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Preemptive Analgesia

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PREEMPTIVE analgesia is an antinociceptive treatment that prevents establishment of altered processing of afferent input, which amplifies postoperative pain. The concept of preemptive analgesia was formulated by Crile[1] at the beginning of the previous century on the basis of clinical observations. Crile advocated the use of regional blocks in addition to general anesthesia to prevent intraoperative nociception and the formation of painful scars caused by changes in the central nervous system during surgery. The revival of this idea was associated with a series of animal studies started by Woolf.[2]

Several years ago, views on the concept of preemptive analgesia were summarized by a statement that evidence for the concept derived from experimental studies is overwhelmingly convincing; however, results of clinical studies regarding the value of preemptive analgesia are controversial.[3] For the past several years, many new studies on preemptive analgesia were published and summarized in several reviews.[4–8] Although these clinical studies did not significantly change the ratio of negative *versus* positive outcomes of preemptive treatments, there was a clear change in opinion: that it was essential to consider the inflammatory injury.

Terms and Definitions

Terms Commonly Used in Studies on Preemptive Analgesia

Central sensitization—persistent postinjury changes in the central nervous system that result in pain hypersensitivity

Central hyperexcitability—exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage

Preincisional treatment—treatment that starts before an initial surgical incision

Postincisional treatment—treatment that starts immediately after the end of operation

Adequacy of Preemptive Treatment Has Two Basic Requirements

The two basic requirements for adequacy of preemptive treatment are as follows:

1. verification of the effectiveness of the direct pharmacologic effect of a treatment, for example, by measuring the degree of a difference between control and treatment groups in the initial nociceptive response (plasma β-endorphin or cortisol level), by verification of the sufficiency of a neural blockade, etc.
2. extension of an antinociceptive treatment into the initial postoperative period, when generation of nociceptive stimuli by the inflammatory process may be very intensive for 12 to 48 h, depending on the type of surgery.

Definitions of Preemptive Analgesia

Three different definitions have been used as the basis for the recent clinical trials. Preemptive analgesia has been defined as treatment that: (1) starts before surgery; (2) prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery); and (3) prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period).

Definition of Preemptive Anesthesia Is the Major Source of Controversy Regarding Its Clinical Relevance

Definitions of preemptive analgesia are far from being uniform. The first definition (1) presented above is an erroneous definition that can lead to a false conclusion in

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a clinical trial. It does not reflect both basic requirements for the adequacy of preemptive analgesia. "Preemptive" means "preventive," not simply "before" incision. There should be proof that an intervention provides at least its direct effect. An insufficient afferent block cannot be preemptive, even if it is administered before the incision. The second definition (2) represents preemptive analgesia only in a narrow sense because it excludes central sensitization caused by inflammatory injury that occurs in the initial postoperative period. Those authors who believe that preemptive analgesia is not clinically relevant usually base their studies on this definition. With the narrow definition of preemptive analgesia, the difference in the outcome measure of an antinociceptive intervention made before and at the end of surgery is evidence of a preemptive effect.

Those who think preemptive analgesia has promise for the effective treatment of postoperative pain (including myself) support the broad definition (3). They define it as treatment that prevents establishment of central sensitization caused by incisional and *inflammatory* injuries; it starts before incision and covers both the period of surgery and the initial postoperative period. The balance between incisional injury and inflammatory injury depends on the nature of surgery; with certain conditions, inflammatory injury can be a very dominant factor.[9,10]

Preemptive analgesia prevents (or reduces) pathologic pain that is different from physiologic pain in several aspects: It is excessive (in intensity and spread) and can be activated by low-intensity stimuli (allodynia, hyperalgesia) and hyperpathia.

Animal Studies

The first study on preemptive analgesia was published by Woolf and Wall[11] in 1986. In a model of central hyperexcitability produced by electrical stimulation of C-fibers and recorded in rat dorsal horn neurons, they showed that the amount of systemically administered morphine needed to prevent the development of hyperexcitability was much less than the amount needed to reverse it after the establishment of hyperexcitability. Animal studies on preemptive analgesia have been extensively reviewed elsewhere.[9] It is interesting that the most impressive evidence of the preemptive effect was obtained with inflammatory models of central sensitization. In a rat model involving a brief surgical incision at the plantar hind paw, there was no difference between preincisional and postincisional treatment with intrathecal bupivacaine or intrathecal morphine.[12] Surgery-induced central sensitization has two phases: incisional and inflammatory (reaction to the damaged tissue). It is possible to suggest that with inflammatory injury playing the dominant role, antinociceptive protection provided by preemptive treatment should extend well into the postoperative period to cover the inflammatory phase. Otherwise it is ineffective, as in the rat paw incisional model.

New experimental evidence indicates that, even for short periods of time, both central mechanisms and afferent input are needed to maintain pain hypersensitivity.[13] Contrary to previous studies with various formalin models of pain hypersensitivity in rats, Taylor *et al.*[14] found that if the paw is anesthetized with a local anes-

Table 1. Recent Reviews of Clinical Studies of Preincisional *versus* Postincisional Treatment

Reference	Topic of Review	Conclusions
Grass, 1998	Local anesthetic infiltration or nerve blocks, neuraxial local anesthetics, neuraxial opioids, systemic NSAIDs, intravenous or epidural ketamine	Inconsistent findings from one study to the next, without any dramatic clinical advantages demonstrated in any study with any preemptive analgesic modality, including a multimodal approach. Preemptive administration of neuraxial opioids alone or with ketamine appears to offer some clinically significant advantages over postincisional administration.
Kehlet, 1999	Local anesthetic blocks, neuraxial and intravenous opioids, NSAIDs, NMDA-receptor antagonists (dextromethorphan and ketamine)	More than 40 controlled clinical studies comparing preoperative *versus* postoperative administration of identical doses of different drugs are reported, but most have been negative. Any positive clinical effects were usually small and without important clinical implications.
Niv et al., 1999	Local anesthetic blockade, epidural analgesia using local anesthetics or opioids, intravenous opioids, systemic NSAIDs, epidural and systemic ketamine	While many studies found no difference in postoperative pain between preincisional and postincisional patient groups, some found a modest but statistically significant benefit to preincisional analgesia. No clear answer can be given as to whether preemptive analgesia does or does not work.
Pasqualucci, 1998	Epidural blocks, nerve blocks, local anesthetic infiltrations	Four of the 11 studies evaluated seem to confirm the validity of preemptive analgesia, and an equal number deny it.
Schmid et al., 1999	Intravenous and epidural ketamine	Results of the studies evaluating effectiveness of preemptive ketamine are promising. The role of ketamine in the treatment of postoperative pain remains controversial.

NMDA = *N*-methyl-D-aspartate; NSAID = nonsteroidal antiinflammatory drug.

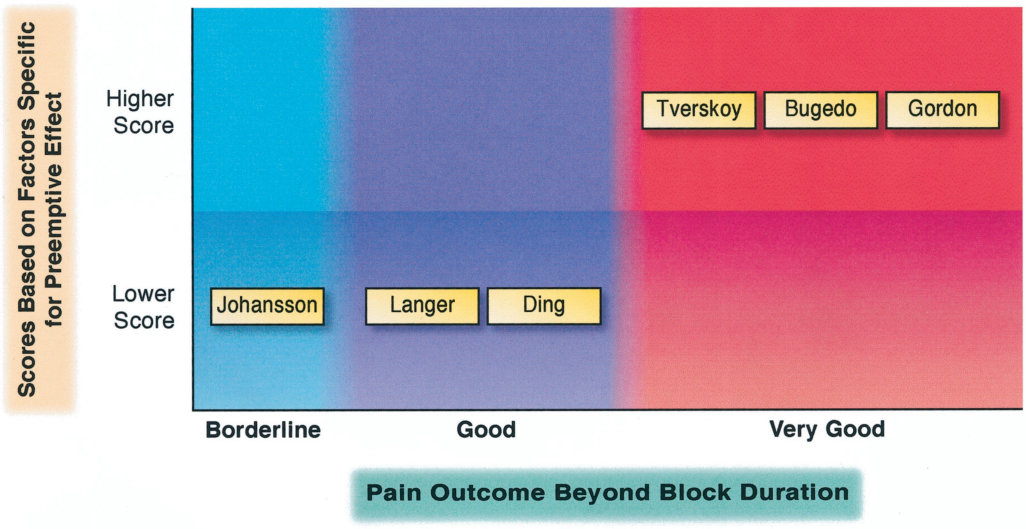

Fig. 1. Analgesic efficacy of nerve blocks beyond block duration. Relation between specific quality score of the studies and estimation of efficacy. Each name represents an individual study.[21–26] Studies were selected if they were randomized and double-blinded. The assessment of the selected studies was performed with the use of criteria specific for the preemptive effect: quality of verification of block sufficiency and the degree of initial difference in nociceptive response between control and treatment groups. Two score levels were used: higher and lower. All studies that excluded patients with incomplete block (Gordon *et al.*,[21] Bugedo *et al.*[22]) were given the higher score level. The profound initial difference in immediate block outcome between control and treatment groups was also a basis for the higher score level (time to first analgesic request 1 h vs. 9 h in Tverskoy *et al.*[23]). Very good outcome refers to studies that showed a statistically and clinically significant difference between control and treatment groups in pain intensity and/or analgesic consumption for more than 24 h postoperatively. Good outcome refers to studies that showed a statistically and clinically significant difference in analgesic consumption for 24 h. Borderline outcome refers to a statistical but not clinically significant difference.

thetic 15 minutes after formalin injection, the signs of hypersensitivity disappear relatively rapidly. If the peripheral afferent input is responsible for maintenance of central sensitization, the established postoperative pain hypersensitivity can be reversed by the blockade of afferent input if it is sufficiently prolonged. This response was demonstrated in a study with carrageenan-induced inflammation in rats: Hyperalgesia (usually lasting >5 d) was permanently reversed by a prolonged (10–12 h) nerve block but not with a block lasting less than 1 h.[15]

Human Studies: Preincisional *versus* Postincisional Treatment

Studies comparing preincisional with postincisional treatment failed to provide convincing evidence for the value of preemptive analgesia. The conclusions of recent reviews of the studies using such an approach are presented in table 1. Many studies could not find differences between treatments. If statistically significant positive effects were reported, they were of relatively small magnitude. Most significant advantages were reported with ketamine. One of the most important factors in the failure to demonstrate clinical significance of preemptive analgesia with preincisional *versus* postincisional treatment trials is the exclusion from such comparison of the results of central sensitization caused by inflammatory injury that occurs after surgery.

Human Studies with Neural Blockade

Figure 1 represents studies with peripheral nerve block. All of the studies with randomization and double-blinding that were criteria specific for preemptive analgesia (verification of block sufficiency and degree of initial difference in nociceptive response between control and preemptive groups) are presented in this figure. Clinical significance of the effect was defined as statistically significant difference between control and treatment groups in postoperative pain intensity and/or analgesic consumption that persisted for 24 h or more (see legend to fig. 1). Of six studies, a clinically significant outcome was observed in five. The three studies with a higher specific quality score than the others (see legend to fig. 1) all had a very good outcome. The figure demonstrates that clinically meaningful effects can be observed when the degree of nociceptive blockade is confirmed and the block is extended into the initial postoperative period.

The important role of sufficiency in the degree of afferent blockade was evident in the studies on preemptive analgesia with epidural anesthesia. Shir *et al.*[16] compared three groups of patients undergoing radical prostatectomy with general, epidural, or combined epidural and general anesthesia. The authors concluded that complete intraoperative blockade is fundamental for observing a preemptive effect.[16]

Another study with well-controlled sufficiency of epidural anesthesia in patients undergoing radical prostatec-

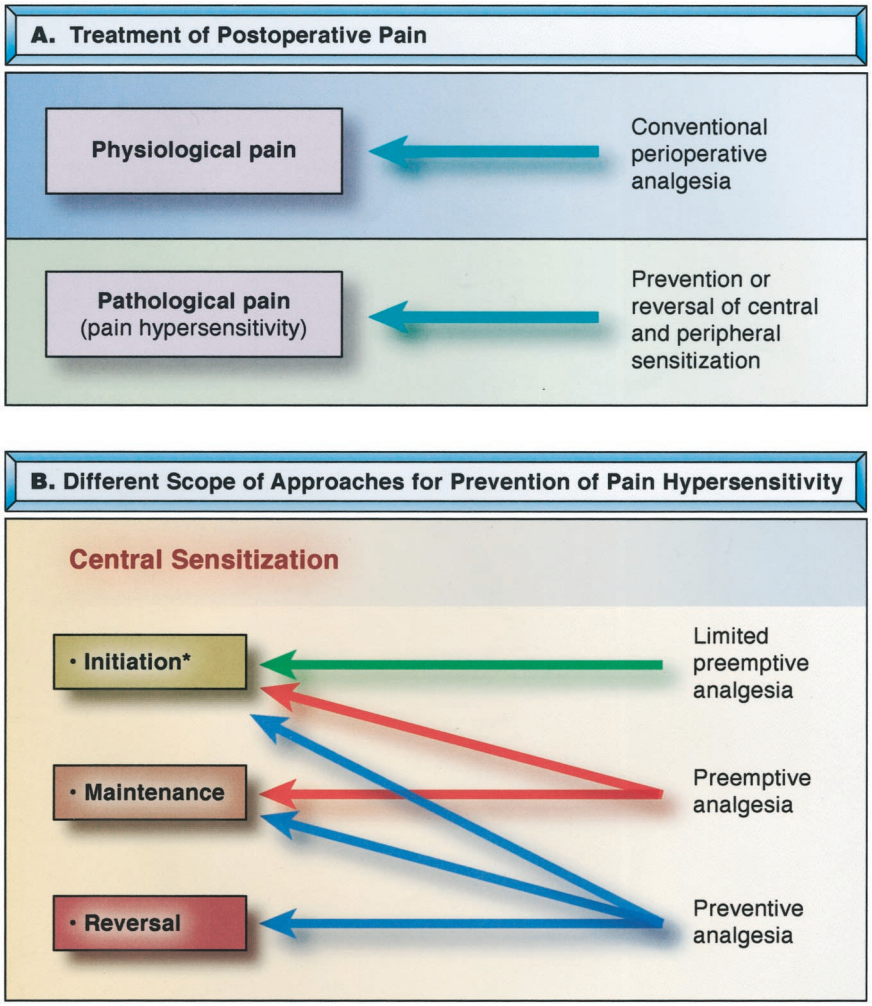

Fig. 2. Central sensitization and postoperative pain. (*A*) In contrast to conventional perioperative analgesia, preemptive analgesia is centered only on the prevention of pathologic pain. (*B*) Different scope of the approaches designed to exclude contribution of central sensitization to postoperative pain. * = Initiation during surgery.

tomy also reported positive results. Gottschalk *et al.*[17] administered epidural bupivacaine or epidural fentanyl before induction of general anesthesia and throughout the surgery, and compared the pain outcomes with those of similar treatment initiated at the fascial closure. Sufficiency of epidural blockade was verified by measurement of the sensory level (at least the fourth thoracic dermatome) before induction of general anesthesia and also in the postanesthesia care unit. Patients who did not have a T4 sensory level were excluded from the study; in addition, the patient's response to injury was assessed by measuring plasma cortisol levels. The authors reported that the patients who received epidural bupivacaine or epidural fentanyl before surgical incision (preemptive analgesia group) experienced less pain while they were hospitalized (visual analog scale [VAS] was one-third less; $P = 0.007$). At 9.5 weeks, 86% of the patients who received preemptive analgesia were pain-free compared with only 47% of the control patients ($P = 0.004$). The authors concluded that, even in the presence of aggressive postoperative pain management, preemptive epidural analgesia decreases postoperative pain during hospitalization and long after discharge.[17]

As indicated above, block of sufficient duration is another requirement for positive clinical outcome of preemptive treatment. Kehlet stated that a key question in this respect is whether the term preemptive analgesia has been used correctly, since it ideally implies prevention of the development of central hyperexcitability, even if it occurs after surgery; a local anesthetic should be applied preoperatively and as a continuous postoperative administration.[7] In patients undergoing total knee arthroplasty, Mϕiniche *et al.*[18] compared the effect of epidural bupivacaine–morphine anesthesia followed by continuous epidural analgesia postoperatively with that of general anesthesia followed by a conventional intramuscular opioid and acetaminophen regimen (control group) in patients undergoing knee or hip arthroplasty. After the cessation of the epidural regimen, the preemptive group received less morphine than did the control group for another 4 days. However, the authors did not observe any important improvements in convalescence

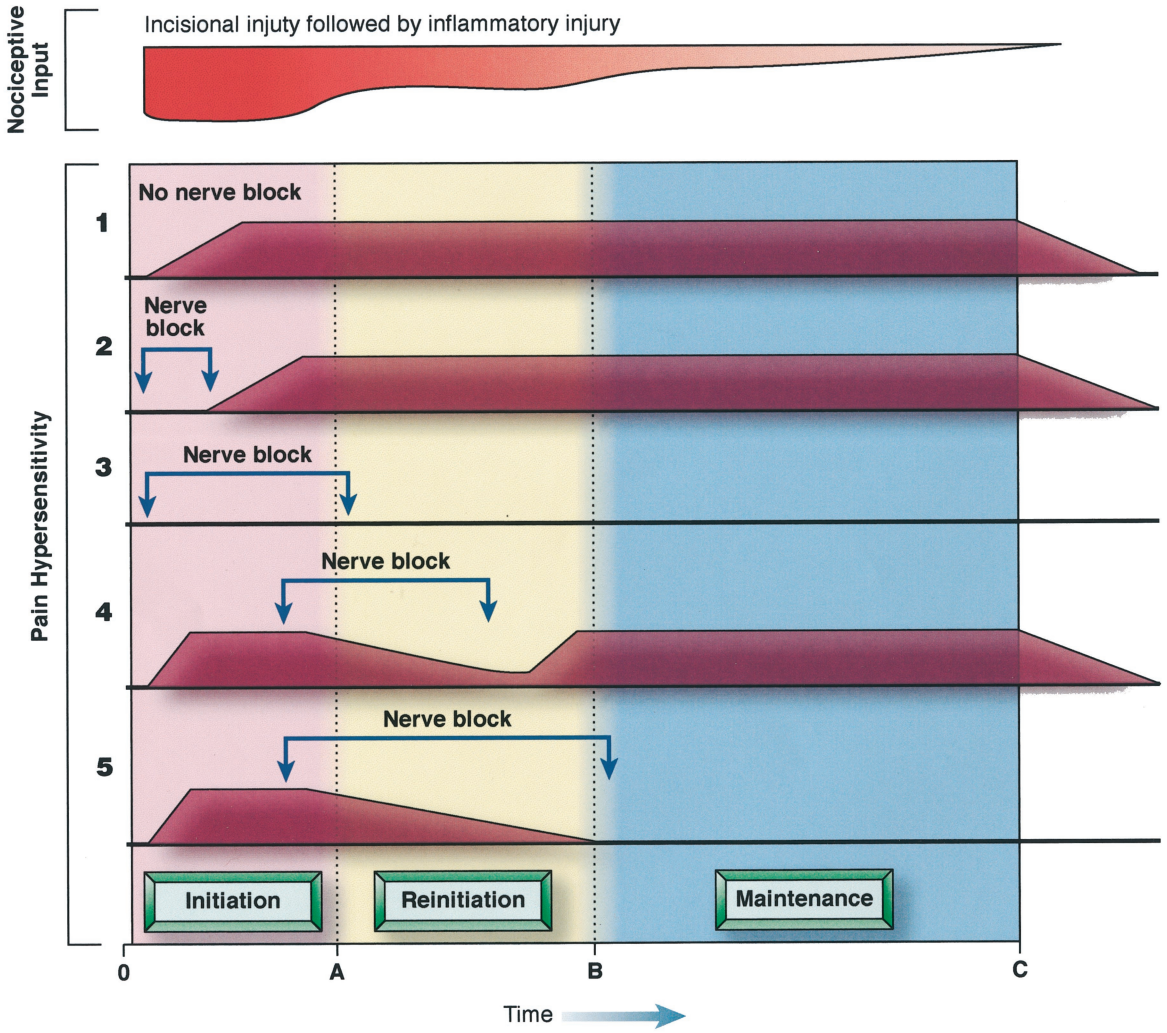

Fig. 3. A model illustrating hypothetical conditions necessary to preempt or reverse pain hypersensitivity with neural blockade. (*Top*) A nociceptive input caused by incisional injury, inflammatory injury, or both, with width of band indicating input intensity. (*Bottom*) Five possible variants of pain hypersensitivity generated in response to the afferent input with different block conditions: No block (1), shorter (2) and longer-lasting (3) preinjury blocks, and shorter (4) and longer-lasting (5) blocks administered when pain hypersensitivity is already established. A = Time after which nociceptive input is unable to initiate pain hypersensitivity yet strong enough to reinitiate it (if it was already established before the block); B = time after which the input is unable to reinitiate pain hypersensitivity but can maintain it (until time C). Periods when initiation, reinitiation, or maintenance of pain hypersensitivity are possible are indicated by pink, yellow, and blue, respectively. The effectiveness of a potential preemptive effect is determined by duration of nociceptive input that can initiate and maintain central hypersensitivity. If the blockade lasts until afferent input subsides to the level at which it cannot trigger central hypersensitivity, the preemptive effect might be clinically meaningful (see points 2 and 3). The reversal of central hypersensitivity (see points 4 and 5) is determined by two factors: persistence of central sensitization and continuance of the afferent input that can initiate, reinitiate, and maintain (respectively, in accordance with the declining level of the input intensity) pain hypersensitivity. The blockade should last until central sensitization subsides and the intensity of the afferent input is below the level that could potentially reinitiate central hypersensitivity (point 5). Because the intensity of afferent input for reinitiation of central hypersensitivity is lower than that for its initiation, blockade for a successful reversal of pain hypersensitivity should be longer (to permit greater input fading) than that for preemptive effect. (Modified with permission from Kissin *et al.*[15])

and hospital stay. Findings regarding the reduction of convalescence time with prolonged epidural bupivacaine have been reported in other studies.[19,20]

Preemptive Effect *versus* Combined Effect on Central Sensitization

The prevention of postoperative pain hypersensitivity should not be narrowed by exclusively focusing on the preemptive effect. The approach should be wider and centered on central sensitization in general (fig. 2). In contrast to conventional perioperative analgesia, this approach is centered only on "pathological," not "physiological," pain. Some pharmacologic agents that do not have any effect on acute "physiological" pain, however, can change the course of central sensitization and thus influence "pathological" pain. *N*-methyl-D-aspartate (NMDA) receptor

antagonists seem to have such properties. The reversal of the established hyperalgesia with the use of glutamate receptor antagonists has been reported in several animal studies. However, clinical studies have not been performed. Reversal of pain hypersensitivity can be accelerated with neural blockade if it is complete and of sufficient duration (fig. 3). Thus, two ways for reversal of central sensitization can be used: direct effect (potentially with glutamate receptor antagonists) or indirect acceleration of the reversal process by blockade of afferent input that maintains sensitization. I suggest that when various approaches attenuating central sensitization are used in combination, the probability of meaningful clinical benefits is increased.

How long could the preemptive effect last (after the block resolution)? For example, Gottschalk *et al.*[17] observed the results of preemptive analgesia 9 weeks after its administration. If the pain hypersensitivity does not last well beyond block resolution, the treatment would not be different from simple perioperative analgesia directed at physiologic pain. Figure 3 helps to assess conditions necessary for prolonged prevention of pathologic pain after neural blockade that preempts or reverses hypersensitivity.

Conclusion

When preemptive analgesia was studied by comparing preincisional *versus* postincisional treatment groups, many authors found no difference in the pain outcome, while some reported statistically significant but clinically modest benefits with preincisional analgesia. It is clear that the above approach is too simple to overcome multiple problems posed by the complexities of central sensitization and the technical difficulties of clinical studies. However, some of the previous positive clinical studies in combination with basic science results are probably sufficient to indicate that preemptive analgesia is a valid phenomenon. The question is how to demonstrate the maximal clinical benefits that can be obtained with the use of preemptive treatment. It is clear that this cannot be done simply by comparing preincisional *versus* postincisional treatment groups. Two conditions for clinical study are especially important: (1) providing effective suppression of the afferent input with sufficient duration of such treatment (that covers the initial postoperative period), and (2) combined treatment approaches aimed at: preemptive treatment, maintenance of the obtained effect, and reversal of central sensitization (in the case of an incomplete preemptive effect). A narrow definition of preemptive analgesia leads to a belief that this concept is clinically meaningless. Preemptive analgesia continues to have promise for the effective treatment of postoperative pain. Evaluation of the true importance of preemptive analgesia will have to await further research with new, more comprehensive approaches.

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