

# From Preemptive to Preventive Analgesia

## *Time to Reconsider the Role of Perioperative Peripheral Nerve Blocks?*

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When I have read the article from Carvalho et al<sup>1</sup> published in this issue of *Regional Anesthesia and Pain Medicine*, two words caught my eyes, “preemptive” and “nerve block.” Why? First, because in the light of our current knowledge about incisional pain mechanisms, the term *preemptive* is definitely obsolete. Second, because when we consider the terms *preemptive analgesia* and *preventive analgesia* in the literature, perineural techniques that have become increasingly popular, for example, plexus and peripheral nerve blocks, have received very little attention in comparison to neuraxial blocks and systemic treatments.

*Preemptive analgesia* has been defined as an antinociceptive intervention that starts before surgical incision and is more effective in relieving acute postoperative pain than the same treatment starting after surgery.<sup>2</sup> The rationale for preemptive analgesia was based on the block of central sensitization before it occurs. Effectively, nociceptive signals initiated by tissue injury induce a state of central nervous system hyperactivity, also called central sensitization, which facilitates pain (ie, amplification and memorization). However, studies in animal model of incisional pain have clearly shown that single analgesic treatment (either peripheral or neuraxial) before the incision does not reduce postoperative pain behaviors beyond the expected duration of the analgesic effect.<sup>3</sup> When the block of nociceptive afferents abates, the wound is able to reinitiate central sensitization. Clinical trials have found similar results.<sup>4</sup>

Therefore, not the timing but both the duration and the efficacy of a perioperative analgesic intervention are important in treating postoperative pain and in preventing central sensitization. It is worth noting that when central sensitization has fully developed, it can become less dependent and even independent of peripheral nociceptive inputs. Treatments that attempt to reduce central neuronal hyperactivity should not be called preemptive analgesia, irrespective of the time the treatment is administered.<sup>3</sup>

*Preventive analgesia* is aimed to block the development of sustained pain. This broader definition includes any regimen given at any time during the perioperative period that will be able to control pain-induced sensitization.<sup>2</sup> Central neuronal sensitization participates to the postoperative pain experience and might be one of the mechanisms underlying the development of persistent pain after tissue trauma.<sup>5</sup> However, to date, the exact role of central sensitization in the magnitude and the duration of acute postoperative pain remains undetermined. Interestingly, drugs like systemic ketamine or spinal clonidine, which are able to modulate central sensitization and to affect the incidence of persistent postsurgical pain do not reduce acute postoperative pain.<sup>6</sup>

Continuous peripheral nerve blocks allow an effective control of postoperative pain, specifically pain associated to mobilization, which is the most difficult to alleviate, as well as reduce opioid-related adverse effects.<sup>7</sup> Their success relies not only on the quite recent use of ultrasounds to perform the blocks<sup>8</sup> but also on the safety of these techniques.<sup>9</sup> As a consequence, perineural analgesia is currently favored over epidural techniques for limbs surgery and is now evaluated as an alternative to epidural blocks for thoracic procedures. Nevertheless, despite their clinical success, the real benefit of peripheral nerve blocks in preventive analgesia remains poorly determined.

Because peripheral mechanisms strongly contribute to hypersensitivity and central sensitization after incision, an intense peripheral nerve block should prevent nociceptive inputs to reach the central nervous system and therefore should reduce the development of central sensitization and decrease the risk for persistent postsurgical pain.

Unfortunately, there seems to be no further benefit of extending an overnight continuous peripheral nerve block to 48 hrs and even to 4 days after knee or hip arthroplasty on the improvement of health-related quality of life including pain between 6 weeks and 12 months after surgery.<sup>10,11</sup>

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These observations contrast with the positive effect found after a 24-hr systemic ketamine infusion, which improved postoperative outcome up to 6 months after total hip arthroplasty.<sup>12</sup> The lack of preventive effect of perineural infusions in orthopedic surgery also contrasts with the long-lasting preventive effect at 12 months associated with paravertebral block during breast surgery.<sup>13</sup> The aforementioned observations question the various mechanisms underlying central sensitization after incision, a fortiori our utilization of perineural blocks for preventive analgesia in the perioperative context.

Continuous peripheral nerve block inhibits clinical inflammation (ie, joint edema and hyperthermia), although it does not affect the local release of inflammatory mediators at the surgical site. The clinical anti-inflammatory effect is probably partly due to improved function and greater mobility under analgesia, and a persistent effect on joint function can occur up to 6 weeks after discontinuation of the block.<sup>14</sup> The severity of postoperative pain is a major factor for the development of chronic postsurgical pain in various surgical procedures,<sup>15</sup> although both the duration and the intensity differ among the various surgical procedures. By example, after knee arthroplasty, the presence of moderate to severe pain during the first week increases by 10-fold the risk for persistent pain.<sup>16</sup> Moreover, as recently highlighted after common orthopedic procedures, moderate subacute pain, that is, until 1 month after surgery, may concern 52% of patients and severe subacute pain 16% of patients.<sup>17</sup> The duration of central nervous system sensitization may extend to a long period in orthopedic surgery, far beyond the duration of any sustained perioperative nerve block.

Preoperative pain also influences perioperative pain as a risk factor for the patient to present higher immediate postoperative pain and to develop persistent pain after surgery.<sup>15</sup> Pain existing before surgery may have already achieved central sensitization and may interfere with the efficacy of perioperative preventive analgesic treatments.<sup>18</sup> Most patients who undergo limb surgery have endured long-lasting preoperative pain, often associated to an important inflammatory reaction, even to a neuropathic component. In patients with osteoarthritis, continuous intense nociceptive inputs from the damaged joints drive central sensitization, which spreads to adjacent spinal segments.<sup>19</sup> Central sensitization results from an imbalance between the inhibitory and the excitatory endogenous pain systems. It is now well established that long-lasting pain may alter these endogenous pain modulatory systems, enhancing excitatory pathways and reducing inhibitory ones.<sup>20,21</sup> Long-term intake of opioid analgesics is also susceptible in reducing the activity of the inhibitory pathways. In this context, the use of peripheral nerve block will only induce a segmental analgesia, whereas a heterosegmental analgesia would be mandatory as well as the use of adjuvant drugs to either reinforce altered inhibitory pathways or suppress excessive excitatory systems.<sup>21</sup> For example, for some patients, the association of a sustained perineural block with the systemic administration of an *N*-methyl-D-aspartic acid receptor antagonist such as ketamine certainly might contribute to enhance the preventive effect of the perineural block<sup>22</sup> as occurs with neuraxial analgesia.<sup>23–25</sup>

Finally, it is worth noting that perioperative peripheral nerve blocks generally consist of perineural infusion of a local anesthetic alone. The use of adjuvant such as clonidine is generally prohibited because it will increase the motor block, that is, interfere with immediate rehabilitation without improving postoperative analgesia. However, surgery performed for tissue inflammation<sup>26</sup> and surgery involving major nerve trauma<sup>27</sup> like amputation might benefit at a longer term, from the addition of clonidine to perineural infusion.

To conclude, the influence of regional analgesia on perioperative outcome, and more specifically on the long-term restoration of function and reduction of persistent postsurgical pain, is difficult to evaluate.<sup>28</sup> To date, epidural analgesia has received more interest in this context than peripheral nerve blocks, which have mostly been evaluated in terms of acute postoperative pain control and reduction of opioids consumption. Going along with the renewed enthusiasm for these techniques, it is time to reconsider peripheral nerve blocks in a larger perioperative perspective including rehabilitation and quality of life, immune modulation and cancer recurrence, and finally persistent postsurgical pain.

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