A crucial administration timing separates between beneficial and counterproductive effects of opioids on postoperative pain

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Background

Tissue injury leads to sensitization of peripheral and central pain pathways, which in turn, enhances clinical pain, including acute postoperative and post traumatic pain. Indeed, studies have shown that painful surgical procedures, mainly but not only those involve nerve injuries, sensitize pain pathways and often result in high levels of postoperative pain [21]. Not surprisingly, about two-thirds of patients who undergo surgery report moderate to severe early postoperative pain [7].

In an attempt to attenuate sensitization of pain pathways and subsequent post-operative pain, analgesic techniques and drugs are often used either before during or after surgery. This includes opioid drugs, which are often administered chronically for the management of chronic (sometimes preoperative) pain, preemptively (immediately before surgery has begun), during surgery (while tissue injury is ongoing) or postoperatively for managing already existing pain.

Although the role of opioid therapy in managing chronic pain is controversial, there is a clear consensus regarding using opioids as the most effective weapon for controlling acute moderate to severe pain around surgery, in many patients [3]. However, in this article we present a new concept, which identifies a crucial administration timing that separates between beneficial and counterproductive effects of opioids on postoperative pain: if administered before surgery ends - either chronically, preemptively or during surgery opioids produce unfavorable outcome, measured by increased post-operative pain intensity and/or by higher opioid consumption. This is in strict contrast to their analgesic effect when administered after surgery has ended. Although observations on each of these unfavorable effects have already been reported separately, the
broader aspect of this new concept is that if present in central pain pathways while injury occurs, opioids augment acute post-operative pain.

**Evidence for counter-productivity of opioids if administered before surgery ends**

(1) **Chronic pre-operative use of opioids and acute post-surgical pain**

At least four studies tested the effect of chronic (4-8 weeks) use of opioids prior to surgery as compared to the use of non-opioid analgesics, on acute postsurgical pain, postsurgical opioid analgesic consumption and duration of hospital stay [1, 5, 18, 22]. Three of these studies included patients undergoing arthroplasty surgeries and one had patients with mixed types of operations (head and neck, shoulder, back, hip, knee). Although methodological limitations in these studies clearly exist, such as lack of randomization, no clear documentation of self-administrated opioid doses and possibly lack of adequate power in some of them, all four studies yielded less favorable results for the opioid treated groups compared to controls. This was evident by increased postoperative pain (both at rest and when walking), increased opioid consumption, longer hospitalization, higher rates of intractable pain and/or stiffness after surgery and slower rate of post-operative pain resolution. Taken together, these results suggest that chronic pre-operative use of opioids actually worsens acute post-surgical pain.

(2) **Preemptive analgesia for post-operative pain**

Two large scale meta-analyses were aimed to determine whether preemptive analgesic interventions are more effective than initiating the same analgesic therapies after surgery in managing acute postsurgical pain [15, 17]. The first, tested the clinical evidence for the effect of timing of analgesia on postoperative pain control. A total of 93 randomized clinical trials with 3,761 patients were included in this meta-analysis, which showed no benefit for preemptive
opioid treatment [15]. The second meta-analysis used methods proposed by the Cochrane Collaboration and therefore included only 66 studies with 3261 patients. Five types of analgesic interventions were reviewed including epidural analgesia, local anesthetics, systemic NMDA receptor antagonists, NSAIDs, and systemic opioids. The primary outcome measures analyzed were pain intensity scores, supplemental analgesic consumption, and time to first analgesic consumption after surgery. Opioids were not only found to have the least favorable outcome of all the tested drugs but they also resulted in a worse outcome when administered prior to surgery as compared to post-surgically. In fact, the preemptive opioid administration showed a trend towards enhancing rather than reducing postsurgical pain as well as worsening the other outcomes [17].

(3) Opioid administration during surgery

Several studies tested the effect of opioid administration during surgery on acute postsurgical pain intensity and opioid requirements [6, 9, 19, see 23 for review]. All studies used a paradigm in which a short (fentanyl) - or an ultra-short (remifentanil) -acting opioid was administered during surgery as compared to either a placebo or a lower dose of the same opioid, administered in a randomized double-blind manner. Most studies exhibited increased postoperative morphine requirements and higher pain rates for up to 30 hours after surgery. The magnitude of the effect can be appreciated by the results of one study, which showed that virtually double postoperative morphine doses were required by patients who underwent major abdominal surgery and received higher compared to lower doses of remifentanil infusions [12]. Of particular interest is a recent trial, which compared the effects of intraoperative fentanyl versus remifentanil. Results showed higher pain intensity and increased morphine requirements in the remifentanil group during the first 24 and 48 hours postoperatively [10]. Hence, this trial suggests that in terms of the effect on
postoperative pain, not only the use of intraoperative opioids matters; the type of opioid administered intraoperatively may be of importance as well.

Noteworthy, at least two trials tested the long-term effect of opioid administration during cardiac surgery on chronic thoracic pain one year after the operation. While one study demonstrated a dose-dependent predictive long-term effect of intraoperative remifentanil [20] the other failed to show similar results [10].

Discussion

Over the last few decades, huge efforts have been made to improve post-surgical pain management, including the introduction of multi-modal analgesia, patient controlled analgesia (PCA), regional anesthesia and analgesia, and more. In spite of these efforts, the management of postoperative pain remains a significant therapeutic challenge and many patients still experience moderate to very severe post-surgical pain [7].

The most recent Guidelines on the Management of Postoperative Pain by the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists’ Committee on Regional Anesthesia, Executive Committee, and Administrative Council strongly recommend the use of a multimodal approach for the management of postoperative pain. Multimodal analgesia refers to the use of a variety of analgesic medications and techniques combined with non-pharmacological interventions. Nonetheless, these and other guidelines unanimously regard opioid analgesics as a cornerstone treatment in the management of moderate to severe pain after surgery [7].

Regardless of this consensus, the cited studies in this review draw a timeline, which sharply separates between a favorable effect of opioids on postsurgical pain when administered post-
surgery, in contrast to a counterproductive effect of the same class of drugs when administered before surgery ends. The latter encompasses both chronic and acute treatment, both preemptively and during the course of the operation. This understanding can have significant clinical implications. First, many patients undergo surgery following considerable periods of opioid therapy. Examples are severe knee or hip osteoarthritis, various types of cancer, chronic pancreatitis and more. Hence, when prescribing opioids for patients with chronic pain who are about to undergo surgery, clinicians should consider the possibility that the prescribed opioids may hamper the ability to effectively control the acute postoperative pain with opioids. Although not directly related to the main topic of this review, it is worth mentioning that the clinical outcomes of patients on chronic opioid treatment, were significantly better 6-12 months after total joint arthroplasty, among patients who were weaned of their opioids in the preoperative period as compared to those who were not [16]. Second, with regards to perioperative opioid administration, opioids should not be used for preemptive analgesia. A previously cited systematic review found opioids to be ineffective preemptively, relative to other analgesic classes such as local anesthetics, non-steroidal anti-inflammatory agents (NSAIDs) and N-methyl-d-aspartic acid (NMDA) receptor antagonists [17]. Thus, the recent American Guidelines on the Management of Postoperative Pain recommend only gabapentenoids and Cox-2 inhibitors for preemptive analgesia [7]. Third, during surgery, anesthetists commonly administer short or ultra-short acting opioids such as fentanyl, remifentanil, sufentanil, etc. along with anesthetic agents in order to better control pain at the time of surgery. While this is unavoidable, it seems to be at the cost of increased acute (and perhaps even chronic) postoperative pain. This should certainly draw attention, especially if high doses of ultrashort intraoperative opioids are
considered [13, 23]. To reduce this cost, intraoperative concurrent multimodal analgesia as well as gradual withdrawal of opioid infusion during surgery have been recommended [8, 23].

Taken together, these observations suggest that if present in the central pain pathways while tissue injury occurs, opioids augment acute post-injury (i.e. postoperative) pain, in contrast to their analgesic effect when administered after tissue injury has ended. The pathophysiological mechanisms underlying this time-related dichotomous effect of opioids are not entirely clear. Suggested explanations are that chronic or even acute opioid use before or during surgery may lead to tolerance, which may reduce the responsiveness of acute postoperative pain to opioids, resulting in the need for higher than expected opioid doses. In such a case, if the postoperative doses administered are not sufficiently high, opioid withdrawal can contribute to an enhanced pain experience after surgery [13]. An alternative explanation relates to the phenomenon of opioid-induced hyperalgesia, which may evolve rapidly, even following a short exposure to opioids, as in the case of preemptive or intraoperative opioid use [1-2, 11, 13-14, 23]. Lastly, another hypothetical explanation relates to the fact one of the mechanisms of opioid action is inhibition of afferent nerve transmission by binding to mu-opioid receptors presynaptically and postsynaptically within the dorsal horn of the spinal cord [4]. This may reduce the level of activity of descending pain inhibitory mechanisms since less pain stimuli are transmitted to the brain during opioid administration. We hypothesize that due to this effect of opioids, after surgery ends, the action of these inhibitory mechanisms remains less efficient thus causing increased post-surgical pain. In summary, evidence raises the possibility that opioid administration before rather than after painful surgical intervention serves to worsen postoperative pain or increase postoperative opioid requirement. This critical 'watershed' timeline
should be acknowledged by all caregivers involved in the care of patients who are scheduled for an operation where opioid therapy is already employed or is expected to be so.

Conflicts of interest

The authors would like to state that there are no conflicts of interest regarding this work.

References


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