THE VALUE OF PRE-EMPTIVE ANALGESIA IN THE TREATMENT OF POSTOPERATIVE PAIN

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Our knowledge and understanding of the physiology of acute pain has improved in recent years. Most of this new information has been gathered from basic science and experimental studies. The recent papers by Wall [40] and Woolf [41] have stimulated much discussion on the potential clinical implications of this knowledge for the management of acute postoperative pain, and the concept of "pre-emptive analgesia" has gained widespread acceptance. This paper is a critical analysis of clinical studies on the effects of pre-emptive analgesia on acute postoperative pain.

BACKGROUND

Tissue injury results in disruption of the normal specialization of the CNS, with alterations in the processing of afferent stimuli [41, 42]. Experimental studies have demonstrated that peripheral injury may result in expansion of receptive fields and decrease in the threshold of dorsal horn neurones [13, 14, 41, 42]. This facilitation may be prolonged, depending on the stimulus and the type of afferents activated [41, 42]. Consequently, innocuous inputs may generate pain (alldynia), with increased pain to suprathreshold stimulation (hyperalgesia) and development of spontaneous pain [41, 42]. The neurophysiological and molecular mechanisms of these changes may involve an increase in synaptic efficacy of excitatory inputs or a decrease in inhibitory inputs [13, 42] mediated by wind-up [31] and neurokinin and N-methyl-D-aspartate (NMDA) receptor mechanisms [10, 14, 42]. Furthermore, changes in second messengers and gene expression may lead to prolonged functional changes in the nervous system [14].

In humans, cutaneous injury is followed by alterations in thermal and mechanical sensibility [19, 25, 26, 33]. "Primary hyperalgesia" refers to changes within the area of injury and "secondary hyperalgesia" to changes in the undamaged tissue surrounding the injury. Primary hyperalgesia is explained by sensitization of peripheral nociceptors [19, 25, 26, 33]. A recent series of elegant studies in humans and primates supported the suggestion that secondary hyperalgesia is caused by altered central processing of mechanoreceptive input from the periphery [2, 24, 25, 36, 38]. Based on these experimental and clinical studies, it has been proposed that surgical trauma in humans may lead to comparable alterations in sensory processing, resulting in amplification and prolongation of postoperative pain, and possibly persistent postsurgical pain [40–42].

To date, only four studies have investigated the effect of surgery on pain sensitivity in humans [7, 17, 18, 27]. Postoperative sensory thresholds were reported to be unaffected [17, 18] or increased [27], but in the latter study, only perception thresholds to electrical stimulation were investigated—not pain thresholds, which would have been more appropriate [27]. Recently, increased sensitivity and pain to noxious electrical stimulation in the A-β range were observed in patients after gynaecological surgery [7]. Furthermore, the threshold of the nociceptive flexion reflex was decreased in the early (48 h) postoperative phase [7]. These observations of alldynia and hyperalgesia in postoperative patients may be a result of postoperative sensitization of central neurones. However, no conclusion on the relative contribution of central sensitization to postoperative pain can be derived from these studies. Thus data demonstrating neuronal plasticity in postoperative patients are limited and the relative contributions of central sensitization to the intensity and duration of acute pain in humans have not been identified. No information is available on the degree or duration of noxious inputs required to induce central changes, or the question if postoperative pain itself may lead to alterations in dorsal horn excitability, independent of the afferent barrage during surgery. Finally, it is not known if the intensity and maintenance of postoperative pain is more dependent on central hyperexcitability than continuous afferent barrage from the wound.

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In experimental studies, acute pain behaviour or hyperexcitability of dorsal horn neurones may be eliminated or reduced if the afferent barrage is prevented from reaching the CNS by pre-injury neural block with local anaesthetics [4, 5, 44] or if...
### Table I: Summary and interpretation of studies used in the discussion on the potential clinical value of pre-emptive analgesia

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of analgesia in pre-emptive group</th>
<th>Type of surgery</th>
<th>Results: does pre-emptive analgesia improve post-operative pain relief?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td>Wound infiltration LA</td>
<td>Inguinal herniorrhaphy</td>
<td>Partially supportive</td>
</tr>
<tr>
<td>[12]</td>
<td>Ileo-inguinal block and wound infiltration LA</td>
<td>Inguinal herniorrhaphy</td>
<td>Not supportive</td>
</tr>
<tr>
<td>[8]</td>
<td>Extradural bupivacaine plus morphine</td>
<td>Colonic surgery</td>
<td>Not supportive</td>
</tr>
<tr>
<td>Section II</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>[30]</td>
<td>Opioid premedication, peripheral LA blocks combination opioid premedication and LA</td>
<td>Various peripheral orthopaedic procedures</td>
<td>Interpretation hindered by methodological deficiencies</td>
</tr>
<tr>
<td>[39]</td>
<td>Wound infiltration LA</td>
<td>Inguinal herniorrhaphy</td>
<td>May be supportive, but other mechanisms than modulation of central hyperexcitability may be effective</td>
</tr>
<tr>
<td>[3]</td>
<td>Ileo-inguinal block + spinal anaesthesia</td>
<td>Inguinal herniorrhaphy</td>
<td>May be supportive, but other mechanisms than modulation of central hyperexcitability may be effective</td>
</tr>
<tr>
<td>[20]</td>
<td>Wound infiltration LA</td>
<td>Tonsillectomy</td>
<td>May be supportive, but other mechanisms than modulation of central hyperexcitability may be effective</td>
</tr>
<tr>
<td>[32]</td>
<td>Subdiaphragmatic LA</td>
<td>Gynaecological laparoscopy</td>
<td>May be supportive, but other mechanisms than modulation of central hyperexcitability may be effective</td>
</tr>
<tr>
<td>[34]</td>
<td>Extradural LA + morphine + systemic indomethacin</td>
<td>Cholecystectomy</td>
<td>Not supportive</td>
</tr>
<tr>
<td>Section III</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>[21]</td>
<td>Extradural morphine</td>
<td>Trans-sternal thymectomy</td>
<td>Not supportive</td>
</tr>
<tr>
<td>[23]</td>
<td>High-dose systemic alfentanil</td>
<td>Abdominal surgery</td>
<td>Not supportive</td>
</tr>
<tr>
<td>[22]</td>
<td>Premedication</td>
<td>Lumbar disc prolapse surgery</td>
<td>Interpretation hindered by methodological deficiencies</td>
</tr>
<tr>
<td>Section IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[15]</td>
<td>Pre- and postoperative flurbiprofen</td>
<td>Oral surgery</td>
<td>Interpretation hindered by methodological deficiencies</td>
</tr>
<tr>
<td>Section V</td>
<td></td>
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<tr>
<td>[1]</td>
<td>Extradural bupivacaine or opioid or combination</td>
<td>Lower limb amputation</td>
<td>Interpretation somewhat hindered by methodological deficiencies. Patients with preoperative pain cannot be extrapolated to other surgical procedures</td>
</tr>
<tr>
<td>[37]</td>
<td>TENS and extradural bupivacaine</td>
<td>Caesarean section</td>
<td>Interpretation hindered by methodological deficiencies</td>
</tr>
</tbody>
</table>

the excitability of the CNS is suppressed with opioids before it receives a nociceptive input \[11, 43\]. Similar antinociceptive procedures were less effective when applied post-injury \[5, 11, 43, 44\], although one study showed spinal anaesthesia 5 min after the injury also to be effective \[4\]. Consequently, the importance of "timing" of analgesia has been suggested to be of potential major importance in the treatment of postoperative pain \[40-42\].

**Clinical studies of pre- and postoperative neural block or wound infiltration with local anaesthetics (table I, section I)**

Only three studies have been published comparing the postoperative analgesic effect of an identical neural block administered before or after the surgical stimulus \[8, 12, 16\]. Two studies compared the effect of pre- and postoperative local infiltration with lignocaine on pain after inguinal herniorrhaphy \[12, 16\]. In one study, there was no difference in pain scores, but the time to first request for additional analgesia (non-steroidal anti-inflammatory drug (NSAID)/opioid) was increased in patients with preoperative infiltration of the surgical area compared with a similar postoperative block \[16\]. However, pain was evaluated for only 6 h after operation \[16\]. In the other herniorrhaphy study, there was no significant difference in times to first request for morphine, total morphine requirements or pain scores at rest or during physical activity,
between patients with an inguinal field block performed before compared with after surgery. Patients were followed up for 7 days after operation [12]. In the third study, patients undergoing colonic surgery received either extradural dose of 9 ml of bupivacaine 7.5 mg ml\(^{-1}\) plus morphine 2 mg before or after surgery, followed by low-dose continuous extradural bupivacaine 0.25 mg ml\(^{-1}\) plus morphine 0.2 mg ml\(^{-1}\) at a rate of 4 ml h\(^{-1}\) for 72 h [8]. The results showed no significant differences in pain scores at rest or during mobilization, or in request for additional morphine [8].

Thus, from these few studies, there is no firm evidence that timing of angesic treatment—that is, pre-emptive analgesia—has important effects on postoperative pain or requirements for additional analgesics. Obviously, more studies in other procedures and with different pre-emptive analgesia regimens are required, and studies are needed to evaluate the effect of such regimens on the occurrence of very late (chronic) postoperative pain.

**Preoperative neural block or wound infiltration with local anaesthetics compared with no treatment or placebo** (table 1, section II)

In a non-randomized, retrospective study, McQuay, Carroll and Moore [30] investigated patients undergoing a variety of surgical procedures on the extremities and receiving either preoperative opioids or no premedication, a variety of local anaesthetic blocks, or both. The results showed that median time to first request for postoperative analgesia was prolonged significantly by opioid premedication, by a local anaesthetic block and by a combination of premedication and a local anaesthetic block, with increased analgesic efficacy in that order. However, this non-randomized study in badly defined analgesic techniques and patients did not address the question of the value of pre-emptive analgesia (that is, timing of analgesia *per se*) and the design of the study prevents interpretation in this context.

In a prospective, randomized study, preoperative incisional local anaesthetic combined with general anaesthesia in patients undergoing inguinal hernia repair was compared with general anaesthesia alone and with spinal anaesthesia [39]. The study is outstanding, as pain at rest and mobilization, and wound tenderness were assessed by algometer. The study was well designed, with well defined postoperative additional analgesic treatment and only one surgeon, performing a well defined procedure. The results showed that preoperative incisional neural block provided superior and prolonged analgesia for 24 h and 48 h after operation, compared with general anaesthesia alone, while the spinal anaesthesia group had an intermediary analgesic response. The prolonged analgesic effects of incisional local anaesthetic obviously could be caused by reduction of central hyperexcitability, although this was not documented by the study, as a similar analgesic procedure applied after operation was not investigated. Another explanation for these positive findings could be reduction of the primary hyperalgesic response resulting from the well documented anti-inflammatory effects of local anaesthetics in *vivo* and experimental studies [39].

In another study, preoperative spinal anaesthesia and percutaneous ileoinguinal nerve block were found to reduce ileoinguinal pain for 48 h after herniorrhaphy, compared with pain in patients operated under spinal anaesthesia only [3]. Pain was assessed at rest and interpretation is somewhat hindered by a badly defined additional analgesic treatment with different drugs, although it was stated that the overall need for additional analgesics was reduced in the combined spinal–inguinal block group [3]. Again, this study may support the concept that preoperative neural block may reduce late postoperative pain in small scale surgery, but a similar analgesic procedure applied after operation was not studied.

A study in 14 patients, aged 6–18 yr, undergoing tonsillectomy demonstrated that 0.25% bupivacaine 3 ml/tonsil significantly reduced the constant pain score for 6 days compared with a saline control group. Pain on swallowing was also reduced significantly by the preoperative block for up to 10 days after operation [20]. Surgery was undertaken by the same surgeon and treatment blinded for the assessor of pain. Postoperative pain was treated with paracetamol, apparently with the same dosing regimen in both groups. Again, these very positive results may be explained by reduction of central hyperexcitability as in the study by Tverskov and colleagues [39], but an effect mediated by reduction of primary hyperalgesia from the anti-inflammatory effects of bupivacaine cannot be excluded.

In a study in patients undergoing day-case laparoscopy, 80 patients were allocated randomly to initial subdiaphragmatic administration of 0.25% bupivacaine 80 ml, 1% lignocaine 80 ml with adrenaline, saline 80 ml or no peritoneal administration [32]. Pain scores at rest were reduced significantly in the local anaesthetic treatment groups compared with the non-treatment groups for up to 48 h after operation. Although no information was given on postoperative additional analgesics in this study, the results again may support the concept of pre-emptive analgesia and reduction in central hyperexcitability, although this was not proven, and an effect on peripheral nociceptors caused by anti-inflammatory effects cannot be excluded.

In two randomized, but not double-blind studies in patients undergoing classical cholecystectomy [34] or laparoscopic cholecystectomy [unpublished observations] (who received intensive preoperative extradural analgesia with 0.5% or 0.75% bupivacaine combined with preoperative extradural morphine followed by continuous extradural combined bupivacaine and opioid treatment), the initial extremely effective analgesia during rest, cough and mobilization did not result in prolonged pain relief during physical activity, when the initial block disappeared. These two studies document clearly that clinically relevant and very effective extradural analgesic regimens, even when administered before operation, have no important effect on later postoperative pain during physical activity and therefore do not suggest that pre-emptive analgesia, even
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when combined with relatively prolonged postoperative analgesia, "prevents" or reduces late postoperative pain.

Pre-emptive analgesia with opioids (table I, section III)

In one randomized, placebo-controlled double-blind study in patients undergoing trans-splanchnic sympathectomy, preoperative extradural morphine 7 mg compared with saline had no effect on postoperative pain scores at rest or on additional analgesic requirements beyond the initial 8-h postoperative period [21]. However, the study was small including only 19 patients. In another randomized, placebo-controlled study, a preoperative bolus of alfentanil 30 μg kg⁻¹ followed by an intraoperative infusion of 40 μg kg⁻¹ h⁻¹ had no effect on postoperative pain scores or requirement for additional opioids [23]. These two studies [21, 23], therefore, do not support experimental studies with minimal trauma [11, 43] to suggest that preinjury administration of opioids can reduce postoperative pain.

Finally, a non-randomized study in patients undergoing lumbar disc prolapse surgery and receiving a variety of premedicant drugs, concluded that additional opioid premedication reduced time to first demand for a postoperative analgesic and the overall need for postoperative analgesia [22]. Because of major methodological deficiencies and differences in sex distribution and with the finding that women required more analgesics than men, this study is unable to make the conclusion that "it is confirmed that opiate premedication diminishes the sustained hyperexcitability of the central nervous system caused by intraoperative stimuli" [22].

Pre-emptive analgesia with NSAID (table I, section IV)

Only one study has examined combined pre- and postoperative NSAID (flurbiprofen) compared with postoperative flurbiprofen alone on postoperative analgesia after removal of the third molar [15]. The results suggested that the combination was more effective, which is not unexpected, as the total dose of NSAID was larger in the combined treatment group, and therefore the results cannot be taken as an argument for increased efficacy of pre-emptive analgesia compared with postinjury treatment.

Other studies (table I, section V)

In the discussion on the potential clinical importance of pre-emptive analgesia, the studies by Bach, Noreng and Tjelliden [1] and Smith and colleagues [37] have been used to support the hypothesis of a preoperative neural block reducing central hyperexcitability, postoperative pain and analgesic requirements [6, 40]. The former study [1] in 26 patients undergoing limb amputation allocated randomly to pre- and intraoperative extradural block or intraoperative block alone, assessed the occurrence of phantom limb pain for the subsequent 12 months. Only patients with preoperative pain were included, but pre- and postoperative pain scores in the two groups were not presented. There was no information on the extradural regimen, except that it was provided for 3 days by extradural morphine or 0.25% bupivacaine or a combination, aiming at freedom from pain, although this was not assessed or documented. The authors stated that patients who continued to have pain despite the preoperative extradural block were excluded from further investigation, but no information was given on the number of patients excluded. However, apparently no patient was excluded [M. Noring, personal communication]. Extradural analgesia was not given after operation in any group. The results showed a significant reduction in phantom limb pain 6 months after operation, with a non-significant similar trend 7 days and 1 yr after operation. The degree of phantom limb pain was not presented. Although very interesting, great care should be taken in the interpretation of this study, because of several inadequacies in its design, and the results cannot be extrapolated to patients undergoing elective surgery who have no preoperative pain. However, despite this criticism, the study has stimulated much constructive debate on pre-emptive analgesia and the potential impact of such treatment on the occurrence of late and chronic, postoperative pain. Obviously, further well designed studies are required to answer this important and clinically relevant question.

A study [37] quoted to support the efficacy of pre-emptive analgesia [6, 40] considered 18 women undergoing elective Caesarean delivery, nine patients receiving transcutaneous electrical nerve stimulation (TENS) and nine placebo stimulation. In addition, and confounding for the interpretation, some of the patients received extradural anaesthesia and some general anaesthesia; exact numbers receiving each were not given [37]. Exact pain data were not presented, but it was mentioned that a non-significant reduction in constant and movement-associated incisional pain was found in the TENS treated women in the extradural group, and that the placebo treated women had significantly less movement-associated pain when receiving extradural analgesia. Obviously, these results in small groups of patients, together with a combination of different analgesic treatments and without presentation of exact data, cannot be taken as an indication of extension of analgesic efficacy of a preoperative neural block into the postoperative period.

COMMENTS AND CONCLUSIONS

Available data from the few studies of identical neural block techniques before compared with after operation have not documented clinically relevant differences in postoperative analgesia or analgesic requirements. Several studies are available on preoperative neural block with local anaesthetics compared with no treatment and most studies have found a reduction in late postoperative pain, request for additional analgesics, or both, compared with no neural block [3, 20, 30, 32, 39]. However, these studies do not demonstrate that such effects result from optimal timing of analgesia or a reduction in central hyperexcitability by preoperative analgesic treatment. Other studies during greater surgical trauma (abdominal surgery) have not been able to
show that intense preoperative extradural analgesia followed by 1–4 days continuous extradural treatment with combinations of local anaesthetics and opioids has any long-lasting effect on postoperative pain during rest or mobilization compared with no neural block [34, unpublished observations].

The difference between the effect of pre-emptive analgesia on postinjury nociceptive processing in experimental studies and pain in clinical studies may have several explanations. Although central sensitization may contribute to postoperative pain in humans, surgical trauma differs from the conditioning stimuli applied in most experimental studies. Contrary to a well-localized thermal or chemical injury, or brief C-afferent stimulation, the afferent input to the CNS during and after surgery is prolonged and extensive, with mixed cutaneous, muscular and visceral components. Central sensitization may be generated not only during surgery, but also in the postoperative period, because of persistent inflammation and hyperalgesia at the wound site. Thus intraoperative nociceptive block may not be adequate to reduce postoperative sensitization of central neurones. Recently, we have demonstrated more efficient reduction in secondary hyperalgesia to a burn injury in volunteers by a pre-burn block compared with an identical post-burn block, thus confirming experimental studies [unpublished observations]. However, this difference was significant only as long as the block was clinically effective [unpublished observations]. Furthermore, conventional analgesic methods (local anaesthetics or opioids) may not provide total C-afferent block during surgery. Thus the negative studies of pre- vs postoperative identical neural block [8, 12] or preoperative extradural block vs no block [34, unpublished observations] may be explained by insufficient afferent block. Thus several studies have documented that such blocks were ineffective in inhibiting potentials evoked by peripheral electrical stimulation [9, 28, 29] or the inflammatory response to surgery [34, 35]. Therefore, the optimal intensity, the duration and the timing of analgesia to prevent alterations in dorsal horn neurones after tissue injury of greater magnitude than that studied experimentally [4, 5, 10, 43, 44], need further investigation before clinical recommendations of pre-emptive analgesia can be established.

In conclusion, more, well designed clinical studies are needed to evaluate the clinical implications of the findings of central hyperexcitability and long-lasting analgesic effects of a pre-injury neural block in experimental studies. The exciting developments in our understanding of the biochemistry involved in the processing of nociceptive stimuli, based upon experimental studies, undoubtedly will have a major impact on the future treatment of acute pain. Prevention of the functional changes in the central nervous system by “pre-emptive analgesia” or other techniques, is a fascinating working hypothesis, but the definition of pre-emptive analgesia with regard to duration compared with the duration of the peripheral stimulus should be evaluated. Future, well designed clinical studies may clarify the relative importance of effective pre-emptive analgesia, compared with continuous analgesic treatment during the period when nociceptive impulses are generated from the wound, or if a combination of such efforts may provide improved pain relief without significant side effects. Finally, the effect of such regimens on the incidence of postsurgical chronic and neuropathic pain should be explored.

Note added in proof: In a recent study by Katz and colleagues, extradural fentanyl 4 μg kg⁻¹ was more effective when administered before compared with 15 min after surgical incision in patients undergoing thoracic surgery [45]. However, pain scores and postoperative morphine consumption were reduced only at one of five assessments (at 6 h and from 12 to 24 h after operation, respectively) during a 48-h study period. Furthermore, the pre-emptive study group was older and included more females than the control group, both of which factors may result in less pain and opioid consumption. Thus this study does not present evidence for a clinically significant effect of pre-emptive administration of opioids on postoperative pain.

REFERENCES
13. Dubner R. Neuronal plasticity and pain following peripheral pain.
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