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CONTINUING EDUCATION ACTIVITY

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

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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

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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.

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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]

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.

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]

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]

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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. ■

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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.)

Smaller Package Size Reduces the Quantity of Opioids Administered

In considering the question whether and how the unit dose of a drug might relate to opioid administration, Ershoff et al devised a study to use alternating sizes of hydromorphone vials. They hypothesized that the unit dose of hydromorphone is an independent determinant of the quantity of hydromorphone administered to patients intraoperatively.

This observational cohort study included 15,010 patients who received intraoperative hydromorphone as part of an anesthetic.

From March 2016 to July 2017, hydromorphone was available as a 2-mg unit dose.

From July 1, 2017, to November 20, 2017, hydromorphone was only available in a 1-mg unit dose. Thereafter, hydromorphone was reintroduced in the 2-mg unit dose.

An interrupted time series analysis was performed using segmented Poisson regression with 2 change points, the first representing the switch from a 2-mg to 1-mg unit dose, and the second representing the reintroduction of the 2-mg dose.

The authors determined that the 2-mg to 1-mg unit dose change was associated with a 49% relative decrease in the probability of receiving a hydromorphone dose greater than 1 mg ($P < 0.0001$). The reintroduction of a 2-mg unit dose was associated with a 48% relative increase in the probability of administering a dose greater than 1 mg ($P = 0.008$).

The conclusion drawn was that, using an interrupted time series analysis, unit dose of hydromorphone (2 mg vs 1 mg) is an independent determinant of the quantity of hydromorphone administered to patients intraoperatively. (*See* Ershoff BD, Grogan T, Hin JC, et al. Hydromorphone unit dose affects intraoperative dosing: an observational study. *Anesthesiology*. 2020;132(5):981-991. doi:10.1097/ALN.0000000000003176.)

Adding a Tolerability Question to the Numeric Rating Scale Improves the Accuracy of Pain Assessment

Limiting pain assessment only to the numeric rating scale (NRS) reduces the expression of chronic pain to a single dimension, thus minimizing the complex effects of chronic pain on quality of life and other factors involved in analgesic decision-making.

Asking patients simply to rate their pain on a scale anchored by a pain-free state (ie, 0 on a scale of 0–10 points) suggests that a pain-free state is a readily attainable treatment goal, thus perhaps contributing to unrealistic expectations.

In this study, the authors hypothesized that the incorporation of a standardized pain tolerability question (PTQ) (ie, "Is your pain tolerable?") would augment the information gleaned from the NRS.

> Asking patients to rate their pain on a 0–10 scale suggests that pain-free is an attainable treatment goal, which may contribute to unrealistic expectations.

Between December 2016 and March 2017, 537 participants were recruited (after exclusions) electronically, after a primary care encounter at 1 of 157 participating primary practices. Median age was 62 years, and 38% were male. Patients had an active prescription for an analgesic medication or an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* visit diagnosis associated with chronic pain.

More than 50% of patients had musculoskeletal disease and more than 1 pain site (eg, osteoarthritis or soft-tissue disorder).

Patients were asked, "Is your pain tolerable?" (Answer choices were "yes," "no," or "not in pain.") and asked to rate average pain intensity (on a scale of 0–10 points) during the previous 24 hours. Responses to the PTQ were compared with responses on the NRS scale using logistic regression.

A pain rating of "intolerable" was associated with the higher NRS ($P=0.01$). In the moderate range of the NRS (ie, 4–6), 40 of 211 patients (19.0%) characterized their pain as intolerable, whereas in the severe range of the NRS (ie, 7–10), 72 of 137 patients (52.6%) considered it intolerable.

The researchers conclude that the findings confirmed the intuitive assumption that most patients with low pain intensity (ie, NRS score 1–3) find their pain tolerable. However, the tolerability of pain rated between 4 and 6 varies substantially among patients, such that if a patient describes pain as tolerable, the clinician's inclination to initiate higher-risk treatments might decrease.

Also, a subgroup of patients with severe pain reported their symptoms as tolerable. This discordance between tolerability and pain intensity may be an opening for a clinician to explore mood, sleep disruption, or the curtailing of activities to control pain. Patient satisfaction regarding communication, treatment goal setting, and treatment effects could perhaps be improved. (*See* Markman JD, Gewandter JS, Frazer ME. Comparison of a pain tolerability question with the numeric rating scale for assessment of self-reported chronic pain. *JAMA Netw Open*. 2020;3(4):e203155. doi:10.1001/jamanerkopen.2020.3155.)

Topics in Pain Management CE Quiz

To earn CME credit using the enclosed form, 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. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **June 30, 2022**. Only two entries will be considered for credit.

Online CME quiz instructions: Go to **http://cme.lww.com** and click on "Newsletters," then select *Topics in Pain Management*. Enter your ***username*** and ***password.*** First-time users must register. After log-in, follow the instructions on the quiz site. You may print your official certificate ***immediately.*** **Please note:** Lippincott CME Institute, Inc., ***will not*** mail certificates to online participants. **Online quizzes expire on the due date.**

To earn CNE credit, you must take the quiz online. Go to **www.nursingcenter.com**, click on CE Connection on the toolbar at the top, select Browse Newsletters, and select *Topics in Pain Management.*

Log-in (upper right hand corner) to enter your ***username*** and ***password.*** First-time users must register. As a subscriber benefit, nurses can earn contact hours when taking CE activities from *Topics in Pain Management* for free. You must enter your subscription number preceeded by LWW, in your registration profile where there is a field for **Link to my subscription**. The 100% discount is applied when payment is requested. Non-subscribers pay a $49.00 fee to earn ANCC contact hours for this activity.

After log-in, locate and click on the CE activity in which you are interested. There is only one correct answer for each question. A passing score for this test is 7 correct answers. If you fail, you have the option of taking the test again. When you pass, you can print your certificate of earned contact hours and access the answer key. For questions, contact Lippincott Professional Development: 1-800-787-8985. The registration deadline for CNE credit is **June 3, 2022.**

1. **All of the following are potential drawbacks of a continuous nerve catheter, *except***
   A. increase in total opioid consumption
   B. requires closer follow-up
   C. need for patient compliance and education
   D. risk of infection
   E. secondary failure
2. **Which of the following is/are a potential route of administration for dexmedetomidine?**
   A. Intravenously
   B. Orally
   C. Perineurally
   D. All of the above
3. **Studies of perineural dexmedetomidine for peripheral nerve block have demonstrated all of the following *except***
   A. prolongation of sensory block duration
   B. longer duration of postoperative analgesia
   C. increase in motor block duration
   D. significant increase in hemodynamic changes
4. **Which one of the following statements regarding IV versus perineural dexamethasone as an adjunct to local anesthetics is *true*?**
   A. Perineural dexamethasone provides superior increase in block duration.
   B. IV and perineural dexamethasone may confer similar benefits as local anesthetic adjuncts.
   C. Perineural dexamethasone provides no clinical benefit.
   D. IV dexamethasone provides significantly longer duration of analgesia.
5. **Which one of the following statements regarding clonidine versus dexmedetomidine is *true*?**
   A. They act on different receptors.
   B. Dexmedetomidine is more selective for alpha-2 receptors than clonidine.
   C. Dexmedetomidine is less expensive than clonidine.
   D. Dexmedetomidine is an older drug than clonidine.
6. **Benefits of perineural dexmedetomidine as an adjunct to local anesthetics include all of the following *except***
   A. increase in sensory block duration
   B. increase in postoperative analgesia duration
   C. cheaper medication that lowers overall cost
   D. increase in motor block duration
7. **All of the following are potential clinical uses for buprenorphine *except***
   A. treatment of chronic pain
   B. treatment of opioid addiction
   C. adjunct to local anesthetics
   D. PONV prophylaxis
8. **Magnesium is thought to exert its analgesic effects via all of the following mechanisms *except***
   A. NMDA receptor antagonism
   B. regulation of calcium influx into neurons
   C. μ-opioid receptor antagonism
   D. modulation of neuronal pathways
9. **Which one of the following is a likely side effect of perineural buprenorphine?**
   A. PONV
   B. Bradycardia
   C. Fever
   D. Increase in blood pressure
10. **In animal studies, which one of the following has demonstrated potential neuroprotective effects?**
    A. Magnesium
    B. Dexmedetomidine
    C. Dexamethasone
    D. Buprenorphine

PAIN MANAGEMENT AMID THE COVID-19 PANDEMIC

IASP Webinars, Congress

The International Association for the Study of Pain (IASP) is offering a free webinar series as part of its 2020 Global Year for the Prevention of Pain. Webinars include physiotherapy to treat pain, nutrition for people experiencing chronic pain, prevention of orofacial pain, and pain prevention after musculoskeletal trauma. Topics will be added over the course of the year. Find out how to register at iasp.org.

IASP has rescheduled the World Congress on Pain in Amsterdam to take place June 27–July 1, 2021. The scientific program created initially for August 2020 will remain as intact as possible for the June 2021 Congress, according to an announcement by IASP. All planned plenaries, lecture-style sessions, hands-on workshops, and more than 2,500 poster presentations (plus late breaking abstracts) will be rescheduled. The IASP is also planning a series of virtual meetings this fall with workshops, posters, and symposia.

The early registration deadline for the 2021 Congress will be February 10, 2021.

WHO Addresses NSAID Risk of Complications With COVID-19

As of early May, there were conflicting reports about NSAIDs might increase the risk of complications in patients with COVID-19. On April 19, 2020, the World Health Organization (WHO) released a scientific brief on the matter after reviewing several studies.

The scientific brief concluded that, "At present there is no evidence of severe adverse events, acute health care utilization, long-term survival, or quality of life in patients with COVID-19, as a result of the use of NSAIDs."

However, the review cited some clear limitations, in particular that the evidence is indirect, based on data about NSAIDs and outcomes in other respiratory conditions.

"No direct evidence from patients with COVID-19, SARS, or MERS was available," the authors wrote. "Therefore, all evidence…should be considered indirect evidence with respect to the use of NSAIDs [in] management of COVID-19."

Only one randomized controlled trial included enough participants to identify rare severe adverse events. Further, the brief stated that it is likely that not all participants in the studies had viral respiratory infections, that not all studies distinguished among various types of NSAIDs, and that some of the older studies likely included patients taking NSAIDs that are no longer available because of adverse effects.

The "rapid systematic review" was carried out in March 2020 using data in MEDLINE, EMBASE, and WHO Global Database. The review included studies conducted in humans of any age with viral respiratory infections exposed to systemic NSAIDs of any kind. The review included all studies, regardless of size, on COVID-19, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS).

The review included a total of 73 studies (28 in adults, 46 in children, and 1 in both adults and children). All studies were concerned with acute viral respiratory infections or conditions commonly caused by respiratory viruses, but none specifically addressed COVID-19, SARS, or MERS. The review showed very low-certainty evidence on mortality among adults and children.

The review could not make clear conclusions about the effects of NSAIDs on the risk for ischemic and hemorrhagic stroke and myocardial infarction in adults with acute respiratory infections. (*See* The use of non-steroidal anti-inflammatory drugs [NSAIDs] in patients with COVID-19. https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19.)

To Our Readers

Please let us know how you are managing your pain patients amid the COVID-19 pandemic.

How are you using telemedicine—even if it's unofficial through Skype, Zoom, or FaceTime?

What kinds of cases have been worth the risk of exposure for you and your patient?

How are you disinfecting your office environment and equipment differently?

How are your patients coping?

Might any of this change pain care in the future?

Please email the associate editor, Anne Haddad, at **Anne.Haddad1@gmail.com**, and include your city and state.

Coming Soon:

- Cold Laser Therapy for Acute and Chronic Pain Management
- Pain Management After Cesarean Delivery
- Systematic Review of Ketamine Use for Pain Management