Research Paper

Volume : 3 | Issue : 2 | February 2014 • ISSN No 2277 - 8179

Pre-Emptive Medication to Relieve Postoperative Pain: To Do Or Not To Do?

Medical Science

KEYWORDS : pre-emptive medications, postoperative pain, analgesia

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ABSTRACT

Pre-emptive medications prior to surgical procedures in order to relieve postoperative pain have been suggested in literature. Pre-emptive analgesia is a treatment that is initiated before and is operational during the surgical procedure in order to reduce the physiological consequences of nociceptive transmission provoked by the procedure. Some studies suggest a beneficial role of the medication. Preventive medicine is the new source of interest in the field of medicine and all efforts to ensure comfort to the patient post operatively need to be enforced. This review article focusses on the mechanisms and the thought behind the applications in our day to day practice.

Pain signals from damaged tissue are not transmitted to the central nervous system (CNS) through 'hard-wired' pathways. In contrast, nociceptive signals, once initiated, will launch a cascade of alterations in the somatosensory system, including an increase in the responsiveness of both peripheral and central neurons. These alterations will increase the response to subsequent stimuli and thus amplify pain. [1]

Pre-emptive analgesia is a treatment that is initiated before and is operational during the surgical procedure in order to reduce the physiological consequences of nociceptive transmission provoked by the procedure. Owing to this 'protective' effect on the nociceptive pathways, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented. [2]

A variety of chemical, mechanical or thermal stimuli can initiate activation of the nociceptors in the periphery. Activation is followed by conduction of the resulting action potentials through small myelinated Aδ and unmyelinated C fibres. Management of postoperative pain included only treatment modalities applied to patients after surgery in an effort to reduce already established pain, simply because it has been difficult to predict the onset of patient's first complaint of pain. In contrast, however, a large body of experimental data over the past 15 years suggests that surgery and other forms of peripheral tissue injury result in a disruption of afferent stimuli processing at the peripheral and central nervous system (CNS) level, which lead to peripheral and central sensitization.

Peripheral sensitization refers to a reduction in the threshold of nociceptor afferent peripheral terminals (e.g. nociceptors become hypersensitive to noxious stimuli). In contrast, central sensitization refers to sensory changes in the undamaged tissue surrounding the injury, due to a hyperexcitability of spinal neurons, which produces secondary hyperalgesia. [3,4] Therefore, whenever in clinical practice central sensitization occurs, pain treatment, to be effective, should not only be managing the nociception related to the tissue trauma, but also the CNS response to the trauma. Accordingly, the prevention of peripheral or central sensitization has been proposed to be a rational step in pain treatment [5].

Pathophysiology of Pain Hypersensitivity

Nociception refers to a series of electrochemical events occurring pathophysiologically between the site of local tissue damage and the site of pain perception in the CNS. Stimuli generated from thermal, mechanical, or chemical tissue damage may activate nociceptors, which are free nerve endings (e.g. A‰- mechanoreceptors, A‰- mechanothermal nociceptors and C-polymodal nociceptors). In contrast to other special somatosensory receptors, nociceptors exhibit high-response thresholds and persistent discharge to supra threshold stimuli without rapid adaptation and are associated with small receptive fields and small afferent nerve fiber endings. Following local injury, the nociceptors become hypersensitive to noxious stimuli, a process specified as peripheral sensitization. This neurophysiological response is probably mediated by the release of algogenic substances in the site of local tissue injury and triggers several events: local vasodilation, oedema, spreading vasodilation, hyperalgesia in the injured area (e.g. decreased threshold to noxious stimuli, primary hyperalgesia) and spread of these changes to uninjured areas (secondary hyperalgesia). Hyperalgesia refers therefore to the responses of the subject and not to the neurophysiological changes following tissue trauma [6].

Three randomized-controlled studies have been published in patients undergoing oral surgery performed under local anaesthesia, using oral flurbiprofen [7], diflusinal [8] and naproxen [9], respectively prior to surgery versus after surgery. All three studies were not able to demonstrate any pre-emptive analgesic effect of these NSAIDs up to 24 h postoperation. In contrast to these studies, intravenous ketorolac administered before hip replacement in patients operated under general anaesthesia significantly reduced pain scores and postoperative opioid consumption up to 6 h postoperation compared to control patients treated after hip replacement surgery [10].

Administration of analgesics in order to effectively pre-empt postoperative pain should start before surgery and furthermore, this treatment should be extended into the postoperative period. Additionally, new drugs like Ltype calcium-channel antagonists (e.g. nimodipine) which cause minimal side effects when administered perioperatively intravenously, seem to be a novel approach in this direction [11]. More well-designed clinical studies are needed to evaluate pre-emptive regimens that effectively block all noxious stimuli generated during surgery and during the initial postoperative inflammatory phase. Another approach, favouring the effective blockade of central sensitization, might be the extensive use of NMDA-channel antagonists in the future. Pre-emptive analgesia, in this sense, should therefore not only be characterized by brief analgesic-sparing effects, but should also imply the possibility of reducing the incidence of chronic and neuropathic pain following surgery as well. Long-term rehabilitative benefits by preventing persistent pain syndromes have been demonstrated by Bach et al. [12]. In patients recovering from below-the-knee amputation they showed that pre-emptive analgesia provided by epidural blockade starting 72 h prior to surgical stimulation and extended into the postoperative period, effectively prevented for up to 12 months the development of chronic stump and phantom limb pain [12]. Additionally, this study implies that analgesia should be extended

not only into the early postoperative period, but in order to effectively pre-empt rehabilitative or convalescence pain following amputation, analgesic regimens could be continued at home as well, by using intravenous or epidural PCA analgesia devices, thus extending the tasks of the multidisciplinary acute pain service well beyond in-hospital activities.

Gordon *et al.* evaluated the effects of blockade of sensory input with bupivacaine for reducing postoperative pain beyond the local anesthetic duration of action. In a double-blind, placebo-controlled study, 48 patients underwent two to four third molar tooth extractions under general anesthesia, randomly receiving either 0.5% bupivacaine or saline intraoral injections without administration of systemic opioids. In addition to 24 and 48 hr postoperative pain and analgesic intake assessments, plasma beta-endorphin levels were measured at baseline, intraoperatively and at one-hour intervals postoperatively as an index of CNS response to nociceptor input. Plasma beta-endorphin levels increased significantly from baseline to the end of surgery in the saline group compared to the bupivacaine group, indicating effective blockade of nociceptor input into the CNS by the local anesthetic. Pain intensity was not significantly different between the groups at 24 hr; however, pain and self-administered oral analgesic intake was lower at 48 hr in the bupivacaine group. The results suggest that blockade of nociceptive input by administration of a long acting local anesthetic decreases the development of central hyperexcitability, resulting in less pain and analgesic intake. Since molar tooth extraction does not usually require an incision, a mild postoperative inflammatory component is expected. The study is therefore supportive evidence for preemptive analgesia by blocking peripheral afferent neuronal barrage from the tissue injury and also reducing CNS hyperexcitability. [13]

Gottchalk *et al.* studied preemptive epidural analgesia on postoperative pain in radical retropubic prostatectomy in a randomized double-blind trial in 100 generally healthy patients. Patients received epidural bupivacaine, epidural fentanyl, or no epidural drug prior to induction of anesthesia and throughout the entire operation, followed by aggressive postoperative epidural analgesia for all patients. The epidural fentanyl or bupivacaine groups experienced 33% less pain during hospitalization compared to the control group. Pain scores in the treatment groups were also significantly lower at 9.5 weeks, but were not significantly different at 3.5 or 5.5 weeks. At 9.5 weeks, 86% of patients receiving preemptive analgesia were pain-free, compared with 47% of the patients in the control group. The authors concluded that even in the presence of aggressive postoperative pain management, preemptive epidural analgesia significantly decreased postoperative pain during hospitalization and long after discharge.[14]

Katz *et al.* prospectively studied the effects of preincisional epidural fentanyl in 30 ASA II patients undergoing elective thoracic surgery through a posterolateral thoracotomy incision in a randomized, double-blind manner. Epidural catheters were placed via the L2–L3 or L3–L4 interspaces preoperatively, and placement was confirmed with lidocaine. The treatment group received epidural fentanyl (4 μg·kg– 1, in 20 mL normal saline) before surgical incision, followed by epidural normal saline (20 mL) infused 15 min after incision. The control group received epidural normal saline (20 mL) before surgical incision, followed by epidural fentanyl (4 μg·kg–1, in 20 mL normal saline) infused 15 min after incision. No additional analgesics were given before or during the operation, which was performed under a general anesthetic. Postoperative analgesia consisted of patient controlled *iv* morphine. Pain scores were significantly lower in the treatment group at six hours after surgery, by which time plasma fentanyl concentrations had decreased to subtherapeutic levels (less than 0.15 ng·mL– 1) in both groups. This low plasma opioid concentration explains the ineffectiveness of the preemptively administered fentanyl to reduce long-term central sensitization.[15]

Richmond *et al.* performed a randomized, double- blind study comparing the effects of parenteral morphine given before or after total abdominal hysterectomy in 60 patients. Morphine 10 mg was given either intramuscularly one hour preoperatively, intravenously at induction of anesthesia, or intravenously at closure of the peritoneum. Morphine consumption was significantly reduced in the second group for 24 hr postoperatively compared with the last group. Pain sensitivity around the wound was reduced in both preoperative treatment groups compared with the last group. The authors concluded that preemptive analgesia with *iv* morphine prevented the establishment of central sensitization during surgery, and reduced the postoperative pain, analgesic requirements, and secondary hyperalgesia.[16]

Conclusion:

Pre-emptive analgesia is not a new concept, but dates to the early twentieth century. It involves delivery of analgesic therapy that precedes, adequately blocks, and outlasts the nociceptive stimuli that accompany tissue injury. The aim is to prevent the peripheral and central sensitization that occurs in response to painful stimuli, while leaving physiological pain responses intact. Such an effect reduces primary and secondary hyperalgesia, allodynia and the receptive field changes of dorsal horn cells. While opioids, NSAIDs, local anesthetics, alpha-2 agonists and NMDA receptor antagonists are considered the main agents in the preemptive analgesic arsenal, a variety of other potentially beneficial agents are under investigation. Until further data are complete, the presently available analgesics administered correctly (on time, for the appropriate duration, and in the proper dosage and manner) can improve patient comfort, decrease postoperative morbidity and have the potential to effect health care savings.

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