline or mepivacaine 2% (10 mL) prior to surgery. While quality of recovery and necessity for blood pressure support were similar between groups, parameters indicating reactivity to surgical stimulation (such as heart rate and blood pressure) were decreased in the horses receiving pre-operative IA mepivacaine prior to joint distension and osteochondral fragment removal. Additional ketamine

supplementation was also required to maintain appropriate anaesthetic depth in two horses in the saline control group.

In other species: The majority of the data regarding the efficacy of IA local anaesthetics comes from human trials and has often been gathered in the setting of arthroscopic knee surgery. A 1999 systematic review that included only randomised, controlled trials found a small decrease in pain scores for up to 4 h after surgery in 60% of the included studies and concluded that the addition of IA LA could be clinically useful even though the differences between groups were small.[43] A 2015 meta-analysis by Sun et al.[71] concluded that IA bupivacaine could provide effective pain relief for up to 24 h, although the authors also noted that the majority of randomised, controlled trials only showed it to be effective for 12 h. A number of individual studies have also demonstrated that IA LA provide effective analgesia after arthroscopic surgery of the knee[6,40,72–76] and TMJ arthroplasty[77] in humans. The duration of meaningful analgesia varied from 30 min[74] to over 7 h[75] and even up to 24 h.[73] The addition of other medications (mainly opioids) to the injection also appeared to significantly increase the duration of analgesia in the majority of studies (see later section on additives), and the timing of injection (pre- vs. post-operatively) may also play a role, with a single study noting that pre-operative administration of bupivacaine 0.5% (5 mL) + fentanyl 0.1 mg provided significantly more profound analgesia than the post-operative administration of this combination or bupivacaine 0.5% alone.[6]

In dogs, the injection of 0.2 mL/kg of 0.5% bupivacaine into the stifle both pre- and post-TPLO surgery significantly increased the time until the first dose of post-operative analgesia from 2.5 h in the control group to 7.3 h in the bupivacaine group as evaluated by hourly pain scoring.[42] Sammarco et al.[41] noted a significant decrease in pain scores for up to 24 h after the injection of a higher dose of 0.5 mL/kg of 0.5% bupivacaine in canine stifles after extra-capsular CCL stabilisation.

Summary of evaluation of efficacy: While data in animal models are sparse, there are several decades of data in humans that indicate meaningful analgesia can be provided peri-operatively with the addition of IA local anaesthetics. The available data available from animal models is similar, in that significant analgesia appears to be achieved with the injection of IA LA in the peri-operative period.

8 | ADDITIVES TO LOCAL ANAESTHETIC INJECTIONS

Rationale behind additives: Various additives have been investigated for coadministration with LA as either preservatives to reduce bacterial growth in solutions, as vasoconstricting agents to prolong duration and intensity of anaesthesia, or as chondroprotectants to minimise the observed local cytotoxic effects of LA to joint tissues.

Preservatives: Methylparaben and sodium metabisulfite are preservatives frequently included in LA solutions with the goal to prevent or reduce bacterial growth within the solution as well as allow for the bottle to be labelled for multiple doses. Alterations in the chondrotoxicity of bupivacaine caused by the addition of methylparaben were investigated by Hennig et al.[52] in both intact and debrided (to simulate osteoarthritis) canine cartilage discs. More significant chondrocyte death was seen in intact cartilage discs treated with bupivacaine and methylparaben versus bupivacaine alone, and greater chondrocyte death was seen in both treatments compared to control in debrided cartilage discs. Dragoo et al.[60] demonstrated a significant degree of cell death in human cultured chondrocytes exposed to sodium metabisulfite (>30%); however, the methylparaben exposed group was not different from control in their study. Alder et al.[62] further evaluated injection of methylparaben in the middle carpal joint of horses compared to lactated ringers' solution as control, and while the mean synovial fluid total protein concentration was higher in the methylparaben group compared to control, no differences were seen in lameness, synovial fluid total nucleated cell count or neutrophil percentage between groups. As to the possible change in the pharmacokinetics of local anaesthetics attributed to inclusion of preservatives, Barry et al.[37] noted that inclusion of methylparaben did not significantly affect the diffusion of bupivacaine 0.5% from the joints of osteoarthritic dogs, as plasma concentrations of bupivacaine were not different between patients that received IA bupivacaine alone or bupivacaine with methylparaben. While there may be a small increase in the cytotoxicity of some LA in the presence of methylparaben, the data taken together indicate that the preservative methylparaben does not induce clinically significant inflammatory effects or increase cartilage damage in joints. The preservative sodium metabisulfite should be avoided at the present time, however, until further data becomes available.

Vasoconstrictors: Epinephrine, a potent vasoconstrictor, has been added to LA solutions to prolong duration of anaesthesia as well as increase intensity of effect.[2,71,78,79] Epinephrine has been described to be most commonly added at a dose of 5 μg/mL (1:200 000 concentration) and is available commercially in conjunction with both lidocaine and bupivacaine at this concentration. Anecdotally, commercial preparations of LA containing epinephrine are relatively less potent compared to solutions to which epinephrine has been added immediately prior to use, although this does not appear to have been studied in any scientifically rigorous manner. Epinephrine also does not appear to prolong the action of ropivacaine when used as a nerve block,[80,81] which has been attributed to the drug itself having inherent vasoconstrictive properties.[82] While reports exist discussing potential side effects of LA containing epinephrine including soft tissue swelling, necrosis, or growth of white hair at the injection site if leakage into the subcutaneous tissue has occurred, these effects have not been observed to the authors' knowledge when properly diluted (<1:100 000).[2,83]

Several studies have investigated the effects of epinephrine, either alone or as an additive, on articular cartilage. Lo et al.[54] evaluated bovine articular cartilage in vivo in which bupivacaine (0.25%), lidocaine (1%), and ropivacaine (0.5%) were compared with and without the addition of exogenous epinephrine (1:200 000, 5 μg/mL). While epinephrine alone did not negatively affect chondrocyte viability, bupivacaine with epinephrine resulted in decreased levels of cell membrane integrity when compared with bupivacaine alone. Interestingly, these effects were not seen when epinephrine was added to lidocaine or ropivacaine, suggesting something unique to bupivacaine contributes to chondrotoxicity in the presence of epinephrine. Dragoo

et al.[60] validated these findings in a live/dead cell staining model of human cultured chondrocytes, noting no difference from control when chondrocytes were incubated with epinephrine at either 1:100 000 or 1:200 000, but significantly higher levels of cell death when epinephrine was added to either lidocaine 1% or bupivacaine 0.25% as opposed to the LA alone. In this model, it was hypothesised that the decreased pH (4.0–4.5) of the epinephrine containing solutions was likely to blame for the changes in chondrocyte toxicity. This cytotoxic effect of changes in pH in combination with epinephrine was noted to decrease at a pH of >5.0.[55,60]

Gomoll et al.[64,65] investigated the effects of a continuous infusion of bupivacaine (0.25%) into the glenohumeral joint of rabbits with and without the addition of epinephrine. The first experiment in 2006 compared histology scores and measured sulfate uptake as an indicator of chondrocyte metabolism. Both bupivacaine and bupivacaine combined with epinephrine group resulted in higher sulfate uptake and worse histology scores compared to saline control; however, no differences were seen between those with and without epinephrine, although epinephrine alone was not evaluated. A second study in 2009 produced similar results, in which the groups of rabbits receiving bupivacaine and bupivacaine with epinephrine had significantly increased levels of PG synthesis and content as compared to the control, but inclusion of epinephrine did not induce greater apparent toxicity. Taken together, these studies suggest that addition of epinephrine, when appropriately diluted and pH adjusted, does not induce greater cytotoxicity compared to LA alone but further evaluation of duration and intensity of effect when administered IA is warranted.

Opioids: While morphine has become a popular analgesic option when used as a stand-alone drug for IA injections,[84,85] a number of opioid/LA combinations have also been evaluated for their analgesic effects in this scenario. The IA combination of ropivacaine and morphine (20 mg each) was shown to produce significantly longer analgesia (>24 h) and had a faster onset than injection of 40 mg ropivacaine alone in an equine LPS induced synovitis model, and no complications were noted for the duration of the study.[86] A significant improvement in analgesia was also noted with the addition of morphine to ropivacaine and delivered as a continuous infusion for 3 days after total knee replacement in humans,[87] although this particular study lacked a contemporaneous LA control group, and obviously cartilage health could not be examined. Interestingly, in the setting of TMJ surgery, the addition of morphine 1 mg to mepivacaine 30 mg decreased the duration of analgesia approximately 3-fold.[77] The addition of morphine (2.85 mg/mL) to either bupivacaine (2.2 mg/mL) or mepivacaine (4.4 mg/mL) does not, however, seem to ameliorate the negative effects of the LA as seen by decreased cell viability and increased gene expression of pro-inflammatory cytokines.[46]

Fentanyl and tramadol also both appear to increase the magnitude and duration of analgesia provided by a single injection of bupivacaine 0.25% after arthroscopic knee surgery in humans, with fentanyl increasing the duration by approximately 2-fold[75] and tramadol 4-fold or more.[76] Both drugs also decreased the amount of supplemental analgesia administered in these two studies. Both morphine and fentanyl have also been shown to have minimal to no cytotoxic effects on chondrocytes in vitro.[46,53,88,89] This may not be true for other opioids, as high dose buprenorphine[90] and meperidine at all doses tested[88] have demonstrated significant cytotoxicity to chondrocytes in vitro.

Corticosteroids: LA have reportedly been combined in clinical situations with corticosteroids or hyaluronic acid when both confirming localisation of lameness to a synovial structure and treating suspected osteoarthritis are desired. Sherman et al.[68] investigated the effects of 1% lidocaine and 0.0625% bupivacaine in combination with methylprednisolone or triamcinolone injected into the shoulder joint of dogs. The treatment groups were saline/control, methylprednisolone/1% lidocaine, triamcinolone/1.0% lidocaine, and triamcinolone/0.0625% bupivacaine. Cell metabolism and subjective synoviocyte viability scores were reduced in the group receiving methylprednisolone/lidocaine in vivo compared to control at 1 day following injection. Cell density and synoviocyte viability were further reduced ex vivo in the methylprednisolone/lidocaine group at day seven, leading the authors to conclude there is potential for cytotoxicity to both chondrocytes and synoviocytes treated with a corticosteroid/LA combination; however, the individual contributions of LA versus steroids was not investigated. Moser et al.[57] investigated in vitro the effects of various LA (lidocaine, bupivacaine, ropivacaine) combined with glucocorticoids (GC), hyaluronic acid (HA) or both using cultured human chondrocytes. When examined under a microscope, chondrocytes had increased branching and enhanced attachment when exposed to HA and GC/HA compared to local anaesthetics alone or local anaesthetics with glucocorticoids. Metabolic activity was also improved in the lidocaine and bupivacaine groups exposed to HA and GC/HA and the number of apoptotic cells were highest in the LA/HA groups, intermediate in the groups exposed to GC and GC/HA, and lowest in the LA alone groups with the notable exception of ropivacaine, which demonstrated cell viability similar to control in all groups. These authors concluded that inclusion of HA may decrease the chondrotoxic effects of LA when injected alone as well as when coadministered with corticosteroids. Further investigation of the additive toxic effects of the combination of LA with corticosteroids at various doses in vivo would provide additional information regarding the clinical relevance of coadministration and whether these observed toxic effects may be mitigated by inclusion of hyaluronic acid or are of long-term significance. However, the current literature does not support a greater risk of synovial sepsis or definitive contribution to osteoarthritis progression by delaying intra-synovial treatment with corticosteroids following diagnostic anaesthesia of the synovial structure.[91,92] As with other combinations of drugs, our conclusions are tempered by the limited information available.

Other medications: Concurrent treatments have been evaluated as potential chondroprotective agents when administered at the same time as LA. Moser et al.[57] in 2021 compared toxicity of 0.5% bupivacaine, 1% lidocaine, and 2% ropivacaine on cell viability of human knee chondrocytes, concluding that cell viability was the highest with ropivacaine and the lowest with lidocaine and that metabolic activity was improved in all groups with the addition of hyaluronic acid or

hyaluronic acid and glucocorticoids.[57] In another study that same year investigating the effect of an injectate containing ropivacaine 0.5%, morphine (0.0625 mg/mL), epinephrine (7.5 μg/mL), and ketorolac (0.375 mg/mL) on human cartilage explants, the combination was not found to have any significant effects on chondrocyte viability as compared to saline solution.[93] The latter study was also notable for attempting to mimic the IA environment by reducing the concentration of the study drugs by ½ every hour for 8 h followed by culture in medium alone. Magnesium sulfate ($MgSO_4$, 37 mg/mL), while having very little effect on chondrocytes or synovial cells by itself, does not appear to decrease the toxicity of either bupivacaine or mepivacaine when coadministered with either LA.[46]

Coadministration of biological therapies including platelet rich plasma (PRP) or nonsteroidal anti-inflammatories have also been investigated for their potential chondroprotective properties when included with LA. Bianchini et al.[56] exposed canine articular chondrocytes to 1% or 1.8% lidocaine alone or in the presence of 10% PRP for 30 min. To simulate the effect of pre-treating a joint with PRP prior to local anaesthetic injection, cells were cultured in media that was serum free, supplemented with 10% bovine serum or supplemented with 10% PRP. Methyl thiazolyl tetrazolium assay and flow cytometry revealed that the presence of lidocaine significantly reduced chondrocyte viability by apoptosis, but that inclusion of PRP restored the number of viable cells. Given the above data, further targeted investigation of the potential for chondroprotection with additives to LA is warranted, especially with HA.

Summary of additives to local anaesthetic injections: These findings support that cytotoxicity of LA may be mitigated through concurrent injection with HA, PRP, and drug combinations including nonsteroidal anti-inflammatories and opioids. Inclusion of preservatives such as methylparaben seemed to have minimal effect in inducing an increased inflammatory response. Vasoconstrictors such as epinephrine may minimise diffusion from the site of injection but elicited greater cytotoxicity when administered with bupivacaine versus other LA.

8.1 | Other clinical considerations

Additional considerations in use of LA include lack of specificity in lameness diagnosis, selection of dose, concurrent administration of other medications, stability of solutions following opening a vial, potential contraindications, and care of the horse following performing diagnostic procedures.

- *Lack of specificity in lameness diagnosis*: While frequently implemented in lameness examinations, it has become increasingly recognised that intra-articular and/or intra-synovial LA administration is non-specific as a result of diffusion to adjacent structures, both distally and proximally within the limb.[94,95] A response of 50%–70% improvement in gait symmetry following intra-synovial analgesia has been previously reported anecdotally to be considered a positive response,[2] although it is recognised that subjective agreement, even among experienced lameness clinicians, is poor.[96] Factors including time elapsed between injection and observation of lameness, volume of LA used, and anatomical variation between patients may further affect specificity in lameness localisation. Inappropriate timing of evaluation of lameness following intra-synovial blocking may lead to misinterpretation in lameness diagnosis. Examination of synovial LA blocks below the carpus and tarsus at 5 min following the injection has been reported,[2,97] as waiting longer than 10 min may decrease specificity. Specific examples where diffusion from the joint resulted in non-specific blocking patterns include reports of IA stifle anaesthesia reducing foot lameness in one third of horses within 30 min,[98] and multiple studies demonstrating diffusion between carpal joints and proximal metacarpal region as well as distal tarsal joints and proximal metatarsal region, as summarised in the review article by Pezzanite et al.,[99] which cautions the practitioner to carefully interpret blocking patterns and supplement with diagnostic analgesia in surrounding locations or more advanced diagnostic imaging to accurately localise lameness in some situations.
- *Selection of dose*: While published doses vary widely for IA analgesia in horses,[1,2,97] use of the lowest volume and concentration that will achieve the desired results is generally recommended. In the setting of lameness localisation and diagnosis, large volumes may also pose additional concerns, as distention of synovial structures with excessive volumes results in increased diffusion and excessive spread of local anaesthetic solutions around the injection site, further contributing to lack of specificity in perceived blocking patterns and misinterpretation of lameness findings.[100,101]
- *Concurrent administration of other medications*: The risk for synovial sepsis following intra-synovial injection is reportedly low (<0.1% of injections) across multiple studies, regardless of medication administered,[91,102,103] and specifically when only local anaesthetics are injected.[91] Furthermore, LA have inherent antimicrobial properties, which may further contribute to the low rate of infection following their administration.[104–107] While consideration has previously been given to whether medication of joints for osteoarthritis on the same day as diagnostic analgesia was performed increased risk of complications or reduced efficacy of treatment, performing an additional injection to administer corticosteroids or hyaluronic acid following improvement to LA has not been shown to increase the risk for septic synovitis.[91,92] However, steroids are likely to augment the chondrotoxicity of LA and decrease chondrocyte viability and should therefore not be admixed for administration in the same injection[108] (see additive section above).
- *Stability of solutions*: Previous literature has suggested that potency and subsequently efficacy of LA solutions rapidly decreases following broaching of a vial.[109,110] While use of unopened vials for each synovial injection may be performed to maintain aseptic technique, more recent evidence suggests that LA frequently used in equine practice are very stable, maintaining efficacy for up to 16 months following vial opening.[111] Best practices for the use of multi-dose vials would be to wipe the stopper of the vial with alcohol prior to broaching each time to maintain this stability and asepsis.

- *Potential contraindications*: In acute lameness, diagnosis of incomplete fractures must be considered prior to local anaesthetic administration, even in mild to moderate cases of lameness severity,[2,110] and radiographic assessment initially may be indicated. Intra-articular analgesia may also be contraindicated in cases with wounds or subcutaneous swelling over the joint to minimise risk of IA inoculation of bacteria through contaminated tissue.
- *Local anaesthetics in regional limb perfusion*: LA may be combined clinically with antibiotics in intravenous regional limb perfusions (IVRP) to decrease discomfort associated with tourniquet placement or soft tissue swelling when antibiotics are administered for treatment of distal limb wounds or infection. The addition of LA to the IVRP has been shown to produce concentrations of LA within the joint, which may be relevant for analgesia. Colbath et al.[112] demonstrated that the combination of mepivacaine with amikacin in IVRP increased mean nociceptive threshold of the forelimb and did not diminish amikacin concentrations achieved in the middle carpal joint following administration, indicating that addition of LA to perfusions may be a means to provide analgesia without diminishing antimicrobial effect. Mensez-Angulo et al.[113] further demonstrated that nociceptive thresholds were increased in horses in which either lidocaine or mepivacaine were administered in IVRP compared to saline controls and that, at doses administered (1.3 mg/kg each), concentrations remained below presumed toxic levels in plasma after tourniquet release.

9 | CONCLUSIONS

Intra-articular local anaesthetic administration has been demonstrated to provide analgesia when used as a diagnostic tool in lameness localisation and has also proven valuable in pain management of diseases localised to synovial structures in horses. IA injections of LA have been performed in equine clinical practice for decades and may be administered in diagnosis of lameness or in conjunction with steroids for the management of orthopaedic pain, as part of a balanced anaesthetic protocol for surgical procedures, or with antibiotics in intravenous regional limb perfusion. In humans the practice of injecting IA LA in the peri-operative period has been routine for over 40 years without significant complications being reported, with the exception of those relating to IA catheters and continuous LA infusions.

As discussed in this review, local anaesthetic selection, dose and addition of additives may mitigate cytotoxic side effects. Greater cytotoxicity has been observed with lidocaine and bupivacaine compared to mepivacaine and ropivacaine, with higher doses and longer exposures resulting in greater reduction of cell viability. Interestingly, there remains a lack of consensus across the literature overall regarding relative toxicity induced when lidocaine is specifically compared to mepivacaine, with some references indicating no significant difference in inflammation or cartilage degradation following administration while others suggesting enhanced inflammation and tissue reaction with lidocaine, which may be due to differences in volume or clinical scenario in which the two drugs have been used. Ropivacaine presents an alternative to bupivacaine as a long-lasting LA that appears to have fewer deleterious effects on chondrocytes, and liposomal bupivacaine (and possible other formulations of encapsulated LA) presents an alternative for continued analgesia although more in vitro studies are needed.

Various additives have demonstrated some chondroprotective and/or additional analgesic effects, ranging from biologic therapies (platelet rich plasma) to opioids to corticosteroids with HA. Opioids such as fentanyl and morphine will increase the duration of analgesia of IA LA, and HA seems to mitigate the negative effects of LA on chondrocytes. The effect of injectate pH also needs to be taken into account, as injections with a pH <5.0 have been shown to have deleterious effects in the IA environment. No studies to date have fully evaluated the effects of various local anaesthetic agents on synovium, which may represent more metabolically active tissues relative to cartilage in their contribution to inflammation or synovitis following intra-articular injection.

Moving forward, in vitro research should focus on mimicking the native joint environment, utilising PK data and joint/injection volumes to more accurately replicate the native environment within the joint and the expected exposures to LA. When the available data is aggregated, it becomes obvious that most research to date has drawn conclusions from implausible if not impossible concentrations and exposure times of chondrocytes to LA. As single cultures or cores are not as good at replicating the complex IA environment, co-cultures of chondrocytes and synoviocytes with synovial fluid could be used as a more realistic substitute, and as a step further the use of microfluidic devices such as a 'joint-on-a-chip'[114] should be prioritised.

In summary, the injection of LA IA carries potential benefits in both diagnosis and management of musculoskeletal disease in horses, but potential for iatrogenic joint damage should be considered by practitioners and may be mitigated through selection, dose, and frequency of injection by this route of administration.

AUTHOR CONTRIBUTIONS

Gregg Griffenhagen, Dean Hendrickson and Lynn Pezzanite contributed to study conception and design. Aaron Webster, Lynn Pezzanite and Gregg Griffenhagen contributed to data acquisition. Aaron Webster, Lynn Pezzanite, Dean Hendrickson and Gregg Griffenhagen contributed to data interpretation. Aaron Webster, Lynn Pezzanite and Gregg Griffenhagen contributed to drafting the manuscript. All authors contributed to and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICAL ANIMAL RESEARCH

Not applicable.

INFORMED CONSENT

Not applicable.

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