EDITORIAL VIEWS

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Preemptive Analgesia

Why Its Effect Is Not Always Obvious

Preemptive analgesia is an antinociceptive treatment that prevents the establishment of altered central processing, which amplifies postoperative pain. The altered sensory processing is caused by high-intensity noxious stimuli *via* several possible mechanisms. Mechanisms that have been identified as playing important roles in the altered central processing of afferent inputs include expansion of receptive fields and a decrease in thresholds of dorsal horn neurons, enhancement of responses of dorsal horn neurons elicited by repetitive C-fiber stimuli (wind-up), and an increase in dynorphine gene expression.[1–3] As a result, different authors have used different terms for the process underlying the amplified, pathologic pain response. In addition to altered sensory processing, the terms central hyperexcitability, central sensitization, and central neural plasticity also have been used.

The concept of preemptive analgesia was formulated by Crile[4] at the beginning of this century on the basis of clinical observations. Crile advocated the use of regional blocks in addition to general anesthesia to prevent pain and the formation of painful scars caused by changes in the central nervous system during surgery owing to unsuppressed access of noxious stimuli to the brain. The revival of this idea was associated with a series of experimental studies started by Woolf[5] in 1983 and highlighted by Wall[6] in a 1988 editorial on the prevention of postoperative pain. The experimental research triggered many clinical studies (for reviews see references 1, 2, and 7 and footnote *). All the reviews agreed that evidence on preemptive analgesia obtained in experimental studies are very convincing. However, the results of clinical studies on the value of preemptive analgesia were not unanimous.

This issue of ANESTHESIOLOGY contains four studies[8–11] on preemptive analgesia, three experimental and one clinical. The results of these studies help to bridge the gap between experimental and clinical investigations and indicate that the controversy in the assessment of preemptive analgesia depends to a great extent on the conditions chosen to demonstrate this effect. At least five potential problems can be identified that could lead to controversy about preemptive analgesia.

Terminology

Preemptive analgesia is a misleading term because it creates an impression that the secondary feature associated with the phenomenon represents its basis. The term preemptive analgesia suggests that an antinociceptive intervention provided preoperatively prevents or reduces pain after surgery. With this definition, the difference in the outcome measure of an antinociceptive intervention made before and at the end of surgery is evidence of a preemptive effect. However, the emphasis should not be on the timing of treatment initiation but on the pathophysiologic phenomenon it should prevent: altered sensory processing (central hyperexcitability). The timing of the treatment should cover the entire duration of high-intensity noxious stimulation initiating the altered sensory processing. High-intensity noxious stimulation is generated not only by incisions (primary phase of injury) but also by the release of chemicals and enzymes from damaged tissues (secondary phase of injury extended well into the postoperative period). The absence of the difference in outcome measures between groups with preincisional and postincisional antinociceptive interventions cannot be a reliable argument against the existence of a preemptive effect because noxious stimuli can initiate altered central processing after the surgery, during the secondary inflammatory phase.

A correct definition of preemptive analgesia should emphasize the importance of treatment that prevents the development of central hyperexcitability, even if it occurs after surgery. It is interesting that Wall[6] in his editorial, *Prevention of Postoperative Pain,* discussed two phenomena: one associated with the blockade of

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*Niv D, Devor M: Does the blockade of surgical pain preempt postoperative pain and prevent its transition to chronicity? IASP Newsletter 1993; Nov/Dec:1–7.

Table 1. Preemptive Analgesia: Questions to Ask

1. Is antinociceptive treatment given before incision more effective than that given after?
2. Does perioperative antinociceptive treatment reduce subsequent postoperative pain (beyond duration of direct antinociceptive effect)?

nociceptive bombardment of the central nervous system produced by surgery and another associated with the treatment that begins before pain occurs. Whether antinociceptive treatment given before incision is more effective than that given afterward, is an important question, but this should be distinguished from the question of whether perioperative antinociceptive treatment reduces subsequent postoperative pain. Studies comparing the blocks given before and at the end of surgery cannot answer the latter question, which is central to the prevention of postoperative pain. Whether we should use different terms for these two different phenomena is another question.[12]

Thus, the meaning of this term for the potential authors determines the study's design and outcome. Table 1 illustrates how terminology can be translated into the crucial question on the aim of the study: preemptive analgesia in a narrow sense is reflected by the first question and in the broad sense, by the second.

Insufficient Afferent Blockade

Another factor contributing to the preemptive analgesia controversy is control of the completeness of antinociceptive blockade. The most important study on this subject was conducted by Shir *et al.*,[13] who compared three groups of patients undergoing radical prostatectomy with general, epidural, or combined epidural and general anesthesia. Preemptive analgesia was observed only with epidural anesthesia because this type of anesthesia allows for even minor discomfort to be noticed and treated during surgery. The authors concluded that "complete intraoperative blockade of afferent signals to the CNS is fundamental in decreasing postoperative pain."

In many studies that failed to find any preemptive effect, the effectiveness of the blockade was not controlled. Studies by Kehlet's group[14] have clearly demonstrated difficulties in providing complete blockade of noxious stimuli during surgery, indicated by an increase in plasma cortisol concentration and other metabolic responses. Kehlet's results show that only an extensive epidural blockade from T4 to S5 prevents the cortisol response to lower abdominal surgery.[15] Kehlet suggested that conflicting results reported in the literature about the effect of neural blockade on the cortisol response are probably attributable to the insufficient afferent block in most studies. The same argument is related to conflicting results regarding preemptive analgesia. According to the study by Rockmann *et al.*[11] in this issue of the journal the use of a balanced analgesic regimen given instead of complete local anesthetic blockade does not provide a meaningful preemptive effect.

Partial Preemptive Effect in Control

The effect of preemptive analgesia is assessed by measuring the difference between outcomes in control and preemptive groups (table 2). However, the use of a routine anesthetic technique used in the control group exploits, to some extent, the advantages of preemptive analgesia. For example, in most of the studies on preemptive analgesia, opioids were used in control groups in induction of anesthesia and during surgery. According to recent experimental studies, nitrous oxide can induce preemptive analgesia.[16,17] However, this anesthetic was used for anesthesia maintenance in several clinical studies in both control and preemptive groups. Finally, with recovery from anesthesia, the effective antinociceptive treatment in the control group during the initial postoperative period is governed by ethical considerations. As a consequence, the difference between groups in terms of degree of "noxious bombardment" of the spinal cord present during general anesthesia could completely disappear after recovery.

Table 2. Causes of Insufficient Difference in Postoperative Analgesia between Preemptive and Control Groups

- Incomplete effect in preemptive group
  - Insufficient duration of antinociceptive protection (primary and secondary phases of injury should be taken into account)
  - Insufficient degree of preventive blockade
- Partial preemptive effect in control group
  - Some preventive effect provided during primary phase of injury (opioids for induction, opioids during surgery)
  - Antinociceptive protection provided during secondary phase of injury (always present due to ethical considerations)
- Surgery with low-intensity noxious stimuli

Intensity of Noxious Stimuli

Surgery with low-intensity noxious stimuli during primary and secondary phases of injury may not generate enough difference between the preemptive and control groups. In addition, low-intensity stimuli may not trigger the altered central processing of afferent inputs. As a result, postoperative pain will represent only "physiologic," not "pathologic" pain (when pain response is amplified and allodynia is present). If pathologic pain is absent, preemptive analgesia has nothing to prevent. One might argue that preemptive analgesia can be observed only when a control group demonstrated that the surgery was painful enough to have preemptive effect.[18]

Outcome Measurement Problems

There are some problems associated with outcome measures used in studies on preemptive analgesia. Pain intensity and opioid consumption are routine measures of outcome. However, opioid consumption probably is not a very reliable index for assessing preemptive analgesia because no convincing evidence exists for proportionality between postoperative pain intensity and analgesic requirements. Opioid plasma concentration-analgesic response curves are surprisingly steep.[19] As a result, the within-patient difference between opioid concentration that is still ineffective, and the concentration that provides complete analgesia is difficult to detect. A quantal nature of the analgesic response can possibly lead to a situation in which opioid consumption primarily reflects the amount of accumulated time intervals when the opioid is needed.

Currently, patient-controlled analgesia commonly is used in studies on preemptive analgesia. However, the use of patient-controlled analgesia for algesimetry has several problems that undermine its usefulness (table 3). In addition to the problem of the quantal nature of analgesic response to opioids discussed earlier, the patient-controlled analgesia method has another potential deficiency. Analgesic usage is significantly influenced by such factors as mood, anxiety, expectations of recovery, and perception of support.[20] As a result, analgesic consumption reflects not only pain intensity but also other postoperative distress factors.

The first two factors indicated in table 3 may be the basis for the patient-controlled analgesia problem associated with coadministration of fixed-rate opioid background infusions when overall opioid consumption is increased. If patients receiving patient-controlled analgesia require the certain amount of an opioid to maintain its effective blood concentration, the addition of a background infusion would contribute to the blood concentration and decrease the demand rate proportionally. However, this has not been observed.[21,22] A similar type problem was reported with the use of demand doses of different sizes: Patients were unable to maintain the demand rate corresponding to the size of the demand dose.[23]

Table 3. Patient-controlled Analgesia Algesimetry Problems

Within-patient opioid plasma concentration-analgesic response curves are very steep.
Opioid consumption with PCA is profoundly influenced by various psychological factors not necessarily related to pain.
Co-administration of the fixed rate opioid infusion with PCA does not proportionally reduce the number of demands made by patients.
Opioid consumption with PCA depends on the size of the demand dose.

PCA = patient-controlled analgesia.

The balance of simultaneous changes in pain intensity and in analgesic consumption represents an additional difficulty for providing statistically significant results. In most studies, changes in one outcome measure counterbalance changes of another outcome measure. As a result, changes of both measures often fail to reach a statistically significant level.

The aforementioned five Intraoperative and Postoperative Sensory Drives problems can make the effect of preemptive analgesia difficult to demonstrate. No doubt that the most important problem is the uncertainty with terminology. If altered central processing of afferent inputs can be initiated during surgery and during initial postoperative period associated with high-intensity noxious stimuli, one can ask "What is the relative importance of these two periods?" This question is unanswered, and we can only offer a suggestion based on a comparison of the results of studies by three different groups of authors.[24–26] All three groups studied preemptive analgesia in patients undergoing inguinal herniorrhaphy with the use of neural blockade. At the same time, the value of the preemptive effect was tested during different injury periods. Ejelerson *et al.*[24] tested the protective coverage only during surgery. Bugedo *et al.*[25] performed the surgery in both treatment and control groups under spinal anesthesia;

therefore, the protective coverage (ilioinguinal and iliohypogastric block) was tested primarily during the initial postoperative period/secondary (inflammatory) phase. Tverskoy *et al.*[26] tested the antinociceptive protection (field block including ilioinguinal and iliohypogastric block) that covered both surgery and the initial 8–10 h postoperatively. All three groups of authors observed a preemptive effect. However, this effect was most pronounced when both surgery and early postoperative periods were covered (Tverskoy *et al.*) and least pronounced when only surgery was covered (Ejelersen *et al.*) with the covered postoperative period (Bugedo *et al.*) being in between. The comparison may suggest that the clinically impressive effect can be observed when blockade of noxious stimuli is extended well into the initial postoperative period.

Experimental studies published in this issue of the journal suggest a similar conclusion. In a study on volunteers, Pedersen *et al.*[8] have demonstrated that a prolonged (8–9 h) saphenous nerve block administered before thermal skin injury reduced hyperalgesia after recovery from the block. At the same time, Yashpal *et al.*[9] have reported that a short-lasting intrathecal lidocaine block in rats could produce a preemptive effect only with weak nociceptive response to the intraplantar injection of formalin; when the strength of the response was increased with higher concentrations of formalin, the effect of the lidocaine pretreatment profoundly declined. In the study by Fletcher *et al.*,[10] hyperalgesia in rats was caused by intraplantar injection of carrageenin, with injury lasting longer than 24 h, and the bupivacaine pretreatment (paw infiltration) did not provide any preemptive effect.

In conclusion, the prevention of postoperative pain is based on two phenomena, (1) the effective blockade of noxious stimuli generated during surgery and during the initial postoperative period (inflammatory phase) reduces subsequent postoperative pain (phenomenon of preemptive analgesia in the broad sense), and (2) an antinociceptive treatment started before surgery is more effective in the reduction of postoperative pain than the treatment given on recovery from general anesthesia (phenomenon of preemptive analgesia in a narrow sense). It was found that both phenomena can be induced by neural blockades with local anesthetics[13,24–27] and by systemic[28] or epidural[29,30] opioids. Clinically impressive effects are observed when the blockade of noxious stimuli is complete and extended into the initial postoperative period (a combination of both phenomena).

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