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Best practices for interventional pain procedures in the setting of a local anesthetic shortage: A practice advisory from the Spine Intervention Society

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ABSTRACT

Representatives from the Spine Intervention Society (SIS) Standards Division and Evidence Analysis Committee have developed the following best practice recommendations for the performance of interventional pain procedures in the setting of a local anesthetic shortage. The practice advisory has been endorsed by SIS, the American Academy of Pain Medicine, the American College of Radiology, the American Society of Neuroradiology, the American Society of Spine Radiology, the North American Neuromodulation Society, the North American Spine Society, and the Society of Interventional Radiology, who support the following best practice recommendations and statements for the performance of intra-articular, extra-articular, paraspinal, and epidural injections in the setting of a local anesthetic shortage.

1. Use of preservative-containing local anesthetics is discouraged in the performance of neuraxial procedures where the injectate may enter the epidural (or intrathecal) spaces.
2. When performing procedures with risk of arterial injection, ropivacaine should not be mixed with dexamethasone and injected due to the risk of crystallization and embolization.
3. Physicians should not withdraw directly from vials of local anesthetic for multiple patients due to infection risk as per Centers for Disease Control and Prevention (CDC) and Joint Commission guidelines [1].
4. Only pharmacists may repackage local anesthetic vials for multiple patients. This must be performed under strict, sterile conditions and only in times of critical need. In such situations, physicians must adhere to the beyond-use-date and storage conditions on the repackaged label [2,3].
5. Joint, tendon, bursa, and/or ligament injections may be performed with local anesthetic with or without preservative.
6. Interventional pain physicians should weigh the relative chondrotoxicity risks associated with each anesthetic when performing joint injections.

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7. Topical anesthetics, infiltration with diphenhydramine, and nonpharmacologic therapies (*i.e.,* cognitive behavioral therapy, guided imagery, virtual reality, mechanodesensitization) may be used as alternatives to skin infiltration of local anesthetic for reducing procedural pain.
8. Use of small-gauge needles (25 gauge or thinner) mitigates the need for local anesthetic prior to needle insertion.
9. For local anesthetic infiltration prior to insertion of large bore needles or incision, 0.5% lidocaine may be as effective as 1%, and for that reason current supplies of lidocaine can be stretched by dilution with normal saline.
10. If using an ester local anesthetic due to an amide local anesthetic shortage, interventional pain physicians should be aware (as always) of the potential for an allergic reaction and should be able to respond accordingly.
11. Local anesthetic systemic toxicity (LAST) differs between the varying local anesthetics, and interventional pain physicians should be well acquainted with these differences when switching between local anesthetics.

Physicians should carefully weigh the risks and benefits of performing procedures without local anesthetic or using an alternative agent in the context of each unique patient's situation and should involve patients in shared decision making before proceeding.

Procedures should be performed following Spine Intervention Society Guidelines [4]. The physician should confirm placement of the needle in at least two imaging planes. Please refer to the SIS Practice Guidelines for the full details and standards related to each unique procedure [4].

Background

The Food and Drug Administration (FDA) defines a drug shortage as a situation where the "total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet current or projected demand at the patient level." [5] The Federal Food, Drug, and Cosmetic Act defines a drug shortage as "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug." [6] Drug shortages can occur for numerous reasons including delivery delays, manufacturing capacity problems, and quality issues [7].

During the last several years, there have been several shortages of medications that are commonly used for interventional pain procedures. In 2022, these shortages included non-ionic iodinated contrast media [Omnipaque (iohexol) 180 and 240], bupivacaine (0.25% and 0.5%), lidocaine (1%, 2%, 4%) and other medications. According to information provided by the FDA**,** the lidocaine hydrochloride (Xylocaine) shortage (with and without epinephrine) was first posted in February of 2012 and was due to increased demand, manufacturing delays, and discontinuation of specific mixtures. The bupivacaine hydrochloride shortage, first posted on February 20, 2018, was reported to be caused by manufacturing delays, shortage of active ingredients, and increased demand. These shortages have been exacerbated by COVID-19 (infections, government shutdowns, and prioritizing vaccine production) and natural disasters [8]. The FDA temporarily allowed import and use of bupivacaine from non-FDA evaluated manufacturers [9]. In some areas of the United States, lidocaine was not available in single-dose vials but could be repackaged in accordance with CDC and Joint Commission guidelines from multi-dose vials into syringes (see Recommendation #3).

The local anesthetic shortage forces physicians to rely on less effective diagnostic and therapeutic alternatives and poses a significant barrier to providing high-quality care. Consequences of the shortage may include.

- Delays in diagnostic and therapeutic procedures and surgeries
- Inability to perform local anesthetic test doses prior to transforaminal epidural steroid injections
- Increased sedative use during interventional pain procedures
- Prolonged use of oral pharmacological agents including opioids if procedures are delayed
- Reduced patient satisfaction due to increased procedural pain
- Procedural anxiety could be increased in patients who are informed that a local anesthetic is not available
- Possibility of a higher rate of false-negative blocks if procedural discomfort is increased

The Spine Intervention Society (SIS) and American Academy of Pain Medicine (AAPM) previously published a dual-society practice advisory addressing best practices during an iodinated contrast media shortage [10]. The following advisory provides recommendations for best practices for interventional pain procedures during a local anesthetic shortage. Depending on the particularity of the shortage of local anesthetic(s), complete or partial, there are various potential solutions. Shortages of specific concentrations of local anesthetics can be resolved by using the available concentration of the same drug in most cases. However, a complete unavailability of a local anesthetic necessitates the use of an alternative agent. This is the case when a specific formulation is required (*e.g.,* preservative-free medication). These scenarios will be addressed in the remainder of this advisory in the form of 10 best practice recommendations, based on evaluation of the relevant published literature.

Recommendation 1: Use of preservative-containing local anesthetics is discouraged in the performance of neuraxial procedures where the injectate may enter the epidural (or intrathecal) spaces.

The primary concern regarding injection of preservative-containing local anesthetics relates to neurotoxicity. Preservatives, antioxidants, and excipients present in preservative-containing local anesthetics may have potential for neurotoxicity when injected intrathecally [11,12], which could lead to arachnoiditis and/or meningitis. The concern for this is primarily when used in neuraxial procedures where the injectate may enter the epidural (or intrathecal) spaces, as preservatives such as parabens and sulfites are known to cause arachnoiditis or flaccid paralysis [5, 13–16]. Undetected injection into the intrathecal space when epidural injection is intended is possible even with image guidance. Studies have revealed negative side effects of injecting preservatives into the intrathecal space and following blind epidural injections, as noted in the 2014 SIS FactFinder "Preservative vs. Preservative-Free: Local Anesthetic Choice for Epidural Injections" [17]. Notably, the FactFinder concluded that "a review of the current literature does not yield reports of adverse consequences from preservatives after properly performed image-guided injections. Since there is a theoretical concern that the epidural and subarachnoid spaces are continuous, the risks and benefits of using medications containing preservatives need to be weighed carefully [17]."

It must be acknowledged that there are no recent data to indicate that this risk still exists with modern preparations of local anesthetics, which have very low concentrations of preservatives and excipients. However, since the sequela of neurotoxicity is potentially devastating, if preservative-free local anesthetics are not available, use of preservative-containing local anesthetics at low volume and low dosage may be

considered after exhausting other resources and clearly discussing potential risks with patients and documenting such discussion in the medical record [18]. It should also be noted that therapeutic epidural injections can be performed with steroid alone if a safe local anesthetic preparation is not available.

Recommendation 2: When performing procedures with risk of arterial injection, ropivacaine should not be mixed with dexamethasone and injected due to the risk of crystallization and embolization.

Steroid and local anesthetics are often combined during epidural injections and other interventional pain procedures [19]. Ropivacaine is known to crystalize with the addition of corticosteroids including triamcinolone, betamethasone, and dexamethasone [20]. This is because ropivacaine precipitates at a pH of 6.9, which is closer to physiologic pH than the precipitation pH of other local anesthetics. The addition of steroid increases the pH of ropivacaine, thereby increasing the likelihood of crystallization [20]. This crystallization is further catalyzed by the addition of sodium bicarbonate 8.4% [21]. The crystal precipitates formed when mixed with these corticosteroids may have the potential to cause an ischemic event if injected into an artery that supplies neural tissue, namely, the vertebral artery or a radiculomedullary artery [20,22,23]. As such, this consideration is most relevant to transforaminal epidural steroid injections but may also apply to other procedures that involve needle placement in close proximity to arterial structures (*i.e.,* sympathetic blocks and atlanto-axial joint injections). However, preservative-free ropivacaine may be used in the epidural space if no corticosteroid is injected, such as during a diagnostic selective spinal nerve block.

Recommendation 3: Physicians should not withdraw directly from the same vial of local anesthetic for multiple patients due to infection risk as per Centers for Disease Control and Prevention (CDC) and Joint Commission guidelines [1].

Recommendation 4: Only pharmacists may repackage local anesthetic vials for multiple patients. This must be performed under strict, sterile conditions and only in times of critical need [1]. In such situations, physicians must adhere to the beyond-use-date and storage conditions on the repackaged label [2,3].

As discussed in the SIS/AAPM ICM practice advisory [10], "clinicians and health facilities must consider CDC, Food and Drug Administration (FDA), state, and local guidance when developing management and conservation measures in response to a shortage of [local anesthetic]. Splitting the contents of a single-dose/single-use vial is a possible means of substantially extending the available resources, but this practice carries risk of substantial harm to patients.

The [local anesthetic] vials typically used by pain physicians should only be used for a single patient as part of a single procedure. They do not contain antimicrobial preservatives and can become contaminated, serving as a potential source of bacterial, viral, or fungal infection [24]. If a single-dose vial must be used for more than one patient, it should be repackaged by pharmacy staff in a sterile compounding environment as required by United States Pharmacopeia (USP) Chapter 797, Pharmaceutical Compounding-Sterile Preparation [2].

When assigning beyond-use-dates (BUDs) and determining storage practices, organizations must consider stability in the repackaged container and the suitable temperature range for the repackaged product [2]. Repackaging is a form of batching and is considered "medium risk" compounding under the current version of USP Chapter 797. […]Per USP Chapter 797, when at controlled room temperature, the maximum BUD for repackaged [local anesthetic] is 30 h, and when stored in a refrigerator, the maximum BUD for [local anesthetic] is 9 days [3]." [10].

On November 1, 2022, the USP published an update that pharmacies have 1 year to implement new maximum BUD parameters of 4 days for items at room temperature and 10 days for repackaged items [25].

If multi-dose vials are to be used, as published in a 2018 FactFinder, "Reuse of MDVs is slightly less onerous but still burdensome. If strict aseptic technique is employed, an MDV may be reused if it "remains in a clean environment that does not have any contact with patients," such as in a dedicated medication preparation room. This precludes drawing up medication from MDVs in the OR, procedure room, or patient bedside. If an MDV is handled properly, after the first use a "beyond-use date" should be written on the label (read the package insert for detailed instructions as duration of safe-use may vary) [4]. From a practical point of view, someone would have to draw up medication for an injection in a room remote from the procedure room using sterile technique, transport it hygienically to the procedure room, and pass it off to the physician. This scenario introduces logistical concerns rendering the practice impractical in most circumstances." [26].

Recommendation 5: Joint, tendon, bursa, and/or ligament injections may be performed with local anesthetic with or without preservative.

Recommendation 6: Interventional pain physicians should weigh the relative chondrotoxicity risks associated with each anesthetic when performing joint injections.

There are no data to suggest that local anesthetics with preservatives are more or less toxic than preservative-free preparations in joint, tendon, or ligament injections. However, local anesthetics have chondrotoxic properties that are dependent on the medication type, concentration, and total dose. This is discussed in-depth in the SIS Fact Finder "Chondrotoxicity: Which Local Anesthetics are Safest for Intraarticular Injection?" [27] Factors for physicians to consider when selecting which local anesthetic to use include.

- 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 of commonly used local anesthetics, *in vitro*.
- Bupivacaine at concentrations of 0.5% or higher appears to be the most chondrotoxic of commonly used local anesthetics, *in vitro*.
- Lidocaine demonstrates chondrotoxicity, particularly at doses 1% or greater *in vitro*.
- 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 [27].

Recommendation 7: Topical anesthetics, infiltration with diphenhydramine, and nonpharmacologic therapies (*i.e.,* cognitive behavioral therapy, guided imagery, virtual reality, mechanode-sensitization) may be used as alternatives to skin infiltration of local anesthetic for reducing procedural pain.

Recommendation 8: Use of small-gauge needles (25 gauge or thinner) mitigates the need for local anesthetic prior to needle insertion.

Recommendation 9: For local anesthetic infiltration prior to insertion of large bore needles or incision, 0.5% lidocaine may be as effective as 1%, and for that reason current supplies of lidocaine can be stretched by dilution with normal saline.

During a lidocaine shortage, interventional pain physicians may consider alternative means of anesthetizing skin and subcutaneous tissues. There is evidence to support the use of topical ethyl chloride spray in lieu of local anesthetic infiltration of skin for joint, tendon, and bursa injections [28]. While in the past concerns related to sterility after topical application of ethyl chloride have been raised, more recent studies do not support bacterial or fungal contamination theories associated with ethyl

chloride [29].

Diphenhydramine has been used in place of lidocaine for dermal anesthesia and dental anesthesia including nerve blocks [14,30–32]. Diphenhydramine injection may be more painful than lidocaine injection. Diphenhydramine injection may cause sedation and anticholinergic effects. Caution should be used in elderly patients and patients who do not have a driver.

There are limited data on whether cognitive behavioral therapy, guided imagery, virtual reality, or other psychological interventions obviate the need for local anesthetic infiltration. However, there is evidence that these strategies may be helpful in reducing pain and anxiety in children and adolescents for needle-related procedures [33]. Mechanodesensitization has been found effective in decreasing pain associated with needle insertion during lumbar medial branch blocks, and in fact, was found to be less painful than subcutaneous local anesthetic injection [34].

However, whether lidocaine topicalization by injection is needed at all is debatable when small-gauge needles (25 gauge or thinner) are used. One study did not find a difference in post-procedure pain scores or at 1-inch needle insertion depth whether lidocaine was used or not [35]. However, a larger gauge needle (22-gauge vs. 25–27 gauge) did significantly negatively impact pain scores in this study [35]. Therefore, use of smaller gauge needles in lieu of using injectable lidocaine is acceptable [36,37].

Conservation of the supply of lidocaine can also prolong availability. In micrographic Mohs surgery, lidocaine 0.5% with epinephrine was equivalent in analgesic effect to lidocaine 1%, and its use has been advocated by other dermatologists [38,39]. A simple dilution with saline in a 1:1 fashion to increase existing supply duration [39].

Recommendation 10: If using an ester local anesthetic due to an amide local anesthetic shortage, interventional pain physicians should be aware (as always) of the potential for an allergic reaction and should be able to respond accordingly.

Amide local anesthetics (lidocaine, bupivacaine, mepivacaine, prilocaine, ropivacaine) are most commonly used for skin and soft tissue anesthesia, as well as for anesthesia of the target structure(s) of presumed/confirmed pain generation during interventional pain procedures. Allergic reactions to amide local anesthetics are uncommon [13–15]. In the case of amide local anesthetic shortage(s), ester local anesthetics (cocaine, procaine, tetracaine, chloroprocaine, and benzocaine) might be considered for use. Physicians should be aware that *para*-aminobenzoic acid (PABA), a known allergen, is a metabolite of ester local anesthetics [13–15]. In addition, methylparaben, used in amide local anesthetics with preservatives, is metabolized to PABA. Thus, patients allergic to ester local anesthetics should avoid amide local anesthetics containing methylparaben. As always, interventional pain physicians should be able to treat allergic and anaphylactic reactions at the site in which they are performing their procedures [4].

Recommendation 11: Local anesthetic systemic toxicity (LAST) differs between the varying local anesthetics, and interventional pain physicians should be well-acquainted with these differences when switching between local anesthetics.

When considering a different anesthetic due to a shortage, LAST is a potential consideration. LAST is important to consider when injecting larger doses of local anesthetics (see Table 1), and/or when injecting in highly vascular regions. Sympathetic blocks (*e.g.,* celiac plexus block, lumbar sympathetic block) create particularly high risks for LAST. In the case of injection of local anesthetic directly adjacent to highly vascular structures, even small volumes and dosages can cause direct, short-lived toxicity such as seizures after inadvertent arterial injection during a stellate ganglion block [40]. When considering alternative local anesthetic choices in the setting of local anesthetic shortages, Table 1 provides information to reacquaint interventional pain physicians with each local anesthetic's maximum dosages to avoid LAST [16,41]. The most catastrophic complication of LAST is cardiac arrest due to direct cardiac toxicity, which is more likely to occur with local anesthetics with narrow therapeutic windows and greater cardiac toxicity (*e.g.,* bupivacaine) [42].

Table 1
Maximum dose for ester and amide local anesthetics[a].

	Anesthetic	Maximum Dose (mg/kg)	Duration (hours)
Esters	Chloroprocaine	12	0.5–1.0
	Cocaine	3	0.5–1.0
	Procaine	12	0.5–1.0
	Tetracaine	3	1.5–6.0
Amides	Bupivacaine	3	1.5–8.0
	Lidocaine	4.5 or 7 w/epi	0.75–1.5
	Mepivacaine	4.5 or 7 w/epi	1.0–2.0
	Prilocaine	8	0.5–1.0
	Ropivacaine	3	1.5–8.0

epi: epinephrine.
[a] Adapted from "Open Anesthesia. Local anesthetics: systemic toxicity." [43].

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