Topics in
PAIN MANAGEMENT

Vol. 35, No. 12 — *Current Concepts and Treatment Strategies* — July 2020

CONTINUING EDUCATION ACTIVITY

Adjuncts to Local Anesthetics for Peripheral Nerve Blocks: A Review of Current Literature

Benjamin Kuo, MD, and Jaime Ortiz, MD, MBA

The purpose of this article is to review current evidence on adjuncts to local anesthetics in prolonging the duration of peripheral nerve blocks.

Learning Objectives/Outcomes: After participating in this CME/CNE activity, the provider should be better able to:

1. Describe the various adjuncts to local anesthetics in peripheral nerve blocks and their proposed mechanism of actions.
2. Evaluate current evidence of efficacy and potential for prolongation of nerve blocks of these adjuncts.
3. Explain the potential drawbacks and side effects that might prevent the use of these adjuncts in daily clinical practice.

Key Words: Local anesthetics, Pain management, Peripheral nerve block, Postoperative pain

The placement of local anesthetics around a nerve to block ion channels from signal transmission is a technique that has been around for a very long time. However, regional anesthesia has gained increasing popularity and importance in the perioperative setting over the last few years, amid the intensifying opioid crisis in the United States, along with an improvement in the ultrasound technology that has made this mode of anesthesia more effective.

In This Issue

Dr. Kuo is Anesthesiology Resident, and Dr. Ortiz is Associate Professor, Department of Anesthesiology, Baylor College of Medicine, One Baylor Plaza, MS: BCM 120, Houston, TX 77030; E-mail: jaimeo@bcm.edu.

The authors, faculty, and staff in a position to control the content of this CME/CNE activity have disclosed that they and their spouses/life partners (if any) have no financial relationships with, or financial interests in, any commercial organizations relevant to this educational activity.

CME Accreditation

Lippincott Continuing Medical Education Institute, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Lippincott Continuing Medical Education Institute, Inc., designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity. To earn CME credit, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. This **CME** activity expires on **June 30, 2022**.

CNE Accreditation

Lippincott Professional Development is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Lippincott Professional Development will award 1.0 contact hours for this continuing nursing education activity. This activity has been assigned 1.0 pharmacology credits. Instructions for earning ANCC contact hours are included on page 11 of the newsletter. This **CNE** activity expires on **June 3, 2022**.

In addition, newer regional blocks, such as the transverse abdominis plane block and erector spinae plane block, have also helped increase the type of surgical procedures that can have regional anesthesia as part of the multimodal pain management approach. Multiple studies have demonstrated that a multimodal perioperative pain management approach is effective in reducing overall opioid consumption.[1]

The longest-acting local anesthetics (excluding liposomal bupivacaine) are ropivacaine and bupivacaine, which can potentially provide up to 24 hours of analgesia with a single-shot technique. Nerve catheters can also be placed to provide continuous infusions and repeated boluses that can offer longer analgesia than a single injection does.

However, nerve catheters come with their own risks and inconveniences. The main drawbacks include risk of infection and need for patient education and compliance for out-of-hospital use. Therefore, adjuncts to local anesthetics with the potential to prolong a single-shot nerve block can prove to be extremely beneficial and efficient in the perioperative clinical setting.

Numerous adjuncts have been studied in recent years with some demonstrating promising results. In this review, we first discuss some recent evidence on drawbacks for peripheral nerve catheters. Then, we provide recent research studies on 5 adjuncts: dexmedetomidine, dexamethasone, clonidine, magnesium, and buprenorphine. We also explore the idea of adding more than one adjunct to a nerve block. The article concludes with recommendations on each of these adjuncts after analysis of the current literature.

The continuing education activity in *Topics in Pain Management* is intended for clinical and academic physicians from the specialties of anesthesiology, neurology, psychiatry, physical and rehabilitative medicine, and neurosurgery, as well as residents in those fields and other practitioners interested in pain management.

Wolters Kluwer

Topics in Pain Management (ISSN 0882-5645) is published monthly by Wolters Kluwer Health, Inc. at 14700 Citicorp Drive, Bldg 3, Hagerstown, MD 21742. **Customer Service: Phone (800) 638-3030, Fax (301) 223-2400, or Email customerservice@lww.com**. Visit our website at **lww.com.**

 Priority postage paid at Hagerstown, MD, and at additional mailing offices. GST registration number: 895524239. POSTMASTER: Send address changes to ***Topics in Pain Management***, PO Box 1610, Hagerstown, MD 21740.

Publisher: Randi Davis

Subscription rates: *Individual:* US $419, international: $531. *Institutional:* US $1079, international $1231. *In-training:* US $164 with no CME, international $188. *Single copies:* $104. Send bulk pricing requests to Publisher.

Topics in Pain Management is indexed by SIIC HINARI and Google Scholar.

Peripheral Nerve Catheters

Compared with single-shot nerve blocks, peripheral nerve catheters are resource-intensive, with many drawbacks. In addition, the theoretical benefit of providing continuous analgesia via the catheter may not be all that straightforward.

In a prospective, randomized study, Elkassabany et al[2] included 159 patients who were receiving adductor canal nerve blocks for total knee arthroplasty. The investigators randomized the patients into 3 groups: single-shot group, 24-hour infusion group, and 48-hour infusion group.[2]

Their results demonstrated that, on postoperative day 2, the proportion of patients reporting severe pain (7–10 out of 10) was 21% for the single-shot group, 14% for the 24-hour group, and 12% for the 48-hour group.[2] However, cumulative opioid usage and functional outcomes at postoperative day 2 were similar among patients in all 3 groups.[2]

In another randomized, double-blinded study by Wyatt et al,[3] the investigators randomized patients who were receiving total knee arthroplasty into 2 groups. Both groups received a single-shot femoral nerve block, followed by placement of a nerve catheter.[3]

In the treatment group, a continuous infusion with 0.125% bupivacaine was provided through the catheter, whereas in the placebo group, the catheter was infused with normal saline.[3]

The results in Wyatt et al[3] demonstrated that there was no significant difference in the visual analogue pain score at 72 hours. Similarly, in the secondary outcomes, there was no difference in the total morphine equivalent requirement, length of hospital stay, range of movement, or motor block.

Thus, although there may be some reduction in pain scores with a continuous local anesthetic infusion, many of the other secondary outcomes measured, especially total opioid consumption, seem to illustrate similar effects in both single-shot nerve blocks and nerve catheter infusions.

More importantly, the resource-intensive nature of nerve catheters and their multiple drawbacks are likely the major reasons for lack of widespread use in the perioperative setting. As with any indwelling catheter, it creates a nidus for infection and potential hematogenous spread in the body.

In addition to the associated risk of infection, the cost of continuous nerve catheters is much higher than that of a single-shot nerve block.

In a retrospective study done by Bomberg et al,[4] the authors looked back at 44,555 patients who received continuous nerve catheters between 2007 and 2014 in 25 centers. After adjusting for confounding factors, they found that the probability of infection-free catheters decreased from 99% at day 4 to 73% at day 15.[4] Most nerve catheters are usually indwelling for fewer than 7 days, but these results still demonstrate the potential for infection.

In addition to the associated risk of infection, the cost of continuous nerve catheters is much higher than that of a single-shot nerve block. Some of these costs include infusion pumps, catheters, and infusion medications.[5]

And even beyond those costs, additional resources are required to safely maintain the catheter from insertion to removal. Providers need to spend time educating the patient about the purpose of the nerve catheters and what complications to look for if they are being sent home with the catheters.[5,6] In addition, there needs to be a robust system for patient follow-up via inpatient visit or outpatient phone calls to ensure the catheters are safely monitored.[5,6] Moreover, patient compliance is also crucial, and the risk of losing a patient to follow-up with an indwelling nerve catheter should be considered.

Although there are potential benefits, there are numerous drawbacks in the effectiveness of the analgesia as well. Compared with single-shot nerve blocks, there may be a decrease in overall pain scores as demonstrated in some studies, but the difference in overall opioid consumption is debatable.[2,3] Furthermore, significant resources and costs are associated with peripheral nerve catheters, rendering them a less obvious choice for analgesia in this age of cost-effectiveness in medicine.[3,4]

Dexmedetomidine

Dexmedetomidine is an alpha-2 agonist that has gained widespread use in recent years. It was first approved by the FDA in 1999 as a sedative for use in intensive care, but its use quickly expanded to the entire perioperative period.[7] Compared with clonidine, it is much more selective and specific to alpha-2 receptors, thereby reducing unwanted alpha-1 effects.[7]

During the preoperative period, dexmedetomidine can be used as an anxiolytic via its oral route, a practice more commonly used in the pediatric population.[7] In the intraoperative period, it can be one of the adjuncts for maintaining total IV anesthesia.[7] And in the postoperative period, it is frequently used for sedation and transition to the intensive care unit setting.[7]

On the other hand, perineural administration of dexmedetomidine is still relatively new and there are debates on whether there are advantages of adding dexmedetomidine to local anesthetics during regional nerve blocks.

In a prospective, randomized, double-blinded trial done by Das et al,[8] the investigators randomized 80 patients into receiving either ropivacaine (R) or ropivacaine with dexmedetomidine (RD) for a supraclavicular block.

The RD group demonstrated a statistically significant shorter time to onset of sensory blockade (10.75 ± 2.71 vs 16.75 ± 2.96 minutes, $P = 0.003$), longer sensory block duration

(379.40 ± 55.09 vs 211.60 ± 47.88 minutes, $P = 0.002$), shorter onset time to motor blockade (14.35 ± 2.58 vs 20.25 ± 4.13 minutes, $P = 0.003$), longer motor block duration (312.0 ± 49.91 vs 184.7 ± 36.76 minutes, $P = 0.002$), and longer duration of postoperative analgesia (413.73 ± 89.92 vs 197.35 ± 28.67 minutes, $P = 0.002$).[8]

Hemodynamics were not statistically significant between the R and RD groups throughout the intraoperative period.[8]

In another 2017 study, Koraki et al[9] randomly assigned patients receiving axillary block into either ropivacaine only or ropivacaine plus dexmedetomidine group. This study again demonstrated a statistically significant increase in duration of sensory and motor block in the group receiving ropivacaine plus dexmedetomidine.[9] The onset of sensory block was shorter in the ropivacaine plus dexmedetomidine group, but the onset of motor block was not statistically significant.[9]

Because dexmedetomidine is often administered intravenously in the operating room, especially in the pediatric population, investigators have also studied using IV dexmedetomidine concurrently alongside a peripheral nerve block. An argument against such a strategy is the concern about potential effects on hemodynamics.

In a 2019 study done by Somsunder et al,[10] 60 patients receiving a supraclavicular block were randomized into 2 groups: receiving levobupivacaine with perineural dexmedetomidine or receiving levobupivacaine with IV dexmedetomidine. These combinations were administered 10 minutes before the start of the block.

Results demonstrated that onset and duration of sensory and motor block, and duration of analgesia, were comparable between the 2 groups.[10] However, there was a statistically significant difference in the incidence of hypotension, with a higher incidence observed in the patients receiving levobupivacaine with IV dexmedetomidine.[10]

Many recent studies have repeatedly illustrated the advantages of adjuvant perineural dexmedetomidine in regional nerve blocks, mainly a longer sensory and motor block duration, and longer analgesia.[10,11]

A few hours' increase in duration of analgesia is both useful and relevant clinically, because this decreases the time pressure for the surgery itself, especially if the nerve block is used as a surgical block. The evidence is especially strong in upper extremity blocks, as that is what most of the studies have focused on. Theoretically, this should be applicable to most nerve blocks. On the other hand, plane blocks work in slightly different physiology and they have not had as much research with regard to dexmedetomidine as an adjunct.[10,11] In addition, there seems to be minimal risk of neurotoxicity from dexmedetomidine, as demonstrated in rat models by Tüfek et al.[11]

Overall, with a low side-effect profile when administered perineurally with local anesthetics, dexmedetomidine may be considered an adjunct to improve the efficacy and duration of the block.

Dexamethasone

Dexamethasone is a corticosteroid medication with very minimal mineral corticoid activity, and it is commonly used in the intraoperative setting.[12] Besides its well-known anti-inflammatory effect via its corticosteroid actions, it is also frequently used as an antiemetic.[12] The use of dexamethasone has been increasingly studied in recent years, with the theory of dexamethasone exerting its direct anti-inflammatory effects on nerves when used perineurally.[13]

A randomized, double-blinded, prospective study by Kumar et al[13] randomized 80 patients who were receiving supraclavicular blocks into either ropivacaine (R) group or ropivacaine plus dexamethasone (R plus dexamethasone) group. The primary outcome measured was the duration of analgesia, as defined by the onset of sensory block until the first request for analgesia.[13]

The results demonstrated that the R plus dexamethasone group had a statistically significant longer duration of analgesia, with 1179.4 ± 108.60 minutes of analgesia, versus the R group having 557 ± 58.99 minutes.[13]

The R plus dexamethasone group also had a lower total analgesia requirement when compared with the R group.[13]

In another study by Hauritz et al,[14] the researchers conducted a similar double-blinded, randomized, prospective, study on sciatic nerve blocks. They randomized 56 patients receiving sciatic nerve blocks for lower extremity surgical procedures into the R and R plus dexamethasone groups, as well.[14] The results demonstrated that the R plus dexamethasone group had a longer duration of analgesia compared with the R group, where the mean time for return of sensory and motor function was 26 hours in the R plus dexamethasone group compared with 16 hours in the R group.[14] In addition, time to first opioid request was also longer in the R plus dexamethasone group, at 34 hours, compared with 15 hours in the R group.[14]

With a low side-effect profile when administered perineurally with local anesthetics, dexmedetomidine may be considered an adjunct to improve the efficacy and duration of the block.

As can be seen, not only are these results statistically significant, they also are useful clinically, as almost 10 more hours of analgesia may be provided.

As with dexmedetomidine, there are also debates whether there is any difference between perineural administration and IV administration of dexamethasone.

In 2 recent studies by McHardy et al[15] and Kahn et al,[16] both were randomized, double-blinded studies comparing perineural versus IV dexamethasone in interscalene blocks.

Interestingly, both studies illustrated that there was statistical difference in duration of analgesia, where the perineural group had 1 to 3 hours longer of analgesia, but all other secondary outcomes were equivalent, including total opioid usage, patient satisfaction, and pain scores.[15,16]

In everyday practice, adjuvant perineural dexamethasone for nerve blocks may not be as useful. This is due to 2 main reasons. First, most clinicians would prefer to use 1 adjuvant medication on top of local anesthetics to avoid polypharmacy in a single-shot nerve block.[15,16] Second, dexamethasone can easily be administered via the IV route with minimal side effects, along with studies demonstrating equivalent clinical benefits compared with perineural dexamethasone.[15,16]

Clonidine

Clonidine is an older, less-selective, alpha-2 agonist compared with dexmedetomidine. It has been around in clinical practice for a while, mainly for the treatment of hypertension; hence, the cost of the medication is much lower than that of dexmedetomidine.[17] The IV form, which is the formulation used for perineural adjuncts, is 3 times more expensive than the oral form, but the major issue with IV clonidine is its availability.[18] Most hospitals have only the oral formulation available, as the IV form is rarely indicated.[18] Nevertheless, several studies have looked at its use as an adjuvant to nerve blocks.

In a randomized, prospective trial done by Ali et al,[17] the investigators recruited 60 patients receiving supraclavicular block and randomized them into either ropivacaine only and ropivacaine with clonidine group. The results demonstrated statistically significant increase in sensory and motor block duration, and length of postoperative analgesia, in the ropivacaine with clonidine group.[17]

In another randomized, prospective trial by Faria-Silva et al,[19] the investigators similarly randomized 53 patients receiving brachial plexus blocks into ropivacaine only and ropivacaine plus clonidine groups.[19] They did notice an increase in duration of motor and sensory blockade in the ropivacaine plus clonidine group, yet they did not observe any difference in the patients' pain scores nor the amount of total opioids used.[19]

A meta-analysis by El-Boghdadly et al[20] combined 14 randomized trials comprising of 868 patients receiving supraclavicular blocks, where these patients were randomized into receiving a local anesthetic plus clonidine or dexmedetomidine. The results demonstrated that the addition of dexmedetomidine to local anesthetics prolonged the sensory and motor block by 20% as compared with clonidine, and increasing the analgesia by 20%.[20] However, they did notice that dexmedetomidine had a higher odds ratio of transient bradycardia and postoperative sedation.[20]

With the increasing availability of dexmedetomidine in clinical settings, it should be considered the adjuvant agent of choice for nerve blocks, especially as the IV clonidine formulation is not common in most hospitals.[18]

In clinical settings, dexmedetomidine should be considered the adjuvant agent of choice for nerve blocks, especially as the IV clonidine formulation is not common in most hospitals.

Magnesium

Magnesium is a medication that has proven to be very versatile, with uses in various fields of medicine. In perioperative pain management, magnesium can be used in IV and intrathecal routes for analgesic purposes. The mechanism of action for magnesium is through its regulation of calcium influx into neurons, hence modulating the neuronal pathways.[21,22] In addition, it has some *N*-methyl-D-aspartate (NMDA) antagonism properties that may contribute to the analgesic property.[21]

Besides analgesic purposes, magnesium has been used for total IV anesthesia and potentiation of neuromuscular blockade in the intraoperative setting.[23] In cardiac surgical procedures, magnesium has been demonstrated to reduce incidence of arrhythmias, mainly atrial fibrillation.[24] Furthermore, it is given to preeclamptic patients for prevention of seizures in the obstetric setting.[23] The use of magnesium in nerve blocks is still a relatively new concept with studies demonstrating mixed results.

In a prospective, randomized, double-blinded trial done by Khairnar et al,[21] the authors recruited 54 patients receiving femoral nerve block and lateral femoral cutaneous nerve block. They randomized the patients into either the levobupivacaine group (L), levobupivacaine plus magnesium sulfate group (LM), or ropivacaine-only group (R).

Their results did not demonstrate any difference with the addition of magnesium, in terms of analgesia duration.[21] All 3 groups demonstrated excellent analgesia duration, but addition of magnesium did not add further value.[21]

In another study by Ekmekci et al,[25] the authors randomized 107 patients undergoing anterior cruciate ligament repair surgery for postoperative block into either receiving levobupivacaine (L) or levobupivacaine plus magnesium (LM) group. They found statistically significant lower visual analogue pain score and verbal rating scale for pain in the LM group.[25] In addition, they noticed lower total opioid consumption and longer time until first mobilization in the LM group.[25]

Side effects observed in these studies, including shivering, nausea, and vomiting, were not statistically different from control to treatment groups.[21,25]

However, there is no in vitro nor in vivo study on the potential toxicity of perineural magnesium injection. Interestingly, there have been randomized, prospective trials looking at using IV magnesium to reduce chemotherapy-induced neurotoxicity.[26] Nevertheless, IV injections are different from perineural injections and so the direct neurotoxicity of perineural magnesium is still unclear at this moment.

Magnesium has demonstrated some promise in prolongation of nerve block duration and lowering overall opioid consumption in some studies, but not in others. Hence, we cannot recommend magnesium as an adjunct to nerve blocks at this point until there are more robust studies with consistent findings.

Buprenorphine

Buprenorphine is known for its partial agonist activity at the μ-opioid receptors, commonly used for treatment of opioid addiction and chronic pain.[27] It also has been demonstrated to bind to voltage-gated sodium channels, thereby explaining its potential effects as a local anesthetic adjunct.[28] Numerous studies have also investigated the use of buprenorphine in nerve blocks as an adjunct and demonstrated it to be a promising agent.[28,29]

In a meta-analysis done by Schnabel et al,[28] the authors included 13 randomized control trials where they compared local anesthetics plus perineural buprenorphine, local anesthetic plus intramuscular buprenorphine, and local anesthetic alone.

Major findings in this meta-analysis include a longer duration of analgesia with addition of buprenorphine, for up to 8 hours.[28] The significant side effect was the increase in incidence of postoperative nausea and vomiting (PONV).[28]

In another study by Candido et al,[29] the authors randomized 103 patients receiving infragluteal sciatic nerve blocks into 3 groups: bupivacaine only, bupivacaine plus intramuscular buprenorphine, and bupivacaine plus perineural buprenorphine.[29] The results demonstrated that only perineural buprenorphine with bupivacaine exhibited statistically significant prolongation of postoperative analgesia, lower numeric pain scores, and lower total opioid usage.[29]

Overall, there seem to be promising benefits with perineural buprenorphine, including prolongation of analgesia and decrease in total opioid usage. However, it should be noted that increase in PONV is a common side effect with this adjunct.[28,29]

Combination of Multiple Adjuncts

As discussed earlier, several adjuncts to local anesthetics have demonstrated promising benefits for analgesia prolongation and decreases in total opioid consumption. More than one adjunct has been added together for single subarachnoid injections with a good safety profile and proven beneftis.[30] Recent studies have begun to investigate whether more than one adjunct can be added in a single-shot nerve block for potentially synergistic effects that further prolong the duration of analgesia.[31]

Recent studies have begun to investigate whether more than one adjunct can be added in a single-shot nerve block for potentially synergistic effects that further prolong the duration of analgesia.

Zhang et al[31] conducted a randomized, prospective, double-blinded trial on 80 patients receiving intercostal nerve block via direct injection by a surgeon for thoracoscopic pneumectomy procedures.

The patients were randomized into 4 groups: ropivacaine only (R), ropivacaine plus dexamethasone (RS), ropivacaine plus dexmedetomidine (RM), and ropivacaine plus both dexamethasone and dexmedetomidine (RSM).[31]

The results demonstrated that there was statistically longer analgesic duration in RSM (824.2 ± 105.1 minutes) than in RS (611.5 ± 133.0 minutes), RM (602.5 ± 108.5 minutes), and R (440.0 ± 109.6 minutes).[31]

In addition, total postoperative fentanyl consumption was lower in RSM (106.0 ± 84.0 μg) than in RS (243.0 ± 175.2 μg), RM (237.0 ± 98.7 μg), and R (369.0 ± 134.2 μg).[31]

Otherwise, adverse effects were comparable among the 4 groups.[31] In another study by Turner et al,[32] they conducted a randomized, double-blinded trial, where 60 patients were randomized into the single-shot adductor canal block group (received bupivacaine plus clonidine, dexamethasone, buprenorphine, and epinephrine) or the continuous infusion group (single shot of bupivacaine plus epinephrine, followed by continuous infusion of bupivacaine).[3] The results demonstrated no difference in movement pain scores at 30 hours, and no statistical difference in the secondary outcomes, including opioid consumption, time to first opioid administration, and length of stay.[32]

The prospect of synergistic effects among different adjuncts that can together prolong the analgesic duration even further is definitely an interesting area for investigation. The concept of synergistic effects among different adjuncts is a relatively new concept itself in peripheral nerve blocks, with few trials and data so far to support its use in clinical practice. Not only do there need to be larger and more robust trials to support the clinical benefits, but also in-depth evaluation of any potential neurotoxicity when mixing multiple medications in

Table 1. Summary Findings: Adjuncts to Local Anesthetics

	Benefits	Drawbacks	Recommendation
Dexmedetomidine	Strong evidence indicating a prolonged analgesia and block duration Possible neuroprotective effects	Higher cost of medication	Strong consideration as an adjunct for peripheral nerve blocks
Dexamethasone	Has been demonstrated to prolong block duration both perineurally and as intravenously	IV administration of dexamethasone has been demonstrated to be equally as effective for prolonging block duration	May recommend using the IV route as similar effects are observed
Clonidine	Prolongs analgesia and block duration, cheaper than dexmedetomidine	Less favorable pharmacokinetic profile, IV clonidine is not widely available	Dexmedetomidine should be used whenever available, but clonidine is a viable alternative
Magnesium	Mixed results regarding analgesia and block duration	Needs more robust studies regarding efficacy and safety profile for incorporation into daily clinical practice	Would not recommend magnesium at this time
Buprenorphine	Has been demonstrated to prolong block duration and lower overall opioid usage	Increase in PONV incidence	Can consider as a possible adjunct
Multiple adjuncts to single-shot nerve block	Not enough evidence to suggest a beneficial effect	Unclear effects on drug interactions and neurotoxicity	More studies need to be done for both efficacy and safety profiles
Peripheral nerve catheters	Ability to run a continuous infusion of local anesthetic medications	Higher cost for patient, resource-intensive in terms of patient education and compliance Risk of infection or catheter migration	Can be an option but requires a shared decision between patient and clinician

PONV, postoperative nausea and vomiting.

a single nerve shot.[33] As a result, we cannot recommend mixing multiple adjuncts to a local anesthetic for a peripheral nerve block at this time.

Neurotoxicity of Adjuncts to Local Anesthetics

Because of the relatively new concept of using adjuncts to local anesthetics, the safety profiles of these adjuvants are currently not well-defined and are undergoing continued study. Local anesthetics have the ability to disrupt signal transmission at neurons, thereby having an inherently neurotoxic nature. The goal is to elucidate whether or not these adjuncts to local anesthetics exacerbate the neurotoxicity or have minimal effects.

Dexmedetomidine is a unique adjunct in that neuroprotective properties have been observed in animal models when given perineurally. As mentioned previously, rat model studies by Tüfek et al[11] have demonstrated decreases in inflammation around the nerve with perineural dexmedetomidine injections.

With regard to clonidine, buprenorphine, and dexamethasone, cellular and animal studies have been performed. In a study done by Williams et al,[33] the researchers bathed neuronal sensory cells in solutions of ropivacaine plus different adjuncts at different concentrations. They found that high concentrations of clonidine, buprenorphine, and dexamethasone increased subsequent neuronal death.[33]

However, at clinically relevant doses, these adjuncts did not impact viability of those neuronal cells.[33]

Furthermore, Williams et al[34] continued their study into in vivo rat models. Clonidine, buprenorphine, and dexamethasone were injected in combination with either saline or bupivacaine into rat dorsal root ganglion (DRG) tissues.[34] Rat behaviors and DRG tissue analysis were performed after 15 days, with results demonstrating no difference in their behaviors and no damages to DRG neurons.[34]

So far, studies on neurotoxicity of these adjuvants have been in vitro or in vivo in rat models. Although results in these models are encouraging, studies done on larger animal models and eventually human trials will be needed for reinforcement of these current findings.[35]

Conclusion

A summary of the findings of this review is presented in Table 1. Increasingly, robust studies in the past decade consistently have demonstrated that certain adjuncts to local anesthetics can prolong the sensory block and analgesic duration of peripheral nerve blocks. However, the safety profile and

cost-effectiveness of these adjuncts are 2 main areas of future research.

As mentioned in previous sections, in vitro and rat models have been conducted to evaluate the neurotoxicity of these adjuncts. Although the results of these studies have so far been favorable, it is crucial to expand these studies into larger animals and human subjects. Federal agency approval for the indicated use of these adjuncts to prolong analgesic duration is the ultimate goal.[36] FDA approval would allow physicians to use these medications without ethical and legal constraints and to allow patients to benefit from the positive effects.[36]

Some adjunct agents are more suitable in certain clinical practices, based on availability and cost. Therefore, we recommend combining these studies with each unique clinical practice setting and patient populations to develop a sustainable and efficient regional block service. ■

References

1. Kumar K, Kirksey MA, Duong S, et al. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. *Anesth Analg*. 2017;125(5):1749-1760. doi:10.1213/ANE.0000000000002497.
2. Elkassabany NM, Cai LF, Badiola I, et al. A prospective randomized open-label study of single injection versus continuous adductor canal block for postoperative analgesia after total knee arthroplasty. *Bone Joint J*. 2019;101-B(3):340-347. doi:10.1302/0301-620X.101B3.BJJ-2018-0852.R2.
3. Wyatt MC, Wright T, Locker J, et al. Femoral nerve infusion after primary total knee arthroplasty: a prospective, double-blind, randomised and placebo-controlled trial. *Bone Joint Res*. 2015;4(2):11-16. doi:10.1302/2046-3758.42.2000329.
4. Bomberg H, Bayer I, Wagenpfeil S, et al. Prolonged catheter use and infection in regional anesthesia: a retrospective registry analysis. *Anesthesiology*. 2018;128(4):764-773. doi:10.1097/ALN.0000000000002105.
5. Joshi G, Gandhi K, Shah N, et al. Peripheral nerve blocks in the management of postoperative pain: challenges and opportunities. *J Clin Anesth*. 2016;35:524-529. doi:10.1016/j.jclinane.2016.08.041.
6. Swenson JD, Davis JJ. Getting the best value for consumable supplies in regional anesthesia. *Int Anesthesiol Clin*. 2011;49(3):94-103. doi:10.1097/AIA.0b013e31821b7bf7.
7. Gertler R, Brown HC, Mitchell DH, et al. Dexmedetomidine: a novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent)*. 2001;14(1):13-21. doi:10.1080/08998280.2001.11927725.
8. Das B, Lakshmegowda M, Sharma M, et al. Supraclavicular brachial plexus block using ropivacaine alone or combined with dexmedetomidine for upper limb surgery: a prospective, randomized, double-blinded, comparative study. *Rev Esp Anestesiol Reanim*. 2016;63(3):135-140. doi:10.1016/j.redar.2015.04.012.
9. Koraki E, Stachtari C, Kapsokalyvas I, et al. Dexmedetomidine as an adjuvant to 0.5% ropivacaine in ultrasound-guided axillary brachial plexus block. *J Clin Pharm Ther*. 2018;43(3):348-352. doi:10.1111/jcpt.12657.
10. Somsunder RG, Archana NB, Shivkumar G, et al. Comparing efficacy of perineural dexmedetomidine with intravenous dexmedetomidine as adjuvant to levobupivacaine in supraclavicular brachial plexus block. *Anesth Essays Res*. 2019;13(3):441-445. doi:10.4103/aer.AER_105_19.
11. Tüfek A, Kaya S, Tokgöz O, et al. The protective effect of dexmedetomidine on bupivacaine-induced sciatic nerve inflammation is mediated by mast cells. *Clin Invest Med*. 2013;36(2):E95-102. doi:10.25011/cim.v36i2.19572.
12. De Oliveira GS Jr, Castro-Alves LJ, Ahmad S, et al. Dexamethasone to prevent postoperative nausea and vomiting: an updated meta-analysis of randomized controlled trials. *Anesth Analg*. 2013;116(1):58-74. doi:10.1213/ANE.0b013e31826f0a0a.
13. Kumar S, Palaria U, Sinha AK, et al. Comparative evaluation of ropivacaine and ropivacaine with dexamethasone in supraclavicular brachial plexus block for postoperative analgesia. *Anesth Essays Res*. 2014;8(2):202-208. doi:10.4103/0259-1162.134506.
14. Hauritz RW, Hannig KE, Henriksen CW, et al. The effect of perineural dexamethasone on duration of sciatic nerve blockade: a randomized, double-blind study. *Acta Anaesthesiol Scand*. 2018;62(4):548-557. doi:10.1111/aas.13054.
15. McHardy PG, Singer O, Awad IT, et al. Comparison of the effects of perineural or intravenous dexamethasone on low volume interscalene brachial plexus block: a randomised equivalence trial [published online ahead of print October 5, 2019]. *Br J Anaesth*. doi:10.1016/j.bja.2019.08.025.
16. Kahn RL, Cheng J, Gadulov Y, et al. Perineural low-dose dexamethasone prolongs interscalene block analgesia with bupivacaine compared with systemic dexamethasone: a randomized trial. *Reg Anesth Pain Med*. 2018;43(6):572-579. doi:10.1097/AAP.0000000000000817.
17. Ali QE, Manjunatha L, Amir SH, et al. Efficacy of clonidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block: a prospective study. *Indian J Anaesth*. 2014;58(6):709-713. doi:10.4103/0019-5049.147150.
18. Hanning SM, Orlu Gul M, Toni I, et al. A mini-review of non-parenteral clonidine preparations for paediatric sedation. *J Pharm Pharmacol*. 2017;69(4):398-405. doi:10.1111/jphp.12662.
19. Faria-Silva R, de Rezende DC, Ribeiro JM, et al. Association of clonidine and ropivacaine in brachial plexus block for shoulder arthroscopy. *Braz J Anesthesiol*. 2016;66(4):335-340. doi:10.1016/j.bjane.2013.06.022.
20. El-Boghdadly K, Brull R, Sehmbi H, et al. Perineural dexmedetomidine is more effective than clonidine when added to local anesthetic for supraclavicular brachial plexus block: a systematic review and meta-analysis. *Anesth Analg*. 2017;124(6):2008-2020. doi:10.1213/ANE.0000000000002014.
21. Khairnar P, Agarwal M, Verma UC, et al. Comparative efficacy of ropivacaine and levobupivacaine in combined femoral and lateral femoral cutaneous nerve block with adjuvant magnesium for postoperative analgesia. *Indian J Anaesth*. 2016;60(8):584-589. doi:10.4103/0019-5049.187794.
22. Mert T, Gunes Y, Guven M, et al. Effects of calcium and magnesium on peripheral nerve conduction. *Pol J Pharmacol*. 2003;55(1):25-30.
23. Do SH. Magnesium: a versatile drug for anesthesiologists. *Korean J Anesthesiol*. 2013;65(1):4-8. doi:10.4097/kjae.2013.65.1.4.
24. Fairley JL, Zhang L, Glassford NJ, et al. Magnesium status and magnesium therapy in cardiac surgery: a systematic review and meta-analysis focusing on arrhythmia prevention. *J Crit Care*. 2017;42:69-77. doi:10.1016/j.jcrc.2017.05.038.
25. Ekmekci P, Bengisun ZK, Akan B, et al. The effect of magnesium added to levobupivacaine for femoral nerve block on postoperative analgesia in patients undergoing ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(5):1119-24. doi:10.1007/s00167-012-2093-4.

26. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). *J Clin Oncol*. 2014;32(10):997-1005. doi:10.1200/JCO.2013.52.0536.
27. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet*. 2005;44(7):661-680. doi:10.2165/00003088-200544070-00001.
28. Schnabel A, Reichl SU, Zahn PK, et al. Efficacy and safety of buprenorphine in peripheral nerve blocks: a meta-analysis of randomised controlled trials. *Eur J Anaesthesiol*. 2017;34(9):576-586. doi:10.1097/EJA.0000000000000628.
29. Candido KD, Hennes J, Gonzalez S, et al. Buprenorphine enhances and prolongs the postoperative analgesic effect of bupivacaine in patients receiving infragluteal sciatic nerve block. *Anesthesiology*. 2010;113(6):1419-1426. doi:10.1097/ALN.0b013e3181f90ce8.
30. Chung JH, Sinatra RS, Severino FB, et al. Subarachnoid meperidine-morphine combination. An effective perioperative analgesic adjunct for cesarean delivery. *Reg Anesth*. 1997;22(2):119-124. doi:10.1016/s1098-7339(06)80029-5.
31. Zhang P, Liu S, Zhu J, et al. Dexamethasone and dexmedetomidine as adjuvants to local anesthetic mixture in intercostal nerve block for thoracoscopic pneumonectomy: a prospective randomized study [published online ahead of print August 8, 2019]. *Reg Anesth Pain Med*. doi:10.1136/rapm-2018-100221.
32. Turner JD, Dobson SW, Henshaw DS, et al. Single-injection adductor canal block with multiple adjuvants provides equivalent analgesia when compared with continuous adductor canal blockade for primary total knee arthroplasty: a double-blinded, randomized, controlled, equivalency trial. *J Arthroplasty*. 2018;33(10):3160-3166.e1. doi:10.1016/j.arth.2018.05.026.
33. Williams BA, Hough KA, Tsui BY, et al. Neurotoxicity of adjuvants used in perineural anesthesia and analgesia in comparison with ropivacaine. *Reg Anesth Pain Med*. 2011;36(3):225-230. doi:10.1097/AAP.0b013e3182176f70.
34. Williams BA, Butt MT, Zeller JR, et al. Multimodal perineural analgesia with combined bupivacaine-clonidine-buprenorphine-dexamethasone: safe in vivo and chemically compatible in solution. *Pain Med*. 2015;16(1):186-198. doi:10.1111/pme.12592.
35. Knight JB, Schott NJ, Kentor ML, et al. Neurotoxicity of common peripheral nerve block adjuvants. *Curr Opin Anaesthesiol*. 2015;28(5):598-604. doi:10.1097/ACO.0000000000000222.
36. Singh S, Bansal P, Dureja J. Off-label use of drugs in regional anesthesia: a need for setting up policies. *J Anaesthesiol Clin Pharmacol*. 2017;33(4):448-449. doi:10.4103/joacp.JOACP_341_15.

ICYMI: IN CASE YOU MISSED IT

Notes from recent studies related to pain management, compiled by Elizabeth A.M. Frost, MD, co-editor of *Topics in Pain Management*

Preoperative Analgesic Regimens Did Not Improve Recovery After Spine Surgery

Recently, several multimodal approaches to pain relief have been suggested to decrease opioid use and improve recovery after surgery.

In a study by Mahwari et al, the authors evaluated the effect of using a combination of 4 nonopioid analgesics, versus placebo, on the quality of recovery, postoperative opioid consumption, and pain scores. The study participants were adults undergoing multilevel spine surgery, a procedure associated with severe postoperative pain.

In a double-blind randomized trial, patients were assigned to placebo therapy or to a multimodal regimen that consisted of:

1. A single preoperative oral dose of acetaminophen 1000 mg;
2. A single preoperative dose of gabapentin 600 mg;
3. An infusion of ketamine 5 µg/kg/min throughout surgery; and
4. An infusion of lidocaine 1.5 mg/kg/h intraoperatively and during the initial hour of recovery.

Placebo management was determined by the routine use of the practitioner. Postoperative analgesia included acetaminophen, gabapentin, and opioids. The primary outcome, quality of recovery, was assessed by a 15-item questionnaire (0–150 points, with 15% considered to be a clinically important difference) on the third postoperative day.

Secondary outcomes were opioid use in morphine equivalents (with 20% considered to be a clinically important change) and verbal-response pain scores (0–10, with a 1-point change considered important) over the initial 48 postoperative hours.

As no differences could be found, the trial was stopped early. The average duration ± SD of surgery was 5.4 ± 2.1 hours. The mean ± SD quality of recovery score was 109 ± 25 in the pathway patients (n = 150) versus 109 ± 23 in the placebo group (n = 149).

There was no estimated difference in means ($P = 0.920$).

Pain management within the initial 48 postoperative hours was not superior in the multimodal analgesic group. The opioid consumption median at 48 hours was 72 mg in the study group and 75 mg in the placebo group. Mean 48-hour pain scores were 4.8 ± 1.8 in the analgesic pathway group versus 5.2 ± 1.9 in the placebo group ($P = 0.094$).

The researchers concluded that a multimodal, perioperative analgesic pathway, as was used, did not improve recovery in patients who had multilevel spine surgery. (*See* Mahwari K, Avitsian R, Sessler D, et al. Multimodal analgesic regimen for spine surgery: a randomized placebo-controlled trial. *Anesthesiology*. 2020;132:992-1002. doi:10.1097/ALN.0000000000003143.)