

Preemptive Analgesia at the Crossroad

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Two approaches have been used to reveal preemptive analgesia. One of them is to demonstrate a reduction in pain intensity and/or analgesic use beyond the drug presence in the biophase. This approach is based on a study design comparing preoperative treatment and nontreatment groups (PRE versus NO). The other approach is to prove that a treatment applied before surgery is more effective than the same treatment provided at the end of surgery (PRE versus POST). The PRE versus NO approach was commonly used in the initial clinical studies on preemptive analgesia (1); the PRE versus POST approach was introduced later (2) and has become the most common study design for preemptive analgesia. Many reviews of the studies based on this approach state that the concept of preemptive analgesia is not clinically relevant (3,4). Two recent articles in *Anesthesia & Analgesia* challenge this view. McCartney et al. (5) do so by revitalizing the PRE versus NO approach; Ong et al. (6) by carefully applying meta-analysis to the PRE versus POST design.

McCartney et al. present a qualitative systematic review of 40 studies on the effects of *N*-methyl-d-aspartic acid (NMDA) receptor antagonists on postoperative pain beyond the duration of their presence in the biophase in concentrations that can provide a direct pharmacologic effect. For the purposes of the review they selected a point in time equivalent to five half-lives of the drug under examination. Decrease in pain intensity or analgesic use beyond this point was regarded as the indirect effect resulting from prevention of pain hypersensitivity. The review revealed extended analgesic benefits in 58% of studies with ketamine and 67% with dextromethorphan.

Preemptive analgesia is a treatment that prevents establishment of the altered sensory processing that amplifies postoperative pain. The treatment should cover the entire duration of high-intensity noxious stimulation that can lead to establishment of central and peripheral sensitization caused by incisional or inflammatory injuries (during surgery and the initial postoperative period). Emphasis on the PRE versus POST design has led to a situation in which establishment of sensitization during inflammatory injuries in the initial postoperative period is excluded from consideration. In 1994 I suggested substituting the term "preventive analgesia" for "preemptive analgesia" and using the term "preemptive analgesia" only for the limited effect on sensitization by the part of preventive treatment that begins before surgery and does not include the postoperative period (7). Katz (8) recently compared outcomes of studies with both approaches designed to reveal the prevention of pain hypersensitivity. He reported that the PRE versus NO design (preventive

analgesia) resulted in a positive effect more frequently than the PRE versus POST design (preemptive analgesia) and that, in general, the effects with the PRE versus NO design were of greater magnitude. These findings illustrate that more complete prevention of sensitization (caused not only by incisional but also inflammatory injuries) has greater clinical value.

The meta-analysis by Ong et al. (9) published in the current issue of *Anesthesia & Analgesia* used a methodology proposed by the Cochrane Collaboration. The authors analyzed 66 studies related to 5 groups of interventions: epidural analgesia, peripheral local anesthetic infiltrations, systemic NMDA receptor antagonists, systemic nonsteroidal antiinflammatory drugs (NSAIDs), and systemic opioids. Only studies with the PRE versus POST design were included. The analyzed outcome measures were pain intensity, supplemental analgesic consumption, and time to first analgesic. They found a pronounced preemptive effect with epidural analgesia, local infiltration, and systemic NSAID administration. Most impressive were reductions (from 44% to 58%) in supplemental analgesic consumption at very high levels of statistical significance. With opioids and NMDA receptor antagonists the results were equivocal.

Clinically significant preemptive analgesia was revealed by this meta-analysis despite several factors that can mask the preemptive effect. First, with the PRE versus POST design, the contribution of pain-induced plasticity during the initial hours of the postoperative period eludes the comparison. Nociceptive input after surgery in the PRE treatment group under certain conditions may initiate marked pain hypersensitivity (10,11); as a result, the difference between groups will be diminished.

The second factor is the difference in drug concentrations in the biophase during the initial postoperative hours. Because of the drugs' pharmacokinetics, the time difference in drug administration between the PRE and POST groups results in significantly larger concentrations in the POST group. Thus, the preemptive effect of the treatment on the postoperative component of pain-induced plasticity may be more pronounced in the POST group (also reducing the difference between outcomes of the PRE and POST groups). Only one study specifically addressed this problem in the assessment of preemptive effect. Norman et al. (12) administered systemic ketorolac immediately after tourniquet inflation above the area of ankle surgery in the POST group (and before tourniquet inflation in the PRE group) so that the PRE and POST groups had similar systemic drug concentrations. The authors demonstrated a significant preemptive effect.

An additional factor interfering with evaluation of the studies on preemptive analgesia is related to the assessment of a study's quality. At a time when the general quality score of a study (based on randomization and appropriate blinding, for example) is usually taken into account, the quality score based on factors specific for preemptive effect (e.g., verification of block sufficiency) (13) is not. Nevertheless, as one can see in the review by Ong et al., the PRE versus POST design can provide strong evidence for clinical value of preemptive analgesia at least for some analgesic interventions.

Several years ago Moiniche et al. (4) published a systematic review of 80 studies based on PRE versus POST design. The authors drew a negative conclusion regarding the potential clinical value of preemptive analgesia in the treatment of postoperative pain. At the same time they noted that the trials of single-dose epidural analgesia resulted in an

improvement in pain control in 7 of 11 studies (the best outcome of all types of analgesic interventions in their review). They stated that validity and clinical relevance of the effect of epidural analgesia were questionable and difficult to interpret; therefore, they concluded that the results reveal lack of evidence for any important effect (rather than evidence for lack of effect). The conclusions of Moiniche et al. are largely at odds with those of Ong et al. Comparing the two reviews, Ong et al. suggested that 10 additional new trials (2001–2003, not included in the review by Moiniche et al.), stricter criteria for inclusion into the analysis, and a different approach for calculation of the pain score differences gave them an opportunity to better demonstrate a real value of preemptive analgesia for several types of analgesic interventions.

These reviews indicate that only reviews of systemic opioids always show a negative outcome regarding preemptive analgesia. This finding may be attributable to a phenomenon that counteracts the effect of preemptive analgesia: the development of acute tolerance to the analgesic effect of opioids (14,15). Thus, the advantage of the prevention of surgery-induced sensitization is lost because of the necessity of using larger doses of opioids to overcome acute tolerance.

Moiniche et al. concluded that “there is no need for further trials to investigate the role of timing of preemptive single-dose analgesic treatment on the postoperative pain pattern.” I tend to agree with this conclusion not because the PRE versus POST design could not reveal clinical value of the preemptive effect but because it is more important to assess the prevention of sensitization without elimination of nociception resulting from surgery-induced inflammation. Whether it is protective analgesia (definition of Moiniche et al.) (4) aimed at prevention of pathologic pain or preventive analgesia (definition of Katz (8) and Kissin (7)) with the identical aim, future studies should be redirected from the question of timing to the question of completeness of interventions. The completeness of interventions should be viewed with regard not only to the duration of an intervention but also to the sufficiency of a direct effect (e.g., blockade of nociceptive stimuli).

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Footnotes

- **Series editor:** Christoph Stein

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