revistachilenadeanestesia.cl

DOI: 10.25237/revchilanestv5209121057

Blocks and adjuvants: Lost in research methodology

Coadyuvantes en bloqueos ¿Extraviados en su metodología de investigación?

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Introduction

Peripheral nerve blocks (PNB) have become an excellent tool to improve perioperative analgesia in a broad set of surgical procedures. Nowadays, PNBs are officially recommended in several guidelines for specific procedures and enhanced postsurgical recovery[1],[2]. However, depending on pharmacokinetic and pharmacodynamic factors, single-shot PNBs might not cover long periods of moderate to severe postsurgical pain. Additionally, single-shot blocks have been related to a higher incidence of rebound pain after blocks wore off. Thus, when postsurgical pain is expected to be moderate to severe and lasting longer than 12-24 h, continuous peripheral nerve blocks (CPNB) would represent the gold standard, along with a strict multimodal analgesic regimen.

When looking for optimal results, CPNBs require expert operators, specialized acute pain services, ambulatory follow-up protocols, more expensive implements, and longer procedural times. Alternatively, different drugs have been used to prolong and improve the analgesic effect of long-acting local anesthetics (LA). Currently, two are the most studied drugs looking for an optimal long-lasting single-shot nerve block. In this issue of Revista Chilena de Anestesia, two trials analyzed the effect of adjuvants in perioperative nerve blocks with interesting results[3],[4]. For a better interpretation, this editorial summarizes the evidence of these adjuncts and describes what we deem as relevant research questions that need to be answered and what we think are the lines that research should follow on this topic. Similar to other technical studies with nerve blocks, a thorough methodological design is necessary to obtain clinically valid results.

Summarizing the evidence

In general, adjuvants have been used in peripheral nerve blocks to accelerate onset, decrease plasmatic absorption and secondary toxic effects, and prolong the block effects. Block onset is mainly relevant for preoperative surgical blocks. In that direction, implementing a block room represents a better long-term measure to increase efficiency. Since systemic toxicity secondary to local anesthetics continues to be a problem nowadays, following existing valid recommendations is highly necessary[5]. Specifically, the addition of epinephrine to anesthetic solutions is recommended when elevated LA doses are used, sites with high vascular absorption are targeted, and for patients belonging to special susceptible populations. Epinephrine has proven to decrease the peak plasmatic LA level after injection[5].

Since CPNBs are not always available or are not the best option for every surgery or patient, the study of block nerve adjuvants has been focused on block quality and duration of analgesia. As mentioned above, dexamethasone and dexmedetomidine have been the most studied. Lately, LAs in long-releasing formulations based on liposomes have appeared but have not proven superiority over standard long-acting LAs formulations in PNBs[6]. Finally, biological adjuvants derived from shellfish toxins have also appeared in the literature but have not defined a safety/efficacy profile[7].

A relevant issue that must always be considered is that block duration depends on factors like the site of injection and technical aspects that determines the precision of injections. Thus, an imprecise injection in a vascularized region might produce a shorter block or a failed one.

A metanalysis (MA) in 2017 determined the average duration of upper extremity nerve blocks with intermediate and long-acting pure LAs. Blocks with intermediate-acting LAs like lidocaine would last an average of 168 min (2.8 h) and 730 min (12.2 h) with long-acting LAs like bupivacaine. The same MA determined that dexamethasone doubled the intermediate-acting effect from 168 to 343 minutes and prolonged almost 10 h long-acting LAs from 730 to 1,306 minutes. At that time, it was impossible to find a difference between intravenous (IV) or perineural (PN) administration routes[8]. After that, another MA incorporating new trials comparing IV and PN dexamethasone found an average analgesia difference of 3.8 h in favor of the PN route. However, when separating upper and lower extremity blocks, this difference was 2.8 h and 7.9 h, respectively. This MA also found a more extended motor block and decreased opioid consumption with the PN adjuvants. Additionally, no differences were found in terms of complications, but since this outcome is infrequent, the study cannot be conclusive on this matter[9]. The following MAs have reported similar results

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in favor of the PN route[10],[11],[12], although some others have not confirmed them[13],[14]. In a direct experience participating in two multicentric trials comparing IV and PN routes summing 300 patients[15],[16] using upper extremity blocks that permit to determine the three components of a block with relative consistency, we found 3.5 to 5 h, 2.8 to 4.7 h and 2.9 to 4 h, longer analgesic, motor and sensitive block duration with PN dexamethasone, respectively. Assuming that most MAs obtained valid results, PN dexamethasone would be superior to its IV counterpart, but the clinical advantages of this extra block period need to be balanced case by case.

The dose of PN dexamethasone would reach a ceiling effect when closing the 4 mg[17]. In a large multicentric trial comparing frequently used doses, there was no difference in motor block between 2, 5, and 8 mg. However, analgesic duration was better with 5 and 8 mg[18].

Perineural Dexmedetomidine has been proven to prolong sensory block, motor block, and analgesia by at least 57%, 58%, and 63%, respectively[19]. Dexmedetomidine also expedited the block onset by 40% and decreased postoperative opioid consumption[19]. All these positive findings were associated with increased odds of bradycardia, hypotension, and sedation[19]. The dose that balances better benefits and side effects would be 50-60 micrograms[19]. Similarly to dexamethasone, the PN route for Dexmedetomidine has been associated with a longer sensory block (1.9 to 7.8 h), motor block (1.6 to 8 h), and analgesia (4.9-8.7 h) when compared to the IV alternative. Additionally, PN dexmedetomidine showed a faster onset and a lower hypotension risk[20].

When comparing both perineural adjuvants, our research team proved that dexamethasone was significantly superior in the duration of sensory block (19 *vs* 15 h), motor block (17 *vs* 14 h), and analgesia (22 *vs* 17 h). Dexmedetomidine accelerated the block onset by 2 minutes with a higher incidence of persistent postoperative sedation, lower blood pressure and lower heart rate. The dexmedetomidine dose in this trial was 100 micrograms. Dexamethasone was not associated with postoperative hyperglycemia up to 6 hrs after surgery[21]. This superiority of dexamethasone was theorized previously by an indirect MA in 2019[22] and confirmed by a subsequent MA[23].

Some studies have analyzed the multimodal concept applied to perineural blocks. In 2019 Zhang et al., combined dexamethasone and dexmedetomidine with LAs in intercostal blocks for patients undergoing thoracoscopic surgeries. The multimodal block offered more prolonged analgesia and decreased postoperative fentanyl consumption when compared to LA alone or LA combined with any of the adjuvants alone[24]. In a more reliable model for analyzing block characteristics, our group compared dexamethasone to the combination of dexamethasone with dexmedetomidine in infraclavicular blocks for distal upper extremity surgery. Again, the multimodal group showed longer sensory block, motor block, and analgesia by 4.2, 4.5, and 2 h, respectively, without significant differences in onset times, hemodynamic changes, or persistent postoperative sedation. In this trial, we decreased dexmedetomidine to 50 micrograms[25].

Adjuvants would also decrease the incidence of rebound pain after single-shot PNBs. Rebound pain has been defined as a dramatic increase in pain once the PNB has dissipated. This entity has been described in up to a 50% of ambulatory surgery. A retrospective cohort investigated the factors associated with rebound pain. It showed an independent association with age, female gender, bone surgery, and absence of intraoperative IV dexamethasone[26]. Two RCTs in arthroscopic shoulder surgeries showed a decreased incidence of rebound pain with PN dexamethasone[27],[28]. The most recent trial showed that dexamethasone decreases a 50% the incidence of rebound pain and 35% the pain intensity after shoulder surgery[28]. In surgery for upper extremity fractures, another trial found that the incidence of rebound pain decreased from 48% to 11%. Dexamethasone also decreased opioid consumption and improved analgesia satisfaction and sleep quality[29]. Definitively, further research is granted in this area to develop better strategies to avoid rebound pain. Future studies need to confirm current findings and also investigate the role of other possible adjuvants and their ideal doses.

Unanswered questions

In order to make better decisions regarding the use of adjuvants for PNBs, some aspects need to be studied in the future.

Several hypotheses have been theorized explaining the mechanisms behind adjuvants in PNBs. Dexamethasone and dexmedetomidine have proven systemic analgesic effects that do not explain the longer duration of motor blockade. From a simplistic perspective, it may just mean that they influence the persistence of the LA blocking of voltage-dependent sodium channels. Steroids and alfa-1 agonists have a well-known vasoconstrictive effect that may determine a decreased clearance of LA after injections. An ongoing trial approaching this hypothesis may help increase our understanding of this aspect (ClinicalTrials.gov NCT05359731). Recently, in a mice model of postoperative pain with sciatic nerve blocks, Matsuda et al. showed that neuronal nitric oxide synthase suppression would be involved in the prolonged analgesic effect after the addition of dexamethasone[30]. A more classic hypothesis is that due to the stimulation of glucocorticoid receptors located on the neuronal membrane, the expression of inhibitory potassium channels increases, and consequently, the unmyelinated C fiber's excitability decreases.

Regarding dexmedetomidine, since it has less alpha-1 effect than clonidine, a vasoconstrictor mechanism is neither hypothesized nor studied. In addition, since the axons do not have alpha-2 receptors, the mechanism would not be related to this receptor. Thus, similarly to clonidine, a direct effect in activated nucleotide-gated channels. Hence dexmedetomidine maintains the A-delta and C neurons in a hyperpolarized state, thereby inhibiting the generation of action potentials[31],[32].

Effective doses for dexamethasone are more or less clear. With dexmedetomidine, what is more certain is where is the balance between side and expected effects. Ideal doses for multimodal perineural approaches have yet to be defined.

Theorizing that the effect of perineural adjuvants depends on their presence in nerve proximity, deposit adjuncts may represent an alternative to obtain longer block effects. A recent retrospective study compared dexamethasone and dexamethasone plus methylprednisolone depot formulation. The selected model was adductor canal blocks and interspace between the popliteal artery and capsule of the posterior knee blocks in total knee arthroplasty. Cumulative opioid consumption and

the highest rest and active pain scores were significantly lower in the methylprednisolone group. The latest evidence in depot LAs formulations (liposomal bupivacaine) has shown no clinical benefit of using them in PNBs[33]. Further research is needed to balance the benefits and disadvantages of this strategy. For instance, the use of depot anesthetics with current adjuncts has not been investigated.

Although the evidence studying intravenous and perineural adjuncts is extensive, trials investigating combined IV and PN routes for the same adjunct are at least scarce and, in our opinion, have used imprecise research models. A trial compared 8mg of IV dexamethasone with and without a 4 mg perineural dose in intercostal blocks with 0.5% bupivacaine. Lower postoperative pain intensity and opioid consumption were found in the dual-route group. Regretfully, the article did not specify the block component's duration, being impossible to rule out systemic steroid effects[34].

Beyond available hypotheses and comparisons, a valid question would be how many more ingredients could be added to a perineural mix to improve LA effects without increasing risks. A prospective study tested the hypothesis that combined buprenorphine, clonidine and dexamethasone extend perineural analgesia compared with no adjuncts in plain bupivacaine nerve blocks used for hip and knee replacement surgery. The time until the start of postoperative pain, no pain relief from blocks, the numbness wore off, and the worst postoperative pain were 26 *vs* 11 h, 32 *vs* 15 h, 37 *vs* 21 h and 39 *vs* 20 h, respectively. Regretfully, some aspects of this study model prevent a complete interpretation of the results[35]. For instance, mixed surgeries and surgical territories not entirely covered by the studied blocks make it impossible to correlate analgesia duration to block effectiveness. Furthermore, comparing several adjuncts against nothing does not permit distinguishing the individual contribution of each drug. At least a previous study had proven the compatibility of the mix and its in vivo safety[36],[37].

In terms of safety profile, mainly in terms of nerve toxicity or injury, it has been described that a proper study needs to recruit more than 16,000 subjects to prove a double risk ratio when considering the low rate of these complications[32]. At least from studies of dexamethasone and dexmedetomidine that have reported neurologic deficit incidence, no special risk can be suspected. Some in-vitro and in-vivo, in-animal studies have increased the certainty level of safety with perineural steroids[38],[39],[40]. However, the published research with Dexmedetomidine is less conclusive, with some studies favoring its safety[41],[42],[43] and some questioning it[44].

A more interesting issue to consider is that the evidence that supports catheters over single-shot PNBs is based on studies comparing continuous blocks to single-shot blocks without adjuncts. Regretfully, consistent research comparing both CPNBs with multimodal PNBs is still scarce[45]. Although continuous techniques are advocated for several painful procedures, more recent evidence-based guidelines do not necessarily support them when the main objective of the perioperative process is enhanced recovery[1],[2]. In our opinion, it is unnecessary to keep looking for the perfect multimodal single-shot PNB to start designing proper research on this topic. Hopefully, trials investigating this matter are appearing soon in the literature. Finally, one could also wonder if catheters and adjuncts are mutually exclusive since there is no fundamental limitation to taking advantage of both, especially in specific settings.

How to plan research properly

From our perspective as researchers, as proposed but not restricted to the above-mentioned ideas, several hypotheses deserve to be investigated in future trials. However, there are two clinical lines of research.

The first one tries to define the effect of an adjunct on nerve block characteristics. In this aspect, we strongly agree that the research model must be as objective as possible in determining changes in the onset and duration of sensory block, motor block, and analgesia. Then, the selected block must have a high success rate since block duration can only be evaluated in those blocks. This fact determines that the block's success requires being objective and easy to assess. Thus, the blocks used for these studies must be unique to the entire surgical area. These requirements can be found in hand and forefoot surgeries, where brachial plexus and sciatic nerve blocks will adequately cover the surgical region and will permit to determine the sensory blockade, analgesia, and probably the most objective component, the motor blockade. Sadly, several trials investigating the possible role of adjuncts fail to select an adequate block model. For instance, truncal blocks represent a challenging model for this line of research. In the trunk, PNBs hardly block all possible pain origins. Then, for instance, a short analgesia duration might not be related to a block wearing off. Furthermore, sensory block assessment for truncal PNB can be challenging as well as a motor blockade. Similarly, readers can make their own assumptions about blocks that do not cover the whole surgical region, like in shoulder, hip, or knee surgeries.

The second strategy for determining the clinical effects of adjuncts might be to test the characteristics proven in first-line studies on a broader set of surgeries and blocks. The main outcome of these studies may turn out to be different and even more ambitious. For instance, pain, rebound pain, opioid consumption, satisfaction, and rehabilitation.

Conclusion

Adjunct's effect still is an ongoing matter of research. We hope that after this editorial, interested readers may improve their analytic skills and criticism when reading trials on this topic.

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