Effectiveness of preemptive analgesia on postoperative pain following third molar surgery: Review of literatures

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Preemptive analgesia; Postoperative pain; Removal of mandibular third molars; Central sensitization; Peripheral sensitization; NSAIDs

Summary We investigated the efficacy of preemptive analgesia for mandibular third molar surgery by, reviewing of randomized controlled trials. In many of the studies, the preemptive use of NSAIDs before, tooth extraction demonstrated that the postoperative pain was better controlled beyond the expected, effect time, compared without such preemptive use. On the other hand, some studies reported that, compared to the administration before removal of the tooth, postoperative administration was, associated with better suppression of postoperative pain. This suggests that in postoperative pain after, removal of mandibular third molars, peripheral sensitization caused by reactive inflammation, following the tooth extraction and secondary central sensitization are more important factors than, direct central sensitization caused by surgical tissue damage. Accordingly, when a mandibular third, molar is removed, central sensitization due to tissue damage should be suppressed by, preadministration of analgesics. In order then to suppress postoperative peripheral sensitization, the, readministration of analgesics is considered more effective. Furthermore, although acid NSAIDs are, effective analgesics, the associated adverse events are of concern. Accordingly, acetaminophen (1000 mg), which, is devoid of anti-inflammatory effects but is a weak cyclooxygenase inhibitor, can be used for, preemptive analgesia administration.

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1. Introduction

In daily dental practice, removal of teeth is a common procedure. Surgery to remove the mandibular third molar is relatively invasive and is often associated with postoperative pain, swelling and trismus, which are frustrating for both patients and surgeons. In particular, postoperative pain increases the patient's suffering and anxiety, and can disrupt the homeostasis of the circulatory and endocrine systems [1–3]. Since it is also reported that postoperative pain can have a negative influence on wound healing, reliable and fast-onset analgesia is needed. For the management of postoperative pain after removal of a tooth, nonsteroidal anti-inflammatory drugs (NSAIDs) are usually prescribed. However, once severe pain occurs, it can be difficult to successfully manage the pain with analgesics. Moreover, given the potential for acid NSAIDs to induce serious side effects in some patients, the type and amount of analgesic must be carefully selected [4].

Specifically after abdominal surgery, hypersensitivity involving severe pain induced by mild skin stimuli may occur or chronic pain may be sustained. This is attributed to increased excitability in the central nervous system caused by surgical invasion or central sensitization [5,6]. Preemptive analgesia is a variety of methods used to manage postoperative pain by preventing central sensitization in advance of the surgical trauma [7]. This concept has also been utilized for the reduction of pain after removal of teeth [8].

Here, we reviewed the scientific literature to investigate the effectiveness of preemptive analgesia for the management of postoperative pain after removal of a mandibular third molar and to find more effective analgesic methods.

2. Concept of preemptive analgesia

Noxious stimuli that are strong enough to induce tissue damage can cause hypersensitivity, hyperalgesia, allodynia and abnormal paresthesia leading to the onset of pain by noninvasive stimuli. This is attributed to the combination of peripheral sensitization associated with the lowered threshold of nociceptors and central sensitization linked to the increased excitability of central nervous system [5,6].

Intractable postoperative pain is also considered to be related to these sensory disturbances. Local tissue damage and inflammation as well as various sympathetic terminal-derived chemical mediators (hydroxyl ions, noradrenaline, bradykinin, histamine, potassium ions, prostaglandins, purines, cytokines, 5-HT, leukotrienes, nerve growth factor and neuropeptides) are responsible for peripheral sensitization, which increases the excitability of dorsal horn neurons followed by central sensitization. Once central sensitization is established, signals transmitted via Aβ fibers from low-threshold mechanoreceptors are perceived as pain at dorsal horn neurons with high excitability. In addition, since Aβ fibers and C fibers from the nociceptors are under peripheral sensitization, pain is enhanced and sustained. Once central sensitization is established, patients respond poorly to analgesics [7].

In contrast, the concept of preemptive analgesia minimizes postoperative pain by preventing central sensitization even before surgery. Let us consider a simplified model of postoperative hyperesthesia. After the establishment of central sensitization due to surgical tissue damage, postoperative hyperesthesia is protracted and it takes additional time for improvement. However, if preemptive analgesia is provided before surgery, central sensitization is suppressed and postoperative hyperesthesia does not occur. On the other hand, if only postoperative analgesic treatment is provided, surgery-induced central sensitization is established. Hence, postoperative hyperesthesia is only temporarily inhibited (Fig. 1) [7].

Preemptive analgesia can be provided via several methods: prevention of input to the nociceptors by local anesthesia; inhibition of inflammation and peripheral sensitization by NSAIDs; and prevention of central sensitization by narcotic analgesics [7–11]. An effective combination of these methods may be able to suppress postoperative pain.

3. Preemptive analgesia for postoperative pain

Among the various disciplines, the fields of thoracic, abdominal and orthopedic surgery have extensively studied the effect of preemptive analgesia [12–17]. Surgery in these fields is frequently associated with postoperative hyperesthesia, allodynia and chronic pain. After surgery, a catheter can be placed and self-controlled administration of opioids (PCA: patient-controlled analgesia) is necessary for analgesia. This is partly responsible for preventing the reduced duration of hospital stays.

Many studies have confirmed the positive effects of preemptive analgesia and investigated various methods of application such as the presurgical administration of NSAIDs, or the presurgical administration of ketamine as an NMDA antagonist and peritoneal infusion of long-acting local anesthetics through abdominal incisions [13–16].

Joel et al. recruited 30 patients undergoing thoracic surgery and allocated them to two groups: one in which fentanyl was extradurally administered 15 min prior to the incision and another in which the administration was 15 min after the incision. Then, the intensity of postoperative pain (VAS: visual analog scale) and the amount of postsurgical morphine consumption (PCA) were compared. As a result, the group that received fentanyl before the incision demonstrated a significant reduction in intensity of postoperative pain and amount of morphine consumption. It was reported that this effect could be the result of the inhibition of central sensitization by preemptive analgesia [9].

In Richmond et al.’s study, 60 hysterectomy patients were classified into three groups: those receiving intramuscular
administration of 10 mg of morphine 1 h prior to surgery; those receiving intravenous administration prior to the induction of anesthesia; and those receiving intravenous administration at the time of the closure of the peritoneum. The intensity of postoperative pain (VAS), postsurgical morphine consumption (PCA) and postsurgical hyperesthesia of skin (VFT: von Frey hairs threshold) were compared. As a result, the group receiving the intravenous administration prior to the induction of anesthesia demonstrated the lowest intensity of postoperative pain. At the same time, secondary hyperesthesia was also inhibited. Accordingly, the authors concluded that this pain suppression was due to the inhibition of central sensitization [10].

On the other hand, a relatively limited number of studies cover the effects of preemptive analgesia in oral surgery other than removal of teeth [8,18–20]. In addition, the study results are not consistent.

Kato et al. compared presurgical versus end-of-surgery administration of flurbiprofen in patients undergoing oral surgery such as fixation of the fractured jaw bone and extirpation of tumors under general anesthesia and concluded that there was no significant difference in the intensity of postoperative pain between the two groups [18]. Nagatsuka et al. compared a group that received multiple analgesic treatments (rectal administration of diclofenac; intravenous administration of 0.1% butorphanol; block and infiltration anesthesia with 1% lidocaine) before surgery versus a group that did not receive analgesic treatment in patients undergoing orthognathic surgery (sagittal splitting ramus osteotomy) under general anesthesia. They reported that analgesic effects were not observed in the postanesthesia care unit [19].

Abe et al. on the other hand, compared three groups: local anesthesia; preoperative administration of ketamine; and preoperative administration of flurbiprofen, in patients undergoing maxillary sinus operation under general anesthesia, based on the intensity of postoperative pain and time to the first rescue medication. All three groups showed significantly lower postoperative pain when compared to the control group. Accordingly, they concluded that preemptive analgesia effects were observable [20].

The reported data suggests that preoperative analgesic treatment may reduce postoperative pain. For the timing of analgesic treatment, however, preoperative administration may not be consistently better. As a result, it may not be possible to validate the concept of central sensitization in oral surgery.

4. Preemptive analgesia in third molar surgery

Although several reports cover the effect of preemptive analgesia on postoperative pain after removal of mandibular impacted third molars, further discussion may be needed. So the literature regarding the effect of preemptive analgesia in third molar surgery is reviewing. The search strategy for articles of preemptive analgesia in third molar surgery was as follows. An electronic database was accessed using PubMed and Japan Medical Abstract Society Web to search for all relevant articles published between 1997 and 2012. Key words for search strategy were preemptive analgesia, postoperative pain, mandibular third molar and removal of tooth. And then the retrieved articles were filtered for inclusion criteria: at least randomized controlled trials (RCTs) in study design by a manual search.

All of the recent studies investigating preemptive analgesia effects on postoperative pain in patients undergoing removal of a mandibular third molar are randomized, prospective and placebo-controlled. The studies are largely classified into randomized, placebo-controlled trial investigating the effect of preemptive analgesic given before surgery and the other investigating the inhibitory effect on postoperative pain by comparing presurgical...
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<td>Ninomiya et al. 1999 [22]</td>
<td>n = 30 prospective randomized, parallel-group</td>
<td>LA: 2% lidocaine + adrenaline (1:80,000) infiltration</td>
<td>Flurbiprofen axietil (100 mg) Ketamine hydrochloride (0.8 mg/kg) Midazolam (0.05 mg/kg)</td>
<td>Preoperatively (30 min.) systemic intravenous</td>
<td>Removal of impacted mandibular third molar</td>
<td>Preemptive flurbiprofen produce greater postoperative analgesia than ketamine hydrochloride</td>
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<td>Ong et al. 2004 [23]</td>
<td>n = 34 prospective randomized, double blind, placebo-controlled, cross-over design</td>
<td>LA: 2% Lidocaine + Adrenaline (1:100,000)</td>
<td>Ketrolac (30 mg)</td>
<td>Preoperatively (30 min) systemic intravenous one side — the other side (ketrolac — placebo or placebo — ketrolac) wash-out period (1 month)</td>
<td>Removal of bilateral impacted mandibular third molar</td>
<td>Preemptive ketrolac extended the analgesia by approximately 2 h</td>
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<td>Morse et al. 2006 [24]</td>
<td>n = 48 prospective randomized, double blind, placebo-controlled</td>
<td>LA: 2% Lidocaine + Adrenaline (1:80,000)</td>
<td>Rofecoxib (50 mg) Ibuprofen (400 mg)</td>
<td>Preoperatively (60 min) systemic oral</td>
<td>Removal of impacted mandibular third molar</td>
<td>Ibuprofen and rofecoxib are effective as preemptive analgesics</td>
</tr>
<tr>
<td>Negishi et al. 2007 [25]</td>
<td>n = 33 prospective randomized, parallel-group</td>
<td>LA: 2% Lidocaine + Adrenaline (1:80,000) infiltration</td>
<td>Zaltoprofen (80 mg) Loxoprofen sodium (60 mg) Etodolac (200 mg)</td>
<td>Preoperatively (60 min) systemic oral</td>
<td>Removal of impacted mandibular third molar</td>
<td>Preemptive NSAID significantly reduced postoperative pain. Inhibition of COX-2 alone is insufficient for preemptive analgesia. NSAIDs acting on bradykinin or non-selective COX inhibitors are more effective for preemptive analgesia</td>
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## Table 1.2 Concise review of positive article group 2.

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<td>Murayama et al. 2009 [26]</td>
<td>Prospective; <em>n</em> = 40 randomized, placebo-controlled, parallel-group</td>
<td>LA: 2% Lidocaine + Adrenaline (1:80,000) infiltration</td>
<td>Acetaminophen (500 mg, 1000 mg) Flurbiprofen axetil (50 mg)</td>
<td>Preoperatively (30 min.) systemic oral and intravenous</td>
<td>Removal of impacted mandibular third molar</td>
<td>Preemptive NSAID significantly reduced postoperative pain. Pretreatment of acetaminophen (1000 mg) is as effective as flurbiprofen axetil (50 mg)</td>
</tr>
<tr>
<td>Ariyoshi et al. 2010 [27]</td>
<td><em>n</em> = 105 prospective randomized, placebo-controlled</td>
<td>LA: 2% Lidocaine + Adrenaline (1:80,000) infiltration</td>
<td>Zaltoprofen (80 mg)</td>
<td>Preoperatively (30 min) systemic oral</td>
<td>Removal of impacted mandibular third molar</td>
<td>Preemptive zaltoprofen significantly reduced postoperative pain</td>
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<tr>
<td>Bauer et al. 2012 [28]</td>
<td><em>n</em> = 47 (94 sides) prospective; randomized, double blind, placebo-controlled, cross-over design</td>
<td>LA: 2% Mepivacaine + Adrenaline (1:100,000)</td>
<td>Ibuprofen (800 mg) Ibuprofen (800 mg) + Dexamethasone (8 mg)</td>
<td>Preoperatively (60 min) systemic oral</td>
<td>Removal of bilateral semi-impacted mandibular third molar</td>
<td>Preemptive ibuprofen is insufficient to inhibit central sensitization. Ibuprofen with dexamethasone is more effective for preemptive analgesia</td>
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<tr>
<td>Al-Sukhun et al. 2012 [29]</td>
<td><em>n</em> = 146 prospective randomized, double blind, placebo-controlled</td>
<td>LA: 2% Lidocaine + Adrenaline (1:80,000)</td>
<td>Celecoxib (200 mg) Ibuprofen (400 mg)</td>
<td>Preoperatively (60 min) systemic oral</td>
<td>Removal of impacted mandibular third molar</td>
<td>Preemptive NSAID significantly reduced postoperative pain. Celecoxib is more effective than ibuprofen for preventing postoperative pain</td>
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## Table 2 Concise review of negative article group.

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<tr>
<td>Zacharias et al. 1996 [30]</td>
<td>n = 40 prospective randomized, double blind, parallel-group</td>
<td>GA: propofol (2–3 mg) atracurium besylate (0.5 mg/kg) alfentanil (10 μg/kg) tenoxicam (20 mg) dexamethasone (8 mg) LA: 2% Lidocaine + Adrenaline (1:100,000)</td>
<td>Diclofenac (100 mg) methadone (10 mg)</td>
<td>Preoperatively (60–90 min) systemic oral</td>
<td>Removal of impacted third molars (upper and lower, bilateral)</td>
<td>No significant differences between the three groups (placebo, diclofenac, methadone)</td>
</tr>
<tr>
<td>Jung et al. 2005 [31]</td>
<td>n = 80 prospective randomized, parallel-group</td>
<td>LA: 2% Lidocaine + Adrenaline (1:100,000)</td>
<td>Talniflumate (370 mg)</td>
<td>Pre- or postoperatively (60 min) systemic oral</td>
<td>Removal of impacted mandibular third molar</td>
<td>No significant differences between the three groups Postoperative analgesics before pain development may be adequate for postoperative analgesia</td>
</tr>
<tr>
<td>Kaczmarzyk et al. 2010 [32]</td>
<td>n = 100 prospective randomized, double blind, parallel-group</td>
<td>LA: 4% Articaine + Adrenaline (1:200,000)</td>
<td>Ketoprofen (100 mg)</td>
<td>Preoperatively (60 min) and postoperatively (60 min) systemic oral</td>
<td>Removal of impacted mandibular third molar</td>
<td>Postoperative administration of ketoprofen is more effective than pretreatment or placebo</td>
</tr>
<tr>
<td>Liporaci Jr 2012 [33]</td>
<td>n = 13(94 side) prospective randomized, double blind, cross-over design</td>
<td>LA: 2% Lidocaine + Adrenaline (1:100,000)</td>
<td>Ketoprofen (150 mg)</td>
<td>2 days before and after 3 days (every 12 h) group 1: ketoprofen + ketoprofen group 2: placebo + ketoprofen</td>
<td>Removal of bilateral impacted mandibular third molar</td>
<td>No significant differences between the preemptive treatment and control</td>
</tr>
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versus postsurgical administration of analgesic (Tables 1 and 2) [21–33].

The tooth subject to remove was an upper or lower bilateral mandibular third molar in two studies, while the others involved a mandibular third molar requiring bone removal and tooth division. Two studies adopted a cross-over study design to compare left and right sides in the same subjects [23,32]. Finally, the mode of anesthesia was a combination of general anesthesia and nerve block in one study while the other studies utilized local infiltration anesthesia alone.

The drugs investigated were mostly acid NSAIDs. Flurbiprofen and ketorolac were administered intravenously while diclofenac, talniflumate, ibuprofen, zaltoprofen, loxoprofen and ketoprofen were administered orally. In addition, rofecoxib and celecoxib as selective COX-2 inhibitors, acetaminophen with weak COX inhibition and methadone as an opioid were investigated as well [24,26,29,30]. These drugs were administered 30 or 60 min prior to removal of the tooth, and the inhibitory effect on postoperative pain was evaluated. Furthermore, when comparing the timing of administration, medications were given 60 min before and 60 min after removal of the tooth. In cases where pain was observed after the removal of a tooth, an oral analgesic was used as a rescue drug. For the studies using NSAIDs, acetaminophen was mainly used as a comparator. For the studies using acetaminophen, NSAIDs were mainly used as a comparator.

Inhibitory effect on postoperative pain was evaluated based on the pain intensity using VAS or another pain scale, time to onset of pain, amount of rescue analgesic used and patient’s overall evaluation.

All RCT studies that investigated presurgical administration concluded that there were preemptive analgesia effects (Tables 1.1 and 2) [21–29]. This conclusion was based on the fact that postoperative pain was inhibited beyond the effect duration of a given drug, that the intensity of pain was weak and that the total amount of rescue drug was reduced. Although acid NSAIDs demonstrated significant preemptive analgesia effects, Bauer et al. showed that ibuprofen alone was insufficient, while a combination with dexamethasone achieved adequate pain control [28]. COX-2 inhibitors showed conflicting results. Morse et al. concluded that it was somewhat weak when given alone [24]. Al-Sukhun et al. reported that it was better than acid NSAIDs [29]. Murayama et al. reported that an increase in the dose of acetaminophen to 1000 mg demonstrated efficacy comparable to intravenous administration of NSAIDs [26].

On the other hand, in a study comparing administration before and after removal of the tooth, postsurgical administration demonstrated longer inhibition of postoperative pain than presurgical administration [30–33]. Accordingly, it was concluded that administration before tooth removing does not provide preemptive analgesia effects (Table 2).

In addition, with regard to the side effects of NSAIDs and other drugs, mild gastrointestinal symptoms were reported. However, the majority of studies did not report any clinically significant adverse events.

5. Discussion

The effect of preemptive analgesia on postoperative pain is more likely to be seen in thoracic, abdominal and orthopedic surgery in which it is firmly established that central sensitization is due to surgical tissue damage. Accordingly, many reports are from these fields [12–17].

In the head and neck region, preemptive analgesia effects have been investigated in surgeries involving nociceptors of a relatively large area as in the case of tumor surgery, maxillary sinus surgery and orthognathic surgery. However, reports indicating central sensitization inhibition are limited [18–20].

In contrast, it is considered that various chemical mediators associated with surgical inflammation continuously stimulate local nociceptors and induce peripheral sensitization. And secondary, the inflammatory reaction may provide a source of sensory signals that could induce central sensitization. For surgery with strong reactive postsurgical inflammation, sensitized severe postoperative pain is likely to occur.

The level of difficulty involved in the surgical removal of a mandibular impacted third molar depends on the type of impaction. The majority of patients reported here underwent surgery that lasted approximately 30 min during which a mucoperiosteal flap was formed and bone removal or tooth division were needed due to the status of the tooth impaction. Thus, these can be considered as a medium level of difficulty. Therefore, compared to thoracic and abdominal surgery, the surgical area was limited and surgical tissue damage smaller. On the other hand, since the surgical invasion was reached to the bone, it can be considered that the surgical stimulations induced peripheral sensitization due to postsurgical reactive inflammation, instead of direct central sensitization.

Many RCT studies confirmed the inhibition of postoperative pain through the administration of NSAIDs before removal of the tooth [21–29]. This is attributed to the inhibition of central sensitization resulting from tissue damage at the time of removal of the impacted third molar and the inhibition of peripheral sensitization resulting from inflammation after tooth removal. The effect on the latter is rather strong and presurgical administration of NSAID is considered to induce preemptive analgesia by inhibiting peripheral sensitization.

On the other hand, in several studies, administration after tooth removing was deemed more effective than before tooth removing [31–33]. This is presumably because of the extended inhibition of reactive inflammation by the postsurgical administration. In these studies however, the postsurgical administration of analgesic was conducted prior to the onset of pain. Since peripheral sensitization induces central sensitization anyway, its prevention is considered to be a preemptive analgesia effect in a broad sense.

In conclusion, for the removal of mandibular third molars, central sensitization due to tissue damage can be inhibited by the presurgical administration of an analgesic. Subsequently in order to inhibit postsurgical peripheral sensitization, analgesia is administered again. This is considered to be a more successful method for suppressing postoperative pain.

References


