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Additives to Local Anesthetics for Peripheral Nerve Blockade

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Abstract

Many additives to local anesthetics to prolong the duration of analgesia for peripheral nerve blocks have been studied. In this review, the authors focus on the more commonly described additives, including epinephrine, clonidine, dexmedetomidine, buprenorphine, dexamethasone, tramadol, sodium bicarbonate, and midazolam. While the primary focus of this review is the effect of the additive on the duration of analgesia, neurotoxicity and other safety concerns are also discussed.

Introduction

Single-shot peripheral nerve blocks as (i) an alternative to general anesthesia and (ii) an opioid-sparing analgesic have become a portion of standard anesthesia practice throughout the world. While perineural catheters for postoperative analgesia for the days after surgery have increased, the majority of anesthesiologists still perform single-shot blocks. Commercially available local anesthetics have a limited duration of analgesia that frequently leaves patients complaining of pain for the first time during their first postoperative night when they are likely most vulnerable. While there are longer acting formulations and new concepts on the horizon, there are limits to what local anesthetics alone can provide. In this review, the authors will describe both evidence and potential future directions for the use of described adjuncts with each other and with long-acting local anesthetics. The focus will be on the onset and analgesic duration of single-shot nerve blocks, along with any neurotoxic concerns or neuroprotective potential.

Epinephrine

While epinephrine certainly has analgesic benefit when used with short- and intermediate-acting local anesthetics, there are limited data regarding the efficacy of epinephrine for prolonging the analgesic duration of long-acting local anesthetics (ropivacaine, bupivacaine, levobupivacaine). Some studies with long-acting local anesthetics (e.g., ropivacaine) failed to show an increased duration of analgesia with co-administration of epinephrine.[1] The limited available data make it impossible to assess the potential analgesic benefits for the addition of epinephrine.

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Disclosures- The University of Michigan has filed a patent for the use of perineural dexmedetomidine in peripheral nerve blocks. Dr. Brummett is the named inventor.

Epinephrine remains the most widely used adjunct for local anesthetics in peripheral nerve blockade; however, the increased use of ultrasound and potential concerns about neurotoxicity may temper the enthusiasm of its use for some anesthesiologists. A review by Neal (2003) notes the differential blood flow of the extrinsic and intrinsic systems in the peripheral nerve and questions whether epinephrine has any true impact on neurotoxicity.[2] Decreases in blood flow[2, 3] and the increased duration of analgesia[4] are due to the α_1-adrenoceptor agonist effect of epinephrine.[4] Some local anesthetics, including lidocaine and ropivacaine, will also cause vasoconstriction and are synergistic with epinephrine. Whether the effect of epinephrine is simply due to decreased systemic uptake leading to a greater effect of the local anesthetic on the peripheral nerve is still not completely understood;[2, 5] however, perineural epinephrine alone does not cause sensory or motor blockade.[4]

The controversy surrounding widespread use of epinephrine in combination with local anesthetics is the argument as to whether it is protective or harmful. There is no question that epinephrine can be a valuable marker for the detection of intravascular injection, and some experts believe that the early detection of intravascular injection greatly outweighs the potential neurotoxic or myotoxic effects. The increased use of ultrasound worldwide allows for visualization of the needle tip and real-time assessment of local anesthetic spread; however, unintentional intravascular injection of local anesthetic with subsequent cardiovascular collapse using ultrasound has still been reported and remains a legitimate concern. Along with other experts, however, we believe that the addition of epinephrine to local anesthetics may increase the potential neurotoxicity, which may be especially concerning in those patients at higher risk for nerve injury (i.e., patients with diabetes mellitus, hypertension, and/or a history of smoking).[6] We still recommend the use of epinephrine as an additive for test dose purposes in out-of-plane ultrasound blocks or nerve stimulator blocks. Beta blockade may limit the use of epinephrine as a marker of intravascular injection. Avoidance of high volume blocks, use of in-plane ultrasound guidance, slow injections, and limited sedation with constant assessment of central nervous system excitatory effects are likely equally or more important for limiting potential cardiotoxicity. *The authors only recommend the use of epinephrine for nerve blocks done without ultrasound guidance, or blocks in which the needle tip and local anesthetic spread is not adequately visualized, as a safety measure to detect intravascular injection.*

Clonidine

Clonidine, an α_2-adrenoceptor agonist, has been used for many years as an additive to short-, intermediate-, and long-acting local anesthetics.[7, 8] Meta-analyses and systematic reviews clearly show an analgesic benefit from the addition of clonidine to local anesthetics.[7, 8] The duration of additional benefit is difficult to assess due to the heterogenous nature of the outcomes measures used in the various studies; however, clonidine likely provides approximately 100 additional minutes of analgesia with long-acting local anesthetics.[7] Most studies used between 100–150 μg, with higher doses showing side effects, including sedation, bradycardia and hypotension.[7] A dose of 100 μg clonidine may produce mild, treatable side effects also seen with other anesthetics; anecdotally, lower clonidine doses may be prudent to use (to avoid hypotension) for patients in the sitting position with spontaneous ventilation, as is commonly the case with arthroscopic or “mini-open” shoulder surgery.ϕ

The mechanism of action of clonidine on the peripheral nerve has been elucidated in basic science studies, but has often failed to be translated to clinical literature. Clinical researchers have written about (i) α_2-adrenoceptor mediated vasoconstriction in the periphery, or (ii)

ϕhttp://www.apsf.org/newsletters/pdf/summer2007.pdf; Last accessed on 12/11/10

centrally mediated analgesia. Multiple studies have clearly demonstrated that the perineural effect of block prolongation is not α_2-mediated, however.[4, 9–11] Instead, the peripheral effects of clonidine are through inhibition of the hyperpolarization-activated cation current (I_h current). This current normally functions to restore nerves from a hyperpolarized state to resting potential for a subsequent action potential. The effect appears to be more profound on C-fibers (pain fibers) than Aα-fibers (motor fibers),[11] thereby making the effects potentially more sensory specific.

While modest efficacy has been demonstrated, the availability and convenience have limited the widespread use of clonidine in nerve blocks. At most institutions in the United States, clonidine is packaged in 1000 μg single-use vials at a cost significantly above that of local anesthetics (University of Michigan costs: 0.5% ropivacaine = $18.20 for a 30 mL vial; clonidine 1000 μg [10 mL] vial = $46.93). As such, much of the vial is wasted, unless prepared in sterile fashion in multiple syringes by a pharmacist, or unless multiple syringes can be separately prepared and immediately used in very high case volume programs. Given that its use in peripheral nerve blocks is not patented, clonidine is unlikely to be packaged with local anesthetics. That said, *both authors routinely use clonidine in their practice*.

Dexmedetomidine

The use of another α_2-adrenoceptor agonist, dexmedetomidine, for peripheral nerve blockade is not as widespread and is not currently approved for use in the United States. Preclinical data have demonstrated increased duration of sensory and motor blockade in bupivacaine and ropivacaine sciatic nerve blocks in rats.[12–14] The effects have been shown to be dose-dependent[14] and peripherally mediated.[12] An *in vitro* model of frog sciatic nerve blockade also demonstrated a reduction in compound action potentials with dexmedetomidine that was more potent than clonidine.[15] This effect was not reversed with α_2-adrenoceptor antagonists.

There are only two studies using dexmedetomidine for peripheral nerve blocks in humans. In a well-designed clinical trial, Obayah et al.[16] showed an increase in the time to first analgesic request following greater palatine nerve blocks cleft palate repair in children when bupivacaine plus dexmedetomidine (1 μg/kg) was compared with bupivacaine alone (22 hr vs. 14.2 hr, $p < 0.001$). In addition, pain scores in the dexmedetomidine group were significantly lower for the first 24 hr. There were no differences in sedation scores or hemodynamic variables between the two groups. A recent prospective, randomized, blinded, controlled trial found an improved onset time and increased duration of analgesia when dexmedetomidine (100 μg) was added to levobupivacaine for axillary nerve blocks in humans.[17] The dexmedetomidine group was associated with more bradycardia and hypotension, which was treated in some cases with atropine. The use of a nerve stimulator-guided block and high volumes (40 ml) of local anesthetic may have lessened the analgesic effects, as the effect of perineural dexmedetomidine is known to be concentration-dependent.[14] In addition, the use of a large volume could have increased the amount of systemic uptake of the dexmedetomidine leading to the higher rates of bradycardia.

Similar to clonidine,[18] dexmedetomidine pretreatment extends the time-to-cardiotoxicity from intravenous bupivacaine infusion in rats, and increases the total dose required to induce cardiac arrest.[19] Whether this cardioprotective effect applies to co-administration with local anesthetics is not known. *While the data to date are supportive, the authors believe that further clinical studies are warranted to better establish the appropriate dosing, potential side effects and safety prior to widespread clinical use.*

Buprenorphine

The use of traditional opioids in peripheral nerve blocks has not been shown to be effective in clinical studies;[20] however, there is ongoing research with buprenorphine. Buprenorphine is an opioid receptor μ-agonist and κ antagonist, having both analgesic and antihyperalgesic properties.[21] The original studies by Candido et al.[22, 23] demonstrated analgesic efficacy from the addition of the addition of buprenorphine to combinations of mepivacaine, tetracaine, and epinephrine. More recently, the same group compared the postoperative analgesic effects of buprenorphine added to bupivacaine compared with controls (including an intramuscular control group) for sciatic nerve blocks, and the results were less impressive than the original studies.[24] While both buprenorphine groups (perineural and intramuscular) had lower pain scores for the first 48 hours when compared with bupivacaine alone, there were no differences between the two buprenorphine groups for pain scores or opioid consumption at any of the assessed time points. The only significant differences were found when the groups were assessed over time through an analysis of variance. Both buprenorphine groups experiences more side effects (especially nausea and vomiting in the absence of antiemetic prophylaxis), while there were no differences in satisfaction between any of the groups.

While there are data to support peripheral anti-inflammatory effects[25] and laboratory studies demonstrating opioid receptors on primary sensory afferents (dorsal root ganglia and terminal endings),[26] it remains unclear as to how buprenorphine acts when added to local anesthetics in peripheral nerve blocks. Future research with other long-acting local anesthetics (or in combinations with other adjuvants) and appropriate controls is warranted. The authors are divided as to the clinical utility of buprenorphine in peripheral nerve blocks. *Dr. Williams regularly uses buprenorphine clinically, while Dr. Brummett does not recommend its use.*

Dexamethasone

In a recent review,[27] dexamethasone (as a corticosteroid) was reported to attenuate C-fiber responses. More recent publications since the aforementioned review indicate that 8 mg dexamethasone added to perineural local anesthetic injections augment the duration of peripheral nerve block analgesia.[28, 29] The increase in the duration of analgesia is unclear, as the two studies found widely divergent results; the latter of which using combined bupivacaine, clonidine, and epinephrine as the active control group.[29] In rats, dexamethasone alone or when combined with aqueous bupivacaine has no effect on the analgesic effects of a sciatic nerve block;[30] but when combined with bupivacaine microspheres, the effects were significant. Clinical data of dexamethasone with long-acting plain local anesthetic alone are not known, while the dexamethasone data with mepivacaine[28] refute the claim of a long duration sensory-selective blockade. Further research is needed to better delineate the impact of dexamethasone with long-acting local anesthetics both with and without other adjuvants. Until more efficacy data are available showing a significant increase in the duration of long-acting local anesthetics or a selective sensory blockade, *the authors recommend detailed attention being directed to potential dose-response efficacy and adverse effects in preclinical models with respect to dexamethasone combined with local anesthetics. Clinically, Dr. Brummett does not recommend the use of perineural dexamethasone, while Dr. Williams sparingly uses dexamethasone restricted to 1–2 mg perineural doses.*

Sodium Bicarbonate

Sodium bicarbonate is widely used in epidural (and to a lesser extent, perineural) anesthesia to hasten the time to sensory and motor block.[31] However, the effects of alkalinization of local anesthetics for peripheral nerve blockade is less clear.[32–35] Some studies report a

shortening of time to block onset, but whether these provide clinically meaningful results is not clear.[34, 35] Sodium bicarbonate does not appear to have any effect on block duration; although adding sodium bicarbonate to a local anesthetic solution containing clonidine offsets the increases to analgesic duration normally resulting from perineural clonidine use.[36] *Given the lack of significant efficacy, the authors do not recommend the use of sodium bicarbonate in peripheral nerve blocks*.

Tramadol

In a recent review,[27] tramadol was described to stimulate serotonin release intrathecally, while inhibiting norepinephrine reuptake centrally. It also is a weak μ- and κ-opioid receptor agonist, and also blocks voltage-gated sodium channels *in vitro* in a fashion that is not opioid-receptor related. While tramadol appears to have effects on *in vitro* models of compound action potientials,[37, 38] the clinical data have been largely negative, especially when combined with long-acting local anesthetics[39–41] or when systemic controls have been included.[41] There appears to be little future value in tramadol as a single adjuvant in local anesthetic nerve blocks, and *the authors do not recommend the use of perineural tramadol in clinical practice*.

Midazolam

The use of midazolam in regional anesthesia has been debated for many years, and its safety and analgesic efficacy remain in question. In a recent review,[27] the authors described the actions of peripheral midazolam as acting on GABA-A receptors in axons of mammalian peripheral nerve trunks, although other mechanisms (e.g., peripheral benzodiazepine receptors) may prove to be relevant.[42] While there are studies demonstrating efficacy,[43] the data are limited. Since this review, only one other study has been reported regarding the perineural (brachial plexus) use of midazolam,[44] yielding identical results as the only other reported use of perineural brachial plexus midazolam.[43] There have been multiple studies showing neurotoxicity when midazolam is administered intrathecally in animals.[45, 46] Given the concerns for neurotoxicity, *the authors do not recommend the clinical use of perineural midazolam combined with local anesthetics in peripheral nerve blocks.*

Neurotoxicity

Neurological sequelae are feared complications for all clinicians, and are likely greatly underreported due to failure of anesthesiologists to routinely assess patients after nerve blocks. Local anesthetics are known to be neurotoxic[47–49] and myotoxic.[50] Whether these effects are clinically significant is not known, yet prospective observational trials assessing postoperative neurological sequelae have demonstrated alarmingly high rates of significant sensory symptoms, along with significant associations between nerve injury and paresthesia and pain during the injection.[51–53] There are no data available to determine whether there is a causal effect with peripheral nerve blockade or possibly more correlation with patient positioning and surgery, but there are strong clinical associations implicating peripheral nerve blockade as a potential contributor. Much of the available literature is based on healthy animals and humans, and is therefore not as applicable to the average patient population. There is a growing belief that a re-evaluation of our standard care with a focus on an enhanced safety profile rather than simply trying not to be worse than the current standard of care (local anesthetics) is warranted, especially in at-risk patients.[6, 27, 54]

The potential additive risk or neuroprotection from some of the described perineural adjuvants has been studied, but is not clear. Epinephrine alone does not appear to have any neurotoxic effects, but when mixed with local anesthetics, neurotoxicity is increased.[2] The clinical implications of epinephrine's enhancement of neurotoxicity is still unclear.[2] Alpha-2

adrenoceptor agonists have been found to be neuroprotective in preclinical models of central nervous system ischemia.[55] In addition, clonidine was shown to attenuate the hyperalgesic response to nerve injury in rats through an α_2-mediated effect on inflammatory cells.[56, 57] Perineural dexmedetomidine attenuates the bupivacaine-induced acute perineural inflammation.[13] A poorly designed trial reported neurotoxicity with epidural dexmedetomidine in rabbits.[58] The study had a high rate of technical failure for epidural placement (25%), failed to include a vehicle control group, and used large catheters. In addition, a "drug effect" was described despite harvesting the spinal cords for histopathology only 60 minutes after injection, which is too early to truly ascribe a drug-related effect (Generally require 24 hours for acute toxicity and 14–21 days to assess delayed toxicity). Randomized, blinded, controlled studies of high-dose dexmedetomidine with long-acting local anesthetics for peripheral nerve blocks in rats found no neurotoxic effects.[13, 14] Whether α_2-adrenoceptor agonists are neuroprotective in peripheral nerve blocks is not known but preclinical data[13, 14] are encouraging. There has been interest in using dexamethasone for a potential anti-inflammatory neuroprotective effect. While the study was underpowered to detect a difference in postoperative neurological sequelae, there were no trends favoring dexamethasone compared with controls added to mepivacaine assessed prospectively at 2 weeks after the nerve block (8 of 24 patients with sensory complaints in the dexamethasone group vs. 5 of 21 in the normal saline control group, $p = 0.248$).[28] Prospective clinical trials of such outcomes are somewhat impractical, therefore clinicians may have to depend on preclinical data to assess potential neurotoxicity and neuroprotective effects.

There are no clinical or preclinical data to support increased risk or safety from the addition of buprenophrine, tramadol, dexamethasone, or sodium bicarbonate. There are *in vivo* intrathecal animal studies demonstrating neurotoxicity associated with midazolam.[45, 46] Since perineural dexamethasone in patients has only been reported at the 8 mg dose, it will be critical to evaluate preclinical models and potential dose-response neurotoxic effects in combination with local anesthetics.

Additional Safety Concerns

Intravascular injection remains one of the most serious concerns in regional anesthesia and is a source of potential morbidity and mortality.[59–61] While ultrasound may decrease the risk for intravascular injection, ultrasound alone does not obviate all risk.[60] Lipid emulsion therapy appears to be beneficial in treating local anesthetic-induced cardiac arrest;[62] however, the trend towards reduction of the dosage and volume of local anesthetics with ultrasound-guided nerve blocks will likely have the greatest impact on safety.[63] There are limited data to support the potential adverse effects associated with additives in the event of intravascular injection. As was noted in the "Epinephrine" section above, epinephrine can be a useful marker for intravascular injection, although its effects can be delayed or blunted by beta blockade. Pretreatment with α_2-adrenoceptor agonists (clonidine and dexmedetomidine) attenuates local anesthetic-induced cardiotoxicity and increases the safety threshold.[18, 19] Whether co-administration of α_2-adrenoceptor agonists and local anesthetics will have similar safety effects is not known and merits further study. Giving a bolus of either clonidine or dexmedetomidine could lead to bradycardia and hypotension. Buprenorphine, tramadol, sodium bicarbonate, and midazolam are all administered intravenously and would not be expected to have any additional adverse effects when co-administered with local anesthetics. Ultimately, local anesthetics have the greatest potential for toxicity, if administered intravenously, and reductions of local anesthetic dosing will likely have the greatest impact on patient safety.

The use of combinations and mixtures increases the potential for human drug error. The Anesthesia Patient Safety Foundation has recently pushed for the use of prefilled and labeled syringes.φ They also advocate for clinicians to create standard concentrations for all medications. While this effort is not focused on regional anesthesia, many of the concerns apply to our field and deserve consideration. This is certainly challenging given that many of the available additives are generic. Vigilance remains a cornerstone for regional anesthesia and particularly applies to careful calculations and drug preparation.

Conclusions

The authors recommend the clinical use of perineural clonidine (100 mcg for the average adult). Epinephrine is recommended as a marker for intravascular injections when performing nerve blocks without ultrasound (1:400,000 ratio), or when out-of-plane ultrasound techniques are employed. While early data for dexmedetomidine are encouraging, the authors recommend against widespread clinical use until further clinical data are available. The use of buprenorphine is only recommended by one (BAW) of the two authors, in the context of clonidine-buprenorphine combinations with local anesthetics. More data for dexamethasone are needed prior to its widespread use, especially related to potential dose-response-related neurotoxicity when combined with local anesthetics. The authors caution against combining midazolam and local anesthetics due to potential neurotoxicity, while sodium bicarbonate and tramadol appear to have little efficacy.

The authors believe that well-designed clinical trials with appropriate and reproducible outcomes of additives to local anesthetics are needed, especially in the age of ultrasound-guided peripheral nerve blocks. While safety should be a focus in such research, future studies should aim to find clinical options that are safer than the standard-of-care local anesthetics.

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φAnesthesia Patient Safety Foundation Newsletter, Spring 2010; Last accessed 12/20/10. http://www.apsf.org/newsletters/pdf/spring_2010.pdf

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