

Pre-emptive analgesia: evidence, current status and future directions

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Summary

Although some studies of pre-emptive analgesia have reported small reductions in post-operative pain or analgesic consumption in favour of pre-incisional vs. post-incisional or post-operative treatment, most have not demonstrated any benefit at all. This paper reviews recent evidence supporting the effectiveness of pre-emptive analgesia and discusses factors that may be responsible for the lack of consistent results. These factors include problems with the accepted definition of pre-emptive analgesia, the potential pre-emptive analgesic effects of other agents (e.g. opioids, nitrous oxide, pentobarbitone) used routinely as part of the general anaesthetic, the role of post-operative inflammation in initiating and enhancing

a state of central sensitization, and the lack of a true placebo control condition. Given the constraints of clinical research and current standards of practice, it is unlikely that studies of pre-emptive analgesia using conventional analgesics or local anaesthetics will yield large reductions in post-operative pain or analgesic consumption. Extending the pre-emptive treatment well into the post-operative period using balanced, multimodal analgesia, may prolong the initial advantage conferred by the pre-operative blockade and possibly interfere with the development of long-lasting pain.

Keywords: ANALGESIA, pre-emptive; PAIN; plasticity; COMPLICATIONS, inflammation.

Introduction

The field of pre-emptive analgesia has developed directly from basic science research carried out over the past decade [1-3]. Studies demonstrate that administration of opioids or local anaesthetics before noxious stimulation prevents development of injury-induced spinal hyperexcitability and pain-related behaviour. By contrast, the same treatments are significantly less effective when administered only minutes later, after the prolonged central excitability or pain behaviours have been established. The editorial in *Pain* by Wall [4] and the accompanying paper by McQuay *et al.* [5] provided the impetus for controlled studies of pre-emptive analgesia in patients scheduled for surgery.

Although initial studies of pre-emptive analgesia showed that pre-operative blockade with local anaesthetics or pre-operative administration of systemic opioids was more ef-

fective in reducing post-operative pain than control conditions involving no treatment (Fig. 1a), the results of subsequent investigations comparing the effects of preoperative treatment with the same treatment initiated after incision or surgery (Fig. 1b,c) have produced inconsistent results (see [6-9] for recent reviews). The reasons for the lack of consistency are not clear. This paper will examine some of the possible factors that have contributed to the inconsistent results.

Studies showing that post-operative pain can be pre-empted have generally found small, albeit significant, reductions in pain and/or post-operative analgesic consumption. For example, pain intensity 72 h after lower abdominal surgery is rated as mild in both pre- and post-treated groups, but it is even milder in the pre-treated group [10]. Typical reductions in morphine consumption amount to

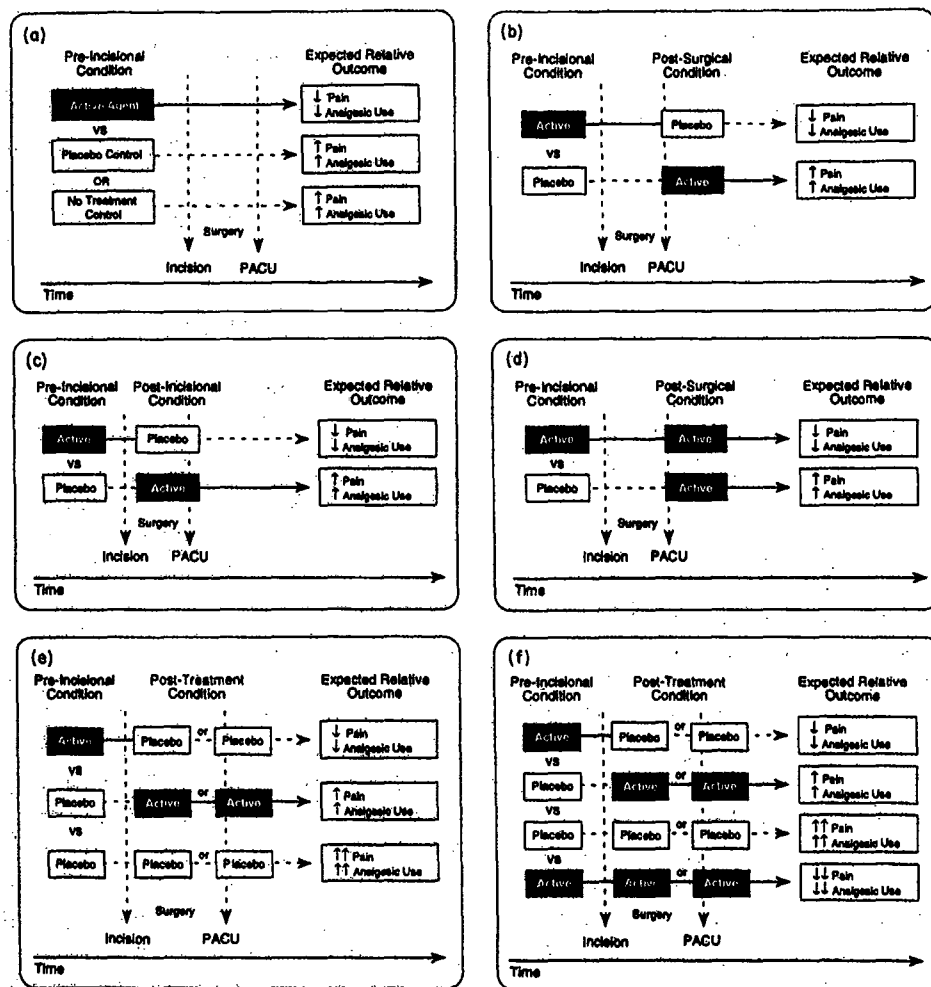


Fig. 1. Various designs used to evaluate the effectiveness of pre-emptive analgesia showing the expected outcomes in terms of post-operative pain and analgesic consumption. (a) Initial studies compared an active agent with a placebo control condition or a no-treatment control condition. (b-c) Later studies examined the effectiveness of a pre-incisional condition with a post-incisional or post-surgical condition. (d) Comparison of a pre-incisional and post-incisional condition with a post-incisional condition in an attempt to isolate the effects of incision and subsequent noxious peri-operative events on post-operative pain. (e-f) Recommended designs for future studies of pre-emptive analgesia. See text for details.

approximately 25% over a 24-h period, but the absolute difference (e.g. 10–16 mg) between pre- and post-treated groups is actually very small [10–12]. The magnitude of these effects suggests that the contribution of sensitized central neurones to the total post-operative pain experience may be overshadowed by the more salient peripheral input [13].

Clinical significance

A frequent criticism of these studies has been the lack of clinically significant effects. However, it is not a simple

matter to define a clinically significant reduction in pain or analgesic consumption. This is in part because clinical significance is not only a function of effect size but of quality (of pain and pain relief) and in part because pain is a subjective experience. The clinical significance of a reduction in pain or analgesic consumption should be evaluated first and foremost from the patient's perspective. This is particularly true of studies in which patients are in control of their post-operative analgesic consumption. Moreover since post-operative pain is not adequately controlled for most patients, any decrease in pain and analgesic consumption without added risk is to be welcomed.

Role of other agents in pre-empting post-operative pain

Perhaps a more valid criticism of some of these studies (e.g. [10, 11]) is their lack of a *clinically relevant* general anaesthetic regimen since in an effort to evaluate the pre-emptive effects of epidural analgesia or anaesthesia, opioids deliberately are not administered pre- or intra-operatively. It is not known whether post-operative pain would be pre-empted to the same degree by pre- vs. post-incisional administration of these agents if patients also received an opioid pre-medication and/or opioids peri-operatively. Although there is evidence both for [12] and against [14] the ability of systemic opioids to pre-empt post-operative pain when used as the target pre-emptive agent, it is likely that they contribute to a pre-emptive effect when administered in studies designed to assess the pre-emptive effects of local anaesthetics or opioids delivered by other routes. This would have the unintended effect of pre-empting pain in both pre-incisional and post-surgical treatment groups and thus contribute to non-significant inter-group differences in post-operative pain and analgesic consumption.

Similarly, it is possible that other agents administered as part of the general anaesthetic regimen, also have subtle, additive pre-emptive effects, which may attenuate the central sensitizing effects of surgery in all patients. In this context, the difference between the degree of attenuation of central sensitization achieved by the target treatment (e.g. local anaesthetic infiltrations, nerve blocks, epidural or spinally administered anaesthetics or opioids) given before vs. after surgery, over and above that produced by the other agents, may make it difficult to detect significant differences in post-operative pain or analgesic consumption.

Although comparable data from the clinical setting are not available, recent studies of pre-emptive analgesia using the rat formalin model have shown that nitrous oxide [15] and pentobarbitone [16] each can pre-empt second-phase nociceptive responses. There is also evidence from a more clinically relevant animal model to support the hypothesis that morphine and pentobarbitone may produce subtle pre-emptive analgesic effects which dilute the potential effect of a target pre-emptive treatment [17]. Rats that received i.v. pentobarbitone, i.v. morphine, and i.t. bupivacaine prior to intra-articular formalin injection had significantly reduced nociceptive responses when compared to a saline control group, but not to a group that

received i.v. pentobarbitone and i.v. morphine prior to injury and post-injury intrathecal bupivacaine. Moreover, although rats given i.v. pentobarbitone, i.v. morphine, and i.t. saline prior to injury showed lower nociceptive scores compared with the saline control group, these groups did not differ significantly. Thus, while the pentobarbitone and morphine did not reduce nociceptive behaviour significantly compared to the control group these agents may have lowered nociceptive responses sufficiently to contribute to the lack of significance between rats treated with i.t. bupivacaine before vs. after injury.

Design issues

Use of the term *pre-emptive analgesia* to refer exclusively to evidence that pre-operative treatment is more effective than post-operative treatment (as opposed to no treatment or a placebo treatment) may be too restrictive and narrow. It has been argued that evidence of pre-emptive analgesia requires control of the same intervention made after surgery but in doing so, it may not be possible, or even desirable, to ensure that the groups are treated similarly with respect to other anaesthetic agents. For example, end-tidal isoflurane was significantly lower over the 60-min interval after skin incision among patients that received lumbar epidural bupivacaine before vs. 30 min after incision [10]. We do not know whether this inter-group difference contributed to the reduced post-operative pain and analgesic consumption observed among the pre-incisional treatment group. As noted above, it is possible that other agents administered during surgery may contribute directly or indirectly to a pre-emptive effect. A good example of this is the finding that halothane antagonizes the pre-emptive effect of nitrous oxide in the rat formalin model [15]. Thus, because of the clinical nature of the research, ensuring that the two groups are treated the same with respect to the target pre-emptive treatment may mean treating them differently in other potentially important ways.

Demonstrating that pre-treatment with analgesics, but not a placebo, lessens pain and decreases post-operative analgesic requirements at a time when the agents are no longer clinically active, suggests that the central component of post-operative pain can be prevented or pre-empted. In the absence of a post-incisional or post-operative control condition, it is not possible to determine whether factors associated with the intra-operative or post-operative period (or both) are necessary for the enhanced post-operative pain experience. Altering the timing of adminis-

tration (Fig. 1b–d) may provide clues to the specific intraoperative (e.g. incision, wound retraction) or post-operative (e.g. inflammation) factors that contribute to the central neural changes underlying the enhanced pain. Nevertheless, in the absence of a post-treatment condition, the finding that pain or analgesic consumption is reduced relative to an untreated control condition (Fig. 1a) after the clinical duration of action of the putative pre-emptive agent is evidence of a pre-emptive analgesic effect: such a design, however, does not provide information about the possible mechanism(s) underlying the pre-emptive effect. The use of incomplete designs that consist of a post-incisional or post-surgical condition (Fig. 1b–d) without a true placebo condition (Fig. 1e, f) may in part be responsible for the small effects of pre-emptive analgesia. Use of designs shown in Fig. 1 (e, f) may extend the focus of attention from pre-empting the effects of noxious intra-operative events to that of post-operative inflammation.

Post-operative inflammation

It has been suggested that failure to demonstrate a pre-emptive analgesic effect may reflect an inflammation-induced state of central sensitization that develops after the pharmacological action of the pre-operative agent has disappeared or in the case of continuous epidural infusion due to insufficient afferent blockade in the post-operative period. Partial support for the possibility that post-operative inflammatory inputs from the wound may initiate a state of central sensitization has been reported in a three-group study that evaluated the effects of 10 mg morphine i.m. administered either 1 h before surgery, i.v. at the time of induction, or i.v. at the time of wound closure [12]. Twenty-four hours after surgery, patient-controlled morphine consumption was significantly lower in the group pre-treated with i.v. morphine compared with the group treated at the time of wound closure. However, movement-associated pain scores 48 h after surgery were *higher* in the i.v. pre-treated group, suggesting that the extra morphine used by patients in the i.v. post group during the first 24 h after surgery pre-empted pain in the second 24-h period.

The results of a study by Katz *et al.* [10] do not show this trend. Twenty-four and 48 h after surgery, cumulative PCA morphine consumption was significantly lower in patients that received epidural bupivacaine before vs. 30 min after incision, but the rate of morphine consumption from 24 h after surgery onward was virtually identical in the pre-

and post-incisional groups (Fig. 2) even though McGill Pain Questionnaire scores were higher in the post-incisional

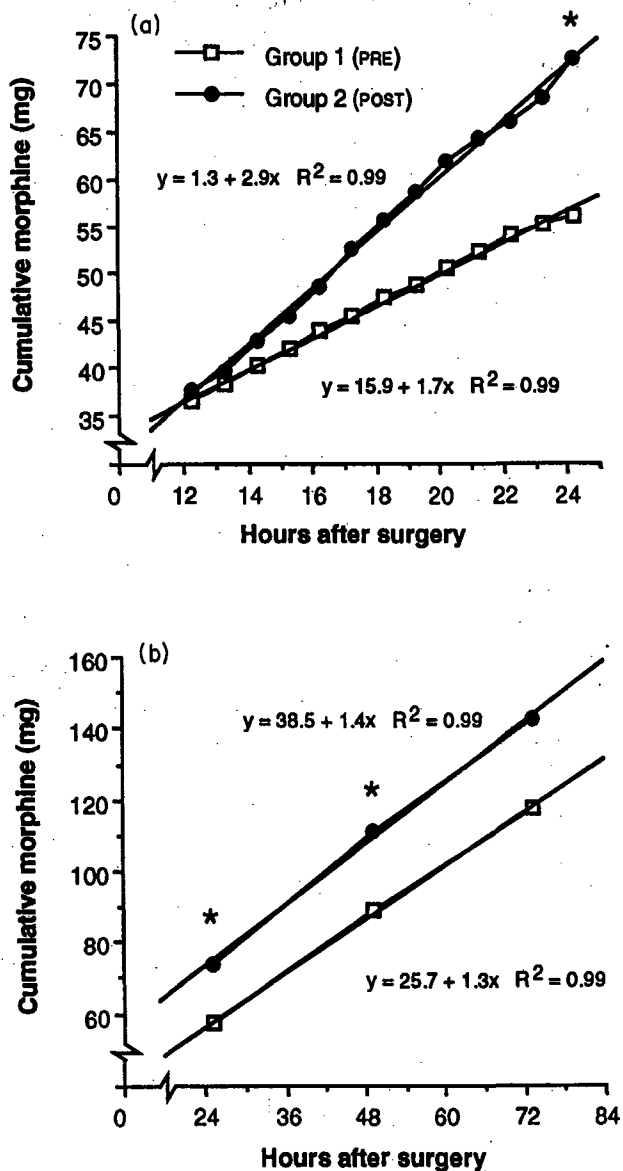


Fig. 2. Post-operative cumulative patient-controlled morphine consumption from (a) 12–24 h and (b) 24–72 h after surgery for patients that received lumbar epidural bupivacaine (15 ml 0.5%) approximately 40 min before incision (Group 1 PRE) or 30 min after incision (Group 2 POST), showing best-fitting least squares lines relating morphine consumption to time after surgery. The greatest divergence in the hourly rate of morphine consumption occurred within the second 12-h period after surgery with groups 1 and 2 self-administering approximately 1.7 mg h⁻¹ and 2.9 mg h⁻¹ respectively (a) while from 24 h onward, the slopes of the least squares straight lines were virtually parallel (b). Data from Katz *et al.* [10] * $P < 0.04$.

group 72 h after surgery. These results do not support the suggestion (a) that a state of central sensitization which may have developed after surgery in the pre-incisional group (group 1) was sufficient to overcome the pre-emptive effect relative to the post-incisional group (group 2), or (b) that the additional morphine used by group 2 in the first 48 h was sufficient to pre-empt subsequent pain relative to group 1. The results suggest that the central sensitization triggered by the initial injury barrage during lower abdominal surgery and the central sensitization that develops over the 72 h after surgery due to ongoing peripheral inflammation make separate contributions to the experience of post-operative pain [13]. The inflammatory inputs in the post-operative period appear to initiate (in the pre-incisional group) and enhance (in the post-incisional group) a state of central sensitization so that pain is amplified leading to additional morphine requirements among patients who received the active treatment after incision compared with the pre-treated patients.

Another possibility is that the development of post-operative inflammation may be attenuated at the level of the spinal cord by a central neural mechanism following pre-emptive epidural or spinal local anaesthesia. Recent animal studies show that joint inflammation in an experimental model of arthritis is significantly reduced following spinal administration of the non-NMDA antagonist CNQX [18]. Thus it may be that pre-incisional spinal local anaesthesia pre-empts pain by more than one mechanism. In addition to attenuating the effects of the afferent barrage associated with surgery, it is possible that the degree of peripheral inflammation may also be reduced. When this is considered in conjunction with the finding that inflammation associated with injection of carrageenan into a rat's paw induces a 30-fold increase in the potency of morphine to inhibit C-fibre-evoked responses in dorsal horn neurones [19], it raises questions about the interpretation of (negative) findings from certain clinical studies of pre-emptive analgesia. The ED_{50} for inhibiting the C-fibre-evoked response in normal animals was 9.17 μ g of morphine. Following the induction of peripheral inflammation the ED_{50} dropped to 0.28 μ g of morphine.

While extrapolation from animal studies to the clinical setting is rarely justified, it is nonetheless interesting to speculate on the meaning of a non-significant difference in pain or morphine consumption if similar mechanisms were operative in humans. If development of inflammation is attenuated by pre-emptive spinal local anaesthesia and if the potency of morphine increases in the presence

of peripheral inflammation, then compared with a pre-treated group, untreated patients or patients treated after incision or surgery would be expected to develop a greater degree of inflammation and pain, but would not require more morphine post-operatively to reduce their pain to a comparable intensity. It is not inconceivable that the pattern of pain scores and analgesic consumption would be similar in the pre- and post-treated groups even though patients may have benefited to a greater degree from the pre-treatment. The typical study of pre-emptive analgesia in which patients control their post-operative opioid consumption would not detect such a benefit. Keeping analgesic consumption fixed while looking for inter-group differences in pain intensity would, in general, provide a more direct test of the predictions of pre-emptive analgesia; namely, less pain when resting and moving about.

Long-term effects of pre-emptive analgesia

Given the small benefits observed in some studies shortly after surgery, it should come as no surprise that longer-term effects have not been found, either in the incidence or intensity of chronic chest wall pain 2 years after thoracotomy, or post-incisional pain 9 months after lower abdominal surgery [20]. The most striking finding is that the incidence of chronic post-thoracotomy pain is unacceptably high (approximately 60%) whether patients received pre-emptive or post-incisional epidural fentanyl during surgery. These results suggest that although some pre-emptive treatments may reduce pain and analgesic consumption in the early days after surgery, the short-term benefits have no bearing on the development of chronic post-thoracotomy pain. Extending the pre-emptive treatment well into the post-operative recovery period, using balanced, multi-modal analgesia [21], may prolong the initial advantage conferred by the pre-operative blockade and possibly interfere with the development of long-lasting pain.

Conclusions

The constraints of clinical research and current standards of practice make it unlikely that studies of pre-emptive analgesia using conventional analgesics or local anaesthetics will yield large reductions in post-operative pain or analgesic consumption. The difficulties in demonstrating that post-operative pain can be pre-empted reflect problems in the definition of pre-emptive analgesia,

the confounding effects of other agents used during general anaesthesia, the role of post-operative inflammation, and methodological factors (use of PCA to indirectly measure pain and incomplete control conditions). Future studies using agents that block the NMDA receptor may prove helpful in preventing acute postoperative pain from becoming chronic.

Acknowledgments

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