Interventional Pain Medicine 2 (2023) 100282

Contents lists available at ScienceDirect

Interventional Pain Medicine

journal homepage: www.journals.elsevier.com/interventional-pain-medicine

FactFinders

FactFinders for patient safety: Preventing local anesthetic-related complications: Local anesthetic chondrotoxicity and stellate ganglion blocks

Mathew Saffarian [a,*,1], Eric K. Holder [b,1], Ryan Mattie [c], Clark C. Smith [d], George Christolias [d], Jaymin Patel [e], Zachary L. McCormick [f], on behalf of the Spine Intervention Society's Patient Safety Committee

[a] Michigan State University, Department of Physical Medicine and Rehabilitation, East Lansing, MI, USA
[b] Yale University School of Medicine, Department of Orthopedics and Rehabilitation, New Haven, CT, USA
[c] Providence Medical Institute, Department of Interventional Pain Management, Providence Cedars-Sinai Tarzana Medical Center, Los Angeles, CA, USA
[d] Columbia University Medical Center, Rehabilitation and Regenerative Medicine, New York, NY, USA
[e] Emory University, Department of Orthopaedics, Atlanta, GA, USA
[f] University of Utah School of Medicine, Departments of Physical Medicine & Rehabilitation, Salt Lake City, UT, USA

ABSTRACT

This series of FactFinders presents a brief summary of the evidence and outlines recommendations to improve our understanding and management of several potential local anesthetic-related complications.

Evidence in support of the following facts is presented. (1) *Chondrotoxicity: Which Local Anesthetics are Safest for Intraarticular Injection?* – There are drug-, concentration-, and time-dependent chondrotoxic effects that vary between local anesthetics. Current evidence related to commonly used local anesthetics indicates that with exposure to equivalent volumes, bupivacaine, at concentrations of 0.5 % or higher, is the most chondrotoxic agent, while ropivacaine, at concentrations equal to or less than 0.5 %, is the least chondrotoxic *in vitro*. There is minimal published evidence that confirms these findings *in vivo*. (2) *Minimizing Risks with Stellate Ganglion Blocks* – Evidence suggests that fluoroscopic or ultrasound guidance reduces the risk and increases the accuracy of SGB. Utilizing ultrasound guidance has the added benefit of soft tissue visualization, especially vascular structures, which has the potential to prevent adverse outcomes when compared to the fluoroscopic technique.

FACTFINDERS FOR PATIENT SAFETY

Chondrotoxicity: Which Local Anesthetics are Safest for Intraarticular Injection?

Eric K. Holder, MD[1]; George Christolias, MD[2]; Mathew Saffarian, DO[3], Jaymin Patel, MD[4], and Zachary L. McCormick, MD[5] on behalf of the Spine Intervention Society's Patient Safety Committee.

[1]Yale University School of Medicine, Department of Orthopedics and Rehabilitation, New Haven, CT, USA;

[2]Columbia University Medical Center, Rehabilitation and Regenerative Medicine, New York, NY, USA;

[3]Michigan State University, Department of Physical Medicine and Rehabilitation, East Lansing, MI, USA;

[4]Emory University, Department of Orthopaedics, Atlanta, GA, USA;

[5]University of Utah School of Medicine, Department of Physical Medicine & Rehabilitation, Salt Lake City, UT, USA.

Myth: All local anesthetics are equally chondrotoxic to joints.

Fact: There are drug-, concentration-, and time-dependent chondrotoxic effects that vary between local anesthetics. Current evidence related to commonly used local anesthetics indicates that with exposure to equivalent volumes, bupivacaine, at concentrations of 0.5 % or higher, is the most chondrotoxic agent, while ropivacaine, at concentrations equal to or less than 0.5 %, is the least chondrotoxic *in vitro*. There is minimal published evidence that confirms these findings *in vivo*.

Background

Intraarticular injection(s) of amide-type local anesthetics are performed in clinical practice without or with corticosteroids for potential diagnostic and/or therapeutic purposes. Presently, there are many local anesthetic agents available, each of which varies with regard to onset of action, half-life, duration of action, and potential cytotoxic effects on

* Corresponding author. Michigan State University, Department of Physical Medicine and Rehabilitation, East Lansing, MI, USA.
E-mail address: saffaria@msu.edu (M. Saffarian).

[1] Denotes co-first authors.

https://doi.org/10.1016/j.inpm.2023.100282
Received 18 September 2023; Accepted 20 September 2023
Available online 27 October 2023

articular chondrocytes [1–3]. *In vitro* studies demonstrate similar findings regarding the chondrotoxic profiles of local amide-type anesthetics; however, *in vivo* analysis of the effects of single-dose, non-continuous administration of amide-type local anesthetics without corticosteroid on human chondrocytes remains limited [1–14]. While there are several *in vitro* studies that have found single-dose, non-continuous administration of local anesthetics to be chondrotoxic, these injections remain quite common in clinical practice without a comparable quantity of available literature confirming these effects *in vivo*. Consequently, there are no consensus guidelines recommending an anesthetic of choice for intra-articular use.

Uniformly, *in vitro* studies addressing the potential chondrotoxic effects of single dose, non-continuous injections of amide-type local anesthetics indicate a spectrum of chondrotoxic effects that are drug-, concentration- and time-dependent [1–14]. Time dependence refers to the duration of exposure and/or time after exposure, whereby longer timeframes are associated with decreased cellular viability. The proposed underlying mechanisms for anesthetic chondrotoxicity include increased cellular apoptosis, cartilage necrosis, mitochondrial dysfunction, extracellular matrix damage and decreased DNA-normalized glycosaminoglycan expression [5,7,9,10]. Macrophages lack access to articular cartilage; thus, the remnants of necrotic and apoptotic destruction remain and can predispose to further tissue degeneration [2]. Likewise, it has been demonstrated *in vitro* that chondrocyte death occurs more rapidly in osteoarthritic cartilage compared to intact, healthy cartilage after local anesthetic exposure [2].

Chondrotoxicity of commonly used local anesthetics

There are several papers that link chondrolysis in both human and animal joints to continuous pain pump infusion of local amide-type anesthetics [15–20]. Literature was evaluated with a specific focus on studies assessing the potential chondrotoxic effects of intraarticular injection of local amide-type anesthetics on human articular chondrocytes. Studies demonstrate a time- and concentration-dependent chondrotoxic effect with all local anesthetics; however, the threshold concentration associated with a cytotoxic effect is variable. Numerous *in vitro* studies have demonstrated that administration of equipotent dosages of local anesthetics have differing deleterious effects on chondrocyte viability [1–14].

Bupivacaine

Based on the collective literature, bupivacaine appears to be the most chondrotoxic local anesthetic in clinical use [1–4,6,8–10]. Studies consistently demonstrate that bupivacaine at concentrations of 0.5 % or higher results in the greatest degree of chondrocyte death when compared to equipotent doses of alternative amide-type local anesthetics. At concentrations less than 0.5 % bupivacaine, the literature is conflicting. Two studies both found that *in vitro,* bupivacaine at a concentration of 0.25 % did not result in a significant difference in cartilage cell death when compared with a control media ($P > 0.01$; $P = 0.856$ respectively) [2,5]. While alternatively other *in vitro* studies found that chondrocytes exposed to 0.25 % bupivacaine show increased cell death when compared to control agents [4,6,7].

Studies assessing bupivacaine consistently demonstrate a time-dependent decrease in human chondrocyte viability after 0.5 % bupivacaine exposure. One study exposed chondrocytes *in vitro* to 0.5 % bupivacaine for 1 h. Compared with saline controls, at 24 h after exposure, viability declined to 63 %±8% ($P < 0.0001$) and to 26 % ± 9 % at 96 h post exposure ($P < 0.0001$) [2]. With the use *in vitro* time-lapsed chondrocyte imaging other investigators found that exposure to 0.5 % bupivacaine resulted in cell viability of 41 % after 15 min, 4 % after 30 min and no living chondrocytes after 60 min ($P < 0.05$) [4]. Similarly, two additional studies determined *in vitro* that there is a significant time-dependent marked decline in chondrocyte viability with exposure to 0.5 % bupivacaine [6,10].

Lidocaine

There are concentration and time-dependent chondrotoxic effects of lidocaine when evaluating concentrations ranging from 0.5 % to 2 % [5, 7,9–12]. Investigators in one study determined that a single dose administration of 1 % lidocaine resulted in significantly more *in vitro* chondrotoxicity when compared with control media (7.9 %±0.7 % vs. 2.9 %±0.4 % respectively; $P < 0.001$) [5]. Another study performed an *in vitro* analysis of chondrocyte culture viability after a single dose 1-h exposure to varying concentrations of lidocaine, ranging from 0.5 % to 2 %. The authors demonstrated that 2 % lidocaine caused “massive” chondrocyte necrosis 24 h after exposure, while 1 % lidocaine caused a detectable but insignificant ($P > 0.05$) decrease in cell viability at 24 h. At 120 h post treatment, all concentrations of lidocaine, 0.5 %–2 %, resulted in significantly decreased cell viability ($P < 0.05$), overall demonstrating a dose- and time-dependent decrease in cell viability [7].

Separate analysis of chondrocytes exposed *in vitro* to 1 % and 2 % lidocaine with and without epinephrine for 15, 30 and 60 min illustrated that the longer the duration of exposure to any of the lidocaine containing solutions, the greater the number of non-viable cells at 7 days after exposure [12]. Regardless of the time frame of exposure, at 7 days nearly all of the cells were dead after exposure to 2 % lidocaine and all values were statistically lower than the saline group ($P = 0.019$, 0.028, 0.032). Fifteen, thirty- and 60-min exposure to 1 % lidocaine without epinephrine resulted in 49 %, 60 % and 94 % non-viable cells at day 7 respectively. In this study 1 % lidocaine with epinephrine appeared to be the least toxic, however, there is conflicting literature regarding the effects of epinephrine on chondrocyte viability [12,14].

Ropivacaine (as compared to bupivacaine & lidocaine)

In vitro assessment found ropivacaine significantly less chondrotoxic than bupivacaine ($P = 0.0006$), and that exposure to ropivacaine at concentrations less than 0.75 % did not result in significant toxic effects on human cartilage explants [2]. This is consistent with another *in vitro* study that found only 0.75 % ropivacaine resulted in a reduced cell viability while lower doses did not significantly influence cell viability [6]. Furthermore, both studies demonstrated that 0.5 % bupivacaine appeared to be more toxic than 0.75 % ropivacaine [2,6].

A separate study found that 0.2 % and 0.5 % ropivacaine did not result in significant chondrotoxic effects at 24 or 72 h after exposure. At 120 h post exposure, 0.5 % ropivacaine did result in a significant reduction in cell viability ($P < 0.05$). However, although not directly compared, 0.5 % bupivacaine and 1 % lidocaine appeared to result in a greater loss of viable chondrocytes [7].

Other investigations reported no effect of 0.5 % ropivacaine on human cartilage explants compared with saline (94.4 %±9.0 % vs. 95.8 % ± 5.7 %; $P = 0.06$). However, they did observe a reduction in viability of cultured chondrocytes. Chondrocyte viability after 0.5 % ropivacaine exposure was significantly greater than after exposure to 0.5 % bupivacaine for both cartilage explants (94.4 %±9.0 % vs. 78 % ±12.6 %; $p = 0.0004$) and cultured chondrocytes (63.9 %±19 % vs. 37.4 % ± 12 %; $p < 0.0001$) [8].

Other studies demonstrate a similar pattern of findings when comparing ropivacaine to bupivacaine or lidocaine. One such study found that human chondrocytes exposed to 0.5 % ropivacaine were more likely to undergo cell death compared to exposure to normal saline but less than with 0.5 % bupivacaine [10]. Another found that 0.75 % ropivacaine exposure resulted in greater chondrocyte death compared to saline control as well as 1 % lidocaine, but less cell death than 0.5 % bupivacaine exposure [9]. Other investigators determined that when compared with controls, 0.5 % ropivacaine showed no significant ($P > 0.05$) chondrotoxic effects after a 12-h exposure to monolayer cultured chondrocytes ($P = 0.084$), as opposed to 3-h exposure to 1 %

lidocaine ($P < 0.001$), which resulted in significant chondrotoxicity [5].

Thus, based on collective literature, *in vitro,* ropivacaine demonstrates concentration- and time-dependent chondrotoxicity, most pronounced at concentrations equal to or greater than 0.75 % [1,2,6]. Ropivacaine at concentrations of 0.5 % or less demonstrates less chondrotoxicity than bupivacaine or lidocaine [1,2,5–10].

Chondrotoxicity of less commonly utilized local anesthetics

Mepivacaine

Assessment of mepivacaine on cultured human chondrocytes, determined that there are significant dose-dependent toxic effects [2]. Specifically, a significant reduction ($P < 0.01$) in cell viability was noted at concentrations of 1 % or greater, while lower concentrations did not demonstrate significant toxic effects. The authors determined that in an escalating order, chondrotoxicity worsened from ropivacaine to mepivacaine to bupivacaine [2].

Levobupivacaine

One study found that *in vitro* that after 1 h of exposure, 0.5 % levobupivacaine is significantly more chondrotoxic than saline controls (25.9 % ±14.1 vs. 9.6 % ±5.4; $P = 0.04$) [13]. Furthermore, 0.5 % levobupivacaine was found to be more chondrotoxic than 0.5 % bupivacaine.

There does not appear to be any substantive literature regarding the potential chondrotoxic implications of the remaining less commonly utilized amide type local anesthetics.

Local anesthetic with corticosteroid

In clinical practice, local anesthetics are commonly mixed with corticosteroid. Rapid onset of relief from the anesthetic may provide immediate diagnostic feedback. Corticosteroid may be added to provide therapeutic benefit. Notably, *in vitro* studies have demonstrated that the combination of corticosteroid with either bupivacaine, lidocaine or ropivacaine results in a greater trend towards cellular apoptosis and necrosis than when compared to saline controls or local anesthetic alone [9,11]. Furthermore, the utility of intraarticular corticosteroid injections has been called into question as there is mounting evidence that serial injections have deleterious effects on the course of cartilage deterioration, and there is conflicting evidence regarding their benefit [21–23]. To our knowledge, there are no studies that have analyzed the chondrotoxic effects of combining corticosteroid with mepivacaine or levobupivacaine [1].

Effects of epinephrine, preservatives, and pH on local anesthetic chondrotoxicity

Due to the potent vasoconstrictive property of epinephrine, it increases the local duration of action of the anesthetic and thus is favored by some practitioners. The preservative sodium metabisulfite is often included in epinephrine-containing local anesthetics to prevent loss of bioactivity while in storage, instead of the more commonly used preservative methylparaben [14]. One study demonstrated that local anesthetics with epinephrine at low pH results in a significant loss of cell viability ($P < 0.001$). Additionally, while their study did not demonstrate any significant decrease in chondrocyte viability with methylparaben after 24 h of perfusion ($P > 0.05$), it was determined that 0.5 mg/mL sodium metabisulfite is chondrotoxic ($P < 0.034$) [14]. Thus, the authors suggest the chondrotoxicity of local anesthetics containing epinephrine appears to be a result of the combined effects of the preservative sodium metabisulfite and low pH [14]. Other investigators also determined that epinephrine was toxic to chondrocytes and synovial cells [10.] However, there is conflicting literature regarding the chondrotoxic effects of epinephrine, with other study suggesting negligible or potential protective effects [1,12]. Further research is needed.

Discussion

It is important to note that most of the studies evaluating the chondrotoxicity of amide-type local anesthetics on human articular cartilage have been performed *in vitro,* and thus, the effects *in vivo* may not be directly translatable. The clearance ratio of the anesthetic and the specific time that the drug is acting at a fixed concentration within the joint is not known [2,13]. Furthermore, the variance in joint synovial fluid volume based on joint size and pathological state may result in dilutional effects that limit the applicability of studies assessing chondrotoxicity *in vitro*. However, based on current study observations, ropivacaine at concentrations equal to or less than 0.5 % is preferred over lidocaine or bupivacaine for intraarticular use. *In vivo* studies are necessary to confirm these findings.

Ultimately, the utility and safety of any intraarticular injection of corticosteroid with or without local anesthetic is currently in question due to potential for accelerated osteoarthritis progression, subchondral insufficiency fracture, complications of osteonecrosis, and rapid joint destruction with bone loss [23]. Investigation is ongoing.

Conclusions

- Decrease in cartilage cellular viability with amide-type local anesthetic exposure is drug-, concentration-, and time-dependent *in vitro*.
- Ropivacaine at concentrations of 0.5 % or less appears to be the least chondrotoxic *in vitro.*
- Bupivacaine at concentrations of 0.5 % or higher appears to be the most chondrotoxic *in vitro.*
- Lidocaine has demonstrated significant chondrotoxicity, particularly at doses 1 % or greater *in vitro.*
- The administration of corticosteroids in conjunction with local anesthetics appears to be more chondrotoxic than local anesthetic in isolation *in vitro.*
- There is conflicting literature regarding the potential chondrotoxic effects of epinephrine combined with local anesthetics on human chondrocytes *in vitro;* further investigation is needed.
- The evidence surrounding amide-type local anesthetic toxicity is primarily based on *in vitro* investigation and additional *in vivo* studies are necessary to confirm applicability to clinical medicine.

Minimizing Risks with Stellate Ganglion Blocks

Mathew Saffarian, DO[1], Ryan Mattie, MD[2], and Clark C. Smith, MD, MPH[3] behalf of the Spine Intervention Society's Patient Safety Committee.

[1]Michigan State University, Department of Physical Medicine and Rehabilitation, East Lansing, MI, USA;

[2]Providence Medical Institute, Department of Interventional Pain Management, Providence Cedars-Sinai Tarzana Medical Center, Los Angeles, CA;

[3]Columbia University Medical Center, Rehabilitation and Regenerative Medicine, New York, NY, USA.

Myth: Stellate ganglion blocks (SGB) pose minimal risk when performed blind, using a landmark-based approach without imaging guidance.

Fact: Evidence suggests that fluoroscopic or ultrasound guidance reduces the risk and increases the accuracy of SGB. Utilizing ultrasound guidance has the added benefit of soft tissue visualization, especially vascular structures, which has the potential to prevent adverse outcomes when compared to the fluoroscopic technique.

Stellate ganglion blocks (SGBs) are used to treat a variety of sympathetically-mediated conditions. In the past, the SGB was performed "blind," that is, without imaging guidance. Accumulated evidence of serious complications such as inadvertent subarachnoid or epidural injection, recurrent laryngeal nerve palsy, seizures, blindness, and death led to the emergence of image-guided techniques: fluoroscopy and ultrasound [24]. Avoiding vulnerable anterior cervical structures with the use of imaging has resulted in fewer complications [25–28].

A systematic review of 260 complications associated with SGB reported that the blind paratracheal approach accounted for 48.5 % of the cases, while fluoroscopic and ultrasound guidance accounted for 26.9 % and 24.6 %, respectively [29]. It should be noted that these data could be misleading given that the number of blind procedures performed may significantly outnumber those done with image guidance. There was one reported death due to hematoma, which occurred in association with the blind approach. All complications of subdural block, intrathecal block, transient locked-in syndrome, and hematoma occurred when the blind technique was used. It was concluded that SGBs are a relatively safe procedure; however, significant complications may occur and can be attributed to vascular disruption, injection of medication into an unintended space, or alterations in autonomic tone [29].

Currently, the use of image-guided techniques is the standard of care [29]. Fluoroscopic guidance decreases the incidence of adverse outcomes [27,29] and increases effectiveness compared to the blind technique [30,31]. Under fluoroscopy, most often a direct antero-posterior (AP) approach is used. The final needle position is the junction of the vertebral body and the uncinate process at C6 or C7. At C7, there is an increased risk of vertebral artery injury, esophageal puncture, and pneumothorax [25]. Anatomic variations such as esophageal deviations or esophageal diverticulum increase the risk of esophageal puncture with a straight AP fluoroscopic approach [26]. An oblique approach to C7 has been described, which avoids the pleura and vascular structures while increasing accuracy [30], but increases the risk of recurrent laryngeal and vagus nerve blockade [27]. Life threatening complications using fluoroscopic guidance are a rare occurrence (1.7 in 1000) [32]. Confirmation of contrast spread to the target location of the stellate ganglion is easily visualized with conventional fluoroscopy and is more difficult and a potential shortcoming of the ultrasound-guided technique. A small test dose of 1 ml of 1 % lidocaine should be administered to detect unintended intravascular needle placement.

Conversely, the use of ultrasound offers several potential advantages. In addition to increasing safety, ultrasound has the potential to improve accuracy and, subsequently, effectiveness [33]. Vascular and other soft tissue structures cannot be directly visualized under fluoroscopy, but can be visualized by ultrasound [27]. With the transducer in the transverse short axis position at the level of the cricoid notch, the anterior aspect of the Chassaignac's tubercle on the C6 transverse process, the carotid artery, internal jugular vein, thyroid gland, trachea, *Longus colli*, *Longus capitis*, prevertebral fascia, the root of C6 spinal nerve, and transverse process of C6 can all be identified [34]. Ultrasound has been shown to decrease the incidence of esophageal puncture compared to a traditional fluoroscopic approach [35]. One retrospective review of 156 ultrasound-guided blocks found transient adverse side effects in 13.5 % of patients, the most common being hoarseness. No severe or life-threatening complications occurred [36].

Because of better soft tissue visualization, another potential benefit of ultrasound is decreased injectate volume needed for an effective SGB compared to other approaches [35,37]. A study that compared blind SGB with 8 ml to ultrasound-guided SGB with 5 ml of injectate [37] measured vasodilation of the upper extremity and face along with the extent of Horner's syndrome to assess effectiveness. Complete SGB was found in all 12 of the ultrasound cases and in 11 of the 12 using the blind approach. Non-serious hematoma formation occurred in three of the blind injections while the ultrasound-guided injections yielded none. Another study comparing blind and ultrasound-guided SGBs for post-stroke complex regional pain syndrome (CRPS) found the ultrasound-guided SGB group had greater improvement in VAS scores and fewer adverse events [33].

CT or MRI guidance for SGBs are also potential image guidance options. Both may be more expensive and time-consuming. Improved accuracy of final needle position upon the C6 tubercle, and identification of a safe trajectory accomplished with CT or MRI may be accompanied by lower complication rates [38].

Conclusions/recommendations

- Risks of potentially life-threatening and other adverse events are substantially decreased when performing SGB under image guidance.
- Effective injections can be accomplished using less volume when proper imaging techniques are utilized leading to less chance of adverse outcomes, such as anesthetic toxicity, seizure, etc.
- Image guidance offers the ability to show real-time needle advancement and provides direct monitoring of injectate spread.
- If a fluoroscopic technique is utilized, and location is confirmed with live contrast administration, a small test dose of local anesthetic should be administered to further reduce the risk of intravascular injection.
- Utilizing ultrasound guidance has the added benefit of soft tissue visualization, especially vascular structures, which has the potential to prevent adverse outcomes when compared to the fluoroscopic technique.

Funding statement

No funding was utilized in the preparation of this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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