From preemptive to preventive analgesia

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Purpose of review

Much effort has been taken to prove that a treatment initiated before surgery is more effective in reducing postoperative pain compared with the same intervention started after surgery. Clinical studies failed to demonstrate major clinical benefits of preemptive analgesia, however, and the results of recent systemic reviews are equivocal. The present review will discuss recent clinical as well as experimental evidence of preemptive analgesia and examine the implications of a preventive postoperative pain treatment.

Recent findings

Recent preclinical and clinical studies give strong evidence that neuronal hypersensitivity and nociception after incision is mainly maintained by the afferent barrage of sensitized nociceptors across the perioperative period. This is in contrast to pain states of other origin in which prolonged hypersensitivity is initiated during the injury. Therefore, not timing but duration and efficacy of an analgesic and antihyperalgesic intervention are most important for treating pain and hyperalgesia after surgery.

Summary

Extending a multimodal analgesic treatment into the postoperative period to prevent postoperative pain may be superior compared with preemptive analgesia. In the future, appropriate drug combinations, drug concentrations and duration of preventive strategies need to be determined to be most beneficial for the management of acute and chronic pain after surgery.

Keywords

central sensitization, chronic postsurgical pain, incision, peripheral sensitization

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Abbreviations

NMDA	N-methyl-D-aspartate
NSAID	nonsteroidal antiinflammatory drug
RCT	randomized controlled trial

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Introduction

Nociceptive signals initiated by a tissue injury are transmitted by polymodal C-fiber and A-fiber nociceptors to spinal cord dorsal horn neurons [1,2]. This injury-induced intense afferent barrage activates a range of neurotransmitters and substances, including the excitatory amino acids (EAA) aspartate and glutamate, substance P and CGRP, resulting in exaggerated responses of dorsal horn neurons [3–5] and facilitation of further input to the dorsal horn (central sensitization or pain memory). A variety of basic science studies indicate that this facilitation process leads to enhanced pain sensitivity (hyperalgesia), pain to light tactile stimuli (allodynia) and prolonged, persistent pain after tissue injuries [2]. Based on this scientific evidence and supported by animal experimental evidence, Wall [6] and Woolf and Chong [7] hypothesized that a preemptive treatment will prevent the establishment of central hypersensitivity, decrease the incidence of hyperalgesia and reduce the intensity of postoperative pain. Importantly, preemptive treatment was defined as an antinociceptive intervention that starts before a surgical procedure and is more effective than the same intervention that starts after surgery [8]. Subsequently, a large body of clinical experimental studies compared a preincisional with a postincisional treatment; however, the results were, at most, contradictory.

Clinical studies on preemptive analgesia

The discrepancy between results from basic science experiments and clinical studies is documented best by three recent systemic reviews of clinical studies about possible superior effects of a preemptive treatment strategy. Moiniche *et al.* [9] reviewed the literature about preemptive analgesia from 1983 to 2000 and selected 80 randomized controlled trials (RCTs) for their quantitative and qualitative systemic review. They analysed the effect of pre compared with postoperative analgesia (Pre vs. Post) on pain scores within 24 h after surgery of 3761 patients (1964 patients received preemptive treatment) treated with systemic nonsteroidal antiinflammatory drugs (NSAIDs), single-dose epidural analgesia, systemic N-methyl-D-aspartate (NMDA) receptor antagonists, systemic opioids or peripheral local anaesthetic infiltration. Only studies with a Pre vs. Post design were included in this review. They concluded that the timing of neither treatment approach influenced the quality of pain control, indicating that a preemptive analgesia is not superior to a postincisional treatment [10].

Recently, Dahl *et al.* [1] presented an update on this systemic review by including 30 new RCTs about the effect of preemptive analgesia on postoperative pain for the period of 2001–2004. They reported that 13 of these new RCTs favour preemptive analgesia and 17 RCTs did not show a significant difference between pre and post-incisional analgesia, confirming largely the results from the previous study by Moiniche *et al.* [9]. Thus, they concluded that preemptive analgesia is not superior to a postoperative pain relief in terms of reduced pain scores or decreased need for supplemental analgesics.

In contrast, a recent meta-analysis by Ong *et al.* [11••] on the efficacy of preemptive analgesia for postoperative pain challenged this view. Ong *et al.* [11••] analysed 66 RCTs on preemptive analgesia for postoperative pain, including the data of 3261 patients [11••]. The three outcome variables were pain intensity scores during the first 24–48 h, total supplemental postoperative analgesic requirements and time to first rescue analgesic evaluated for five types of analgesics or interventions (systemic NSAIDs, single-dose epidural analgesia, systemic NMDA receptor antagonists, systemic opioids or peripheral local anaesthetic infiltration), similarly to the treatment groups utilized by Moiniche *et al.* [9]. Based on their analysis, preemptive epidural analgesia resulted in consistent improvements in all three outcome variables whereas preemptive local anaesthetic wound infiltration and systemic NSAID administration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores (Table 1; [9,11••,12]). With preemptive systemic NMDA receptor antagonists and systemic opioid administration, the results of the currently available studies were equivocal. The disparity between the results of the recently published systemic reviews by Moiniche *et al.* [9] and Dahl *et al.* [1] and the meta-analysis performed by Ong *et al.* [11••] could be due to different inclusion criteria of selected studies or a diverse approach for calculation of pain scores.

Mechanisms behind postoperative pain: new insights with regard to studies on preemptive analgesia

The usefulness of preemptive analgesia has been reported [7,13] in several animal models of inflammation, chemical irritation or neuropathic pain, hypothesizing that a blockade of noxious input to the spinal cord before tissue injury will also reduce postoperative pain more than a blockade after a surgical injury. Thus, a beneficial effect of a preemptive treatment was suggested for clinical pain states, including postoperative pain.

In a recently developed animal model of incision-induced pain behaviors [14], however, spinal administration of morphine, bupivacaine [15] and EAA receptor antagonists [16] did not reduce pain behaviors beyond the expected duration of the analgesic effect. These data and the contradictory clinical results in postoperative patients indicate that when the early effect of a pharmacologic treatment diminishes, the surgical wound appears capable of generating pain behaviors equivalent to a posttreatment group. In contrast to other more persistent and intense tissue injuries like inflammation or nerve injury, incision-induced sensitization of spinal dorsal horn neurons is maintained at least initially by excitation of primary afferent fibers (peripheral sensitization; [17]). Duration of treatment, rather than time initiated, appears to be important for an effective postoperative pain relieve. A preemptive analgesic effect on mechanical hypersensitivity, however, may be age or developmentally dependent. As demonstrated by Ririe *et al.* [18], a preoperative sciatic nerve block was beneficial in 2-week-old rats but not in 4-week-old rats after a surgical incision.

In conclusion, it is important to recognize that neuronal hypersensitivity and nociception caused by different tissue injuries is likely a result of distinct neurochemical and electrophysiological mechanisms. Results from experiments in animals [19] and human volunteers [20] after an incision may therefore specifically advance our understanding about mechanisms for incisional pain to develop effective treatment strategies.

Clinical implications: from preemptive to preventive analgesia

Incision-induced neuronal hypersensitivity and nociception is maintained by the afferent barrage of sensitized nociceptors, indicating that noxious input across the entire perioperative period may be able to initiate central sensitization. Therefore, it has been proposed that not the timing of the analgesic treatment but the duration

Table 1 Comparison of the reviews performed by Moiniche *et al.* [9], Ong *et al.* [11••] and Dahl *et al.* [12]

	Moiniche *et al.* [9]; Dahl *et al.* [12]	Ong *et al.* [11••]		
	Pain score	Pain score	Analgesic consumption	Time to rescue analgesic
Epiduralanalgesia	⇔	✙	✙	✙
Local anesthesia	⇔	⇔☆	✙	✙
NMDA antagonist	⇔	⇔	⇔☆	⇔☆
NSAID	⇔	⇔☆	✙	✙
Opioids	⇔	⇔	⇔☆	⇔☆

⇔ No beneficial effect; ⇔☆ meta-analysis of currently available studies yielded equivocal finding; ✙ positive effect. Modified from [11••].

and efficacy of an analgesic intervention are important for treating pain and hyperalgesia after surgery [1,9,21,22]. As supported by preclinical and clinical studies, the analgesic or antihyperalgesic effect of a drug in the postoperative period may, at least under certain conditions, exceed the expected duration of action of the drug (Table 2; [1,9,21,23••,24]). This treatment approach, aimed to control the development of central sensitization in the postoperative period, has been defined as preventive analgesia [8,21]. In a recent systematic review, Katz and McCartney [24] analyzed 27 clinical studies evaluating preemptive or preventive analgesia and reported a benefit with preventive analgesia but equivocal or no benefit from preemptive treatment after surgery. Thus, extending a treatment intended to reduce central sensitization into the postoperative period may be beneficial for the treatment of postoperative pain. Preventive analgesia is therefore a broader definition of preemptive analgesia including any perioperative analgesic regimen able to control pain-induced sensitization. Although timing of a preventive analgesia is not paramount, a preincisional start with preventive analgesia may block the stress response during surgery. As indicated, adequate preventive analgesia should include multimodal techniques with several drugs to attenuate peripheral and central hypersensitivity and with a sufficient duration of treatment [21,22,25,26••,27,28].

Several substances attenuating incision-induced central sensitization and hyperalgesia appear to be useful for a preventive treatment in the perioperative period. McCartney *et al.* [29] reported that systemic application of the NMDA receptor antagonists ketamine or dextromethorphan show preventive analgesic effects; no positive effect was seen in four studies using magnesium. In agreement, Lavand'homme *et al.* [30•] demonstrated that epidural analgesia combined with systemic application of ketamine decreases the area of hyperalgesia surrounding a surgical incision in patients after colectomy and influence late, residual pain. Thus, there is growing evidence that systemic NMDA-receptor antagonists are able to produce preventive effects in the perioperative period and may improve the treatment of acute and prolonged (chronic) postsurgical pain.

Table 2 Definition of preemptive and preventive analgesia [23••]

Preemptive analgesia (Pre vs. Post Design)	Preemptive analgesia is a treatment that is initiated before the surgical incision and is operational during the surgical procedure in order to prevent the establishment of altered sensory processing that amplifies postoperative pain [1,21]. Its effect on analgesic consumption or pain ratings after surgery needs to be greater compared with the same treatment initiated after surgery (Pre vs. Post design)
Preventive analgesia (Pre vs. No Design)	Postoperative pain or analgesic consumption is reduced relative to another treatment, a placebo treatment or no treatment, as long as the effect is observed at a point in time that exceeds the expected duration of action of the target agent. The intervention may or may not be initiated before surgery [9,21,24]

Perioperative application of systemic gabapentin – an antiepileptic drug with a known effect on chronic pain – reduces pain scores, decreases Opioid consumption and attenuates hyperalgesia after surgery [31,32]. Although a preventive effect of gabapentin has been hypothesized [12,33,34•,35], further studies are needed to determine the clinical significance. Similarly, epidural administration of neostigmine started before surgery and extended into the postoperative period was able to produce a prolonged analgesic-sparing effect in patients after thoracotomy [36]. Neostigmine was combined with bupivacaine and morphine in the postoperative period, supporting that a multimodal treatment approach is most effective.

Lidocaine – a sodium channel blocker with an inhibitory effect on mechanoinsensitive nociceptors – is another substance with a possible preventive analgesic effect in the perioperative period. Koppert *et al.* [37] reported that a perioperative intervention with systemic lidocaine reduced overall morphine consumption and produced lower postoperative pain scores during the first 72 h, implicating a preventive effect of intravenous lidocaine and an important role of a peripheral sensitization process for the generation of postoperative, prolonged pain and hyperalgesia after surgery. In agreement, there is increasing experimental evidence [17,38–40] that substances targeting the activation and sensitization of nociceptors during and after a surgical incision may be of great value for the concept of preventive analgesia.

Further RCTs are warranted, however, in order to find more substances with preventive analgesic effects and to determine the appropriate drug dose and duration of preventive analgesic treatments required to reduce central sensitization and hyperalgesia after surgery.

Persistent (chronic) postsurgical pain, caused by specific neurobiological changes due to ongoing inflammation or iatrogenic nerve injury, occurs in 10–50% of individuals after surgery and lasts for more than 3–6 months [26••]. As the intensity of early postoperative pain among others may correlate with the development of chronic postsurgical pain [26••,41,42], it has been hypothesized that a preventive multimodal pharmacological treatment may be beneficial. Clinical data are contradictory, however, and future studies should determine the effect of a preventive multimodal analgesia on chronic postsurgical pain [22].

Conclusion

The disparity between the results of the recently published systemic reviews by Moiniche *et al.* [9] or Dahl *et al.* [1] and the meta-analysis performed by Ong *et al.* [11••] indicate that not the timing of the analgesic treatment but the duration and efficacy of analgesic intervention are important for treating pain and hyperalgesia after surgery.

The limited clinical benefit of preemptive analgesia may be due to a distinct central sensitization process caused by a surgical incision. In contrast to other more persistent and intense tissue injuries like inflammation or nerve injury, incision-induced sensitization of spinal dorsal horn neurons is maintained at least initially by excitation of primary afferents fibers (peripheral sensitization) [17]. Therefore, an appropriate postoperative pain treatment may start before surgery, last long enough after surgery to avoid pain-induced sensitization processes and includes effective analgesic interventions (preventive analgesia). The concept of preventive analgesia includes multimodal antinociceptive techniques with analgesics that exceed the expected duration of action of these drugs and that attenuate peripheral or central hypersensitivity.

For the future, experimental animal and clinical studies are warranted, answering questions about the duration of postoperative analgesia, which analgesics or interventions are most appropriate to inhibit hyperalgesia and which treatment strategies will prevent the development of chronic postsurgical pain.

References and recommended reading

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- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 588–589).

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