Application of sequential multimodal analgesia before and after impacted mandibular third molar extraction: Protocol for a randomized controlled trial

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ABSTRACT

Background: Several analgesics have been applied under various protocols to control the moderate-to-severe postoperative pain caused by the surgical extraction of an impacted mandibular third molar. However, a consensus on optimal pain management while minimizing side effects is yet to be reached.

Methods: This multi-center, prospective, double-blind, randomized controlled trial aims to evaluate the efficacy and safety of sequential multimodal analgesia combined with postoperative zaltoprofen along with multiple preemptive analgesics. A total of 80 participants with bilateral impacted mandibular third molar from two hospitals were randomized into two groups. Two surgical extractions were performed at one-month intervals, and in a crossover design, celecoxib or tramadol/acetaminophen was administered before one extraction and placebo before the other extraction. Following extraction, all subjects took zaltoprofen for 5 days. The outcome measures included pain at specific times, time and intensity of the first pain onset after extraction, need of rescue drugs, and occurrence and frequency of side effects.

Conclusions: This ongoing clinical trial was designed to provide evidence regarding a new protocol for effective postoperative pain management of a commonly performed surgical extraction. The results of this study will provide guidance to clinicians regarding the timing and combination of oral analgesics in various oral surgeries performed under local anesthesia.

Trial registration: KCT0005450, registered on October 7, 2020.

1. Introduction

The third molar is the last tooth that erupts among human dentitions, generally between the ages of 18 and 24 years. Throughout the process of evolution, the size of the human jawbone has gradually decreased, and the insufficient stimulation of jawbone growth because of changes in eating habits and decreased mastication tendencies often result in the partial or complete impaction of teeth due to the lack of space [1,2]. In particular, the impaction of the mandibular third molar occurs most frequently, and according to a meta-analysis study in 2016, the global prevalence of the impaction of the mandibular third molar is approximately 24.4%, with reports ranging from 3.08% to 68.60% in various population groups [3,4]. Although the impacted mandibular third molar

(iMnM3) is sometimes asymptomatic, it may cause problems, including dental caries, pericoronitis, periodontitis and root resorption of adjacent teeth, cysts, and tumors; hence, its surgical extraction is one of the most common procedures performed in dental clinics [5–7].

The surgical extraction of an iMnM3 is an invasive procedure accompanied by odontotomy and ostectomy following flap elevation, and its most common complication is postoperative pain [8,9]. Conventionally, pain is controlled via oral analgesic administration after surgical extraction; however, there remains a prevalence of cases with moderate-to-severe postoperative pain after the effect of anesthesia has worn off [10]. This is attributed to the tissue damage that occurs during tooth extraction, which elevates peripheral sensitization due to the secretion of inflammatory chemical mediators and the sequential

increase in the excitability of the dorsal horn neurons along the pain transmission pathway, thereby inducing central sensitization [11,12]. When central sensitization occurs, the pain threshold is lowered, resulting in postoperative hyperalgesia or allodynia, and sometimes, atypical pain [13].

Preemptive analgesia is defined as the administration of an analgesic prior to an invasive procedure to relieve postoperative pain and prevent central sensitization [14,15]. In particular, it is essential to reduce the secretion of the inflammatory chemical mediators secreted due to peripheral tissue damage and block the mechanism by which pain signals are transmitted to the ascending neurons [15,16]. While the usefulness of preemptive analgesic therapy has been widely established in various surgical fields, including chest, abdominal, and orthopedic fields, there have been conflicting reports on its effectiveness in the maxillofacial area [16–19]. Several prospective, randomized, and double-blind studies have evaluated the effectiveness of preemptive analgesic administration versus conventional analgesic therapy during the surgical extraction of iMnM3 with inconsistent conclusions. In addition, there has been a report stating that the analgesic effect of preemptive analgesic administration wears off more rapidly than that of conventional postoperative analgesic administration [19,20].

Multimodal analgesia is performed by combining drugs with different mechanisms, such as non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and local anesthetics, to increase the analgesic effect while minimizing the drugs' side effects. Especially in surgical procedures accompanied by moderate-to-severe postoperative pain, non-opioid analgesics are employed to minimize opioid use and opioid-related side effects [21–24]. In the surgical extraction of iMnM3, usually NSAIDs, acetaminophen (AAP), and opioids are prescribed for post-surgery pain management; however, a clear consensus on optimal pain management is yet to be reached [25,26].

The authors hypothesize that sequential multimodal analgesia will relieve postoperative pain more effectively than single postoperative analgesia without significant adverse events. The aims of this randomized controlled study are to evaluate the efficacy and clinical safety of sequential multimodal analgesia, using either celecoxib or tramadol/AAP preemptively and zaltoprofen postoperatively.

2. Materials and methods

2.1. Study design

This is a multi-center, prospective, randomized, double-blind, placebo-controlled, crossover study. A total of 80 participants are planned to be recruited through competitive enrollment in two hospitals in South Korea. This is a crossover within-subject study, wherein each subject will take either an analgesic or placebo before extraction during the two appointments at 1-month intervals. The study protocol was approved by the Institutional Review Board of Chungnam National University Hospital (IRB No. 2020-06-042) in accordance with all relevant requirements of the Declaration of Helsinki. This is a currently ongoing clinical trial after registration with Clinical Research Information Service (KCT0005450; https://cris.nih.go.kr) on October 7, 2020. This trial is being monitored regularly by the Safety Monitoring Board of Clinical Trial Center in Chungnam National University Hospital.

2.2. Eligibility criteria

The participants were recruited from the patients who visited the hospitals for iMnM3 extraction, with a similar degree of impact on both sides of the mandible. The participants who meet the following inclusion criteria are eligible:

1. Healthy adult males and females without systemic diseases and aged 19–40 years

2. No abnormal findings on blood tests (complete blood count, activated partial thromboplastin time, prothrombin time) performed within the last 3 weeks
3. Based on Pell & Gregory classification [27], corresponding to class II or III for ramus relationship, and level A, B, or C for depth of teeth (both iMnM3 are classified into the same category and require surgical extraction)
4. Provision of signed informed consent

Participants who meet the following exclusion criteria will not be enrolled:

1. Past history of allergy for drugs used in this study
   (celecoxib, tramadol, AAP, cefaclor, zaltoprofen, rebamipide)
2. Presence of pericoronitis or benign lesions on the iMnM3
3. Need to take the analgesic drugs continuously until the time of extraction
4. Pregnant or lactating person
5. Smokers and others who are judged to be inappropriate to participate in clinical trials

In case a subject requires additional medication due to complications after tooth extraction, which may affect the study data, or needs to discontinue the study, the subject will be dropped out of the trial. In addition, a dropout will include any case wherein the participant meets any of the exclusion criteria during the study period or if consent is withdrawn.

2.3. Sample size estimation

The sample size was calculated using the G* power online calculator. According to previous literatures on the surgical extraction of iMnM3, a sample size of 34 subjects for each group was required to provide the trial with a 95% power for detecting the superiority of the experimental treatment over control, at a two-sided alpha level of 5%. We assumed a 15% dropout rate. Based on this, a sample size of 80 participants (40 subjects per group) was planned to be recruited.

2.4. Randomization, allocation concealment, and blinding

The participants were randomly assigned to either group A (celecoxib vs. placebo) or B (tramadol + AAP vs. placebo) based on the preemptive analgesia administered. Randomization by group to either group A or B was determined by a random number table in a 1:1 ratio according to the recruitment order. The order of analgesics/placebo administration for each subject within a group was decided by a coin toss, and the results were stored and managed independently by one of the unblind researchers. This unblind researcher was only responsible for determining the group allocation of the participants and the order of drug administration, thereby maintaining a double-blind state of the entire study and avoiding outside exposure.

2.5. Interventions

The participants were instructed to not take any pain-relieving medication from 3 days prior to the tooth extraction. The overall flow of the study is summarized in a schematic diagram (Fig. 1).

At visit 1, each participant took an analgesic or a placebo, according to the assigned group, 1 h before the tooth extraction. After 1 h, one of the three experienced oral and maxillofacial surgeons performed block anesthesia of the inferior alveolar nerve using 2% lidocaine with 1:1000 000 epinephrine, followed by the conventional procedures (including flap elevation and ostectomy, and odontotomy if needed) to perform unilateral iMnM3 surgical extraction. One hour after the tooth extraction, zaltoprofen as an analgesic, antibiotics, and gastroprotective agents were administered for 5 days. From the time of local anesthesia
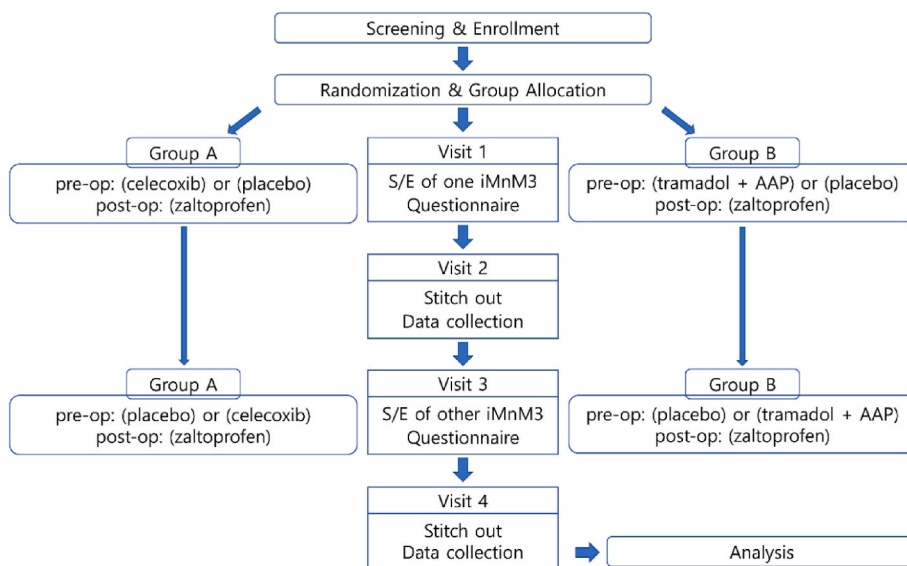
Fig. 1. Flow diagram illustrating the study process. S/E indicates surgical extraction.

administration until 3 days after tooth extraction, the degree of pain per time period, need of rescue drugs, and occurrence of side effects were recorded on the questionnaire as per the visual analog scale (Fig. 2). After a week, during visit 2, the stitches were removed and the completed questionnaire was submitted.

Visit 3 occurred after a wash-out period of at least four weeks. A placebo or an analgesic was taken 1 h before the tooth extraction, according to the assigned group, and the same surgeon extracted the opposite iMnM3 after block anesthesia of the inferior alveolar nerve. The subsequent process was the same as in visit 1, and a week later, during visit 4, the stitches were removed, and the completed questionnaire was submitted. The administration regimen of each group is shown in Table 1.

2.6. Objectives and outcome measures

The primary study objective is to evaluate the efficacy of sequential multimodal analgesia before and after the extraction of iMnM3 compared with postoperative analgesia alone. The corresponding outcome measures are as follows:

Table 1
Drug regimen for each group. Rescue drugs are additionally taken when postoperative pain is severe and unbearable even after taking postoperative zaltoprofen. *tid p.o.* means that the drugs are taken orally three times a day.

	Preoperative medication (Take 1 h before extraction)	Postoperative medication (Take 1 h after extraction, up to ~5 days)
Group A	Celexib 1C (celecoxib 200 mg) or placebo 1C	Ceclin 1C (cefaclor 250 mg) Zyrofen 1T (zaltoprofen 80 mg)
Group B	Trimacet 1T (tramadol HCl 37.5 mg + AAP 325.0 mg) or placebo 1T	Rebamipide 1T (rebamipide 100 mg) *tid p.o.* for 5 days
Rescue drug	AAP 300 mg	

- Intensity of pain at certain timepoints (when injecting local anesthetics/1,2,3,6,9,12,24,48,74 h post-extraction).
- Intensity of pain and the time taken from the end of an extraction to the first moderate pain onset.
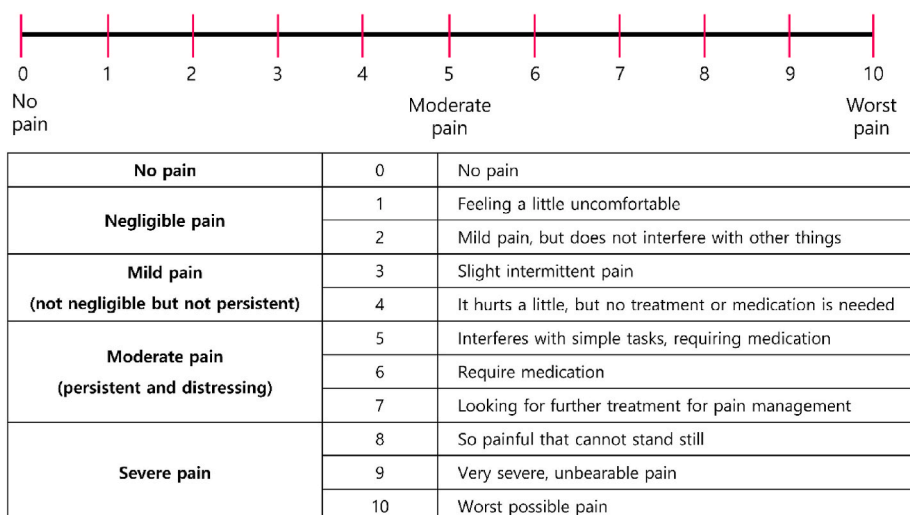- Need for a rescue drug (the number of times required and time taken after extraction).

Fig. 2. Visual analog scale and its description used in this study.

The secondary study objective is to evaluate whether there is a significant increase in side effects due to the addition of preemptive analgesics to postoperative analgesics. The corresponding outcome measures are as follows:

● Presence and frequency of adverse events, such as gastrointestinal disturbance, nausea, vomiting, and delayed hemorrhage.

The presence of side effects and adverse events was evaluated at every visit. Subjects were also instructed to contact the researchers and clinical research coordinators to report any serious adverse events that occurred during the study.

2.7. Data collection

Outcome measures were collected by filling out a questionnaire provided to the subjects. In addition, age, sex, weight, height, and blood test results were investigated as basic patient information following the registration of the participants in the study. On the day of the extractions (visits 1 and 3), vital signs (blood pressure and heart rate) were measured prior to the extraction, and the duration of the surgical extraction (incision start time–suture completion time) was recorded after extraction. The data were recorded in individual case report forms by the clinical research coordinator, and only authorized members were allowed to access the database.

2.8. Statistical analysis

For the baseline characteristics of each group, categorical variables were expressed as observation frequency and percentage, and continuous variables were expressed as mean ± SD. For all the groups, the duration of operation, pain intensity per time period, time taken for the onset of moderate pain following tooth extraction and pain intensity at that time for both control and test groups were analyzed using an independent *t*-test. When data was insufficient or did not satisfy the assumptions required for a parametric test, the corresponding non-parametric test, Mann–Whitney U or Wilcoxon rank-sum test, was used. The need and frequency of rescue drug administration and occurrence and frequency of side effects were expressed in terms of observed frequency and percentage and were compared using $\chi 2$ or Fisher's exact test. Unless otherwise specified, all analyses were performed with a two-tailed test at the significance level of 5%, and the missing values were not replaced.

3. Discussion

For rapid recovery following a surgery, it is necessary to enable early functioning via optimal pain relief, considering the surgery's characteristics. Moreover, effective pain management has been proven to speed up ambulation and reduce the hospitalization period compared with control groups in various fields [22,28]. While dental pain encompasses a small range of tissue injury, it is relatively more painful than surgeries with a larger range of tissue injury, such as thoracotomy, thus requiring more active pain control [29]. Most of the studies on analgesic effects in the dental field have been conducted on the surgical extraction model of the iMnM3 [30]. Although this is a common procedure, it is relatively invasive, and patients often complain of moderate-to-severe postoperative pain even while taking pain medication. Moderate-to-severe pain following tooth extraction under local anesthesia occurs within 12 h after surgery, peaking at 6–8 h [10,31]. In dental clinics, pain control after surgical extraction conducted under local anesthesia is usually performed with oral analgesics, with NSAIDs, AAP, tramadol, and opioids being most commonly prescribed [25,30–32].

The Oxford League Table summarizes several systematic reviews and lists the single-dose analgesics providing at least 50% pain relief lasting 4–6 h in patients experiencing severe-to-high acute postoperative pain.

According to this data, NSAIDs are the most effective in managing postoperative pain. Opioids or AAPs alone are not as effective as NSAIDs, but show enhanced effect when combined with other analgesics, and this result was similar for dental pain [33,34]. In clinical practice, NSAIDs are widely prescribed as a drug of choice after tooth extraction due to their analgesic and anti-inflammatory effects by inhibiting cyclooxygenase (COX) enzyme activity and reducing peripheral inflammatory reactions [35]. In this study, zaltoprofen was selected as the postoperative analgesic. Zaltoprofen is one of the propionic acid derivatives and is also a selective COX-2 inhibitor. So it is known as a potent anti-inflammatory and analgesic drug with little gastrointestinal disturbance [36].

The step-by-step afferent pain pathway by noxious stimuli is as follows: The first step is transduction, which is the conversion of mechanical, thermal, and chemical stimuli applied to the periphery into an electrical signal (action potential) by the nociceptors present at the afferent nerve endings; in the second step (conduction), the action potential travels through axons to the pre-synaptic terminal and reaches the spinal cord; in the third step (transmission), signals are transmitted from first-order neurons to second-order neurons via synapses; in the fourth step (modulation), during the process of transmitting pain information, it is regulated, processed, and modified by the neurons and glial cells of the brain and spinal cord; in the final step, pain signals arrive at the somatosensory cortex of the brain, which the brain perceives as pain, leading to central sensitization and hyperalgesia [37–39].

The objective of sequential administration of multimodal analgesia is to obtain the advantages of both preemptive and multimodal analgesia. The main principle of preemptive analgesia is to reduce the secretion of inflammatory mediators and suppress the transmission of pain signals through the administration of analgesics before the occurrence of tissue damage [16,40]. The purpose of multimodal analgesia is to obtain a synergy of analgesic effect with fewer side effects by inhibiting pain reception at various locations occurring throughout the afferent pain pathway [21,41]. Specifically, the transduction of pain signals can be inhibited by NSAIDs or local anesthetics, conduction can be slowed by local anesthetics, and modulation and perception can be regulated by opioids, AAPs, anticonvulsants, and antidepressants [42]. Hence, we believe that the advantages of preemptive analgesic administration can be better utilized to obtain multimodal analgesia before and after surgery than by only a single-dose analgesic administration after surgery. So, this study was conducted in a split-mouth design targeting patients who had similar level of both lower third molar impaction according to the Pell & Gregory classification. Pell & Gregory classification categorizes the level of impaction by relative positions of the ramus and the occlusal surface of the lower second molars [27].

Celecoxib 200 mg was selected as the preemptive analgesic for group A and a combination of tramadol HCl 37.5 mg + AAP 325.0 mg was selected for group B. Celecoxib was selected to minimize the synthesis of inflammatory mediators following incision, and zaltoprofen was taken for its continuous inhibition 2 h after the surgery. Celecoxib is a COX-2 selective inhibitor that better minimizes the risk of gastrointestinal complications compared with non-selective NSAIDs [43,44]. The tramadol/AAP combination was chosen because opioid and AAP combinations have been previously reported to be effective for pain control after tooth extraction; thus, tramadol, a relatively weak opioid, was chosen, and half the normal single dose was taken to minimize side effects, such as drowsiness and headache. In particular, AAPs mainly inhibit the central COX (COX-3), and although it has a weak anti-inflammatory effect, a good synergy without increasing side effects can be obtained when used with NSAIDs [45,46].

The main hypothesis of this study was that sequential multimodal analgesia would relieve postoperative pain more effectively than single postoperative analgesia without significant adverse events. The primary objective of this clinical trial is to evaluate the efficacy of additional pre-administration of celecoxib or tramadol/AAP as part of multimodal analgesia in third molar surgery. If positive results for the hypothesis are

obtained through this trial, a new study would be possible to replace postoperative analgesic with other NSAIDs in countries where zaltoprofen is not used. The time of preemptive drug administration was determined to be 1 h before tooth extraction considering the existing papers on preemptive analgesia [19]. As of yet, to the best of our knowledge, no clinical trials have been reported on pain management after extraction of impacted teeth employing the same drug combination and study design used in the present study.

4. Conclusions

This paper describes a prospective, randomized, double-blind, placebo-controlled, crossover study to find a pain management method with fewer side effects while effectively suppressing pain after the surgical extraction of iMnM3. If sequential multimodal analgesia combining celecoxib, tramadol, AAP, and zaltoprofen is found to have a positive effect, it will become a new alternative for optimal pain management after tooth extraction.

Author contributions

Soo-Ho Kim contributed to the conceptualization, methodology, and writing – original draft. Somi Kim contributed to the conceptualization, methodology, and writing – original draft. Yoon-Seon Kim contributed to the methodology and writing – review & editing. Mi-Kyoung Song contributed to the visualization and writing – review & editing. Ji-Yeon Kang contributed to the conceptualization, methodology, and writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101078.

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