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Efficacy of Preemptive Ibuprofen Combined with Paracetamol in Lower Third Molar Surgery: A Double-blind Randomized Controlled Clinical Trial

Pichai Vittayakittipong[1], *Thippapa Areewattana*[2]
[1]*Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Prince of Songkla University, Thailand*
[2]*Sathing Phra Hospital, Thailand*

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Corresponding Author: ***Associate Professor Pichai Vittayakittipong,*** *Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Prince of Songkla University, Songkhla 90110, Thailand. (E-mail:* ***pichai.v@hotmail.com****)*

Abstract

Objectives: The aim of this study was to assess the preemptive analgesic efficacy of ibuprofen 400 mg combined with paracetamol 500 mg after lower third molar surgery.

Methods: A randomized double-blinded controlled clinical trial was conducted. Patients were randomized into the preemptive group (ibuprofen 400 mg combined with paracetamol 500 mg) and the control group (placebo) using block randomization. Preemptive drugs and the placebo were administered to patients orally 1 hour before undergoing lower third molar surgery. The following outcomes were assessed: postoperative pain assessed with visual analog scale (VAS), number of patients who received rescue medications, number of pain-free patients, time at first requirement for rescue medications, number of patients who received rescue medications, and drug satisfaction.

Results: The 48 patients were randomized, 24 to the control group and 24 to the preemptive group. The time until first requirement for rescue medications in the preemptive group was significantly longer than that of the control group (p=0.003). The other outcomes were not significantly different between groups.

Conclusions: Preemptive ibuprofen 400 mg combined with paracetamol 500 mg did not reduce postoperative pain after lower third molar surgery; however, the preemptive therapy delayed the time required for rescue medications.

Keywords: ibuprofen, lower third molar surgery, paracetamol, preemptive analgesic

Introduction

Lower third molar surgery is a common invasive dental procedure in the outpatient setting. It is often accompanied by moderate to severe pain, facial swelling, and limited mouth opening postoperatively. Postoperative pain increases the patient's discomfort and anxiety, and can also disrupt the homeostasis of the circulatory and endocrine systems. The management of postoperative pain after the removal of a tooth is therefore very important.[1,2] Surgical removal of an impacted mandibular third molar causes pain and has been used as an excellent clinical model for pain studies.[3] It is well documented that the pain after removal of an impacted third molar has a short duration and reaches a maximum intensity in the early postoperative period. Seymour *et al*.[4] found that pain usually occurred during the first 12 hours after third molar surgery. The maximum pain level presents 6-8 hours postoperatively under local anesthesia.[3,5]

Oral analgesics such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase (COX)-2-selective inhibitors, and opioids are available for the treatment of acute pain, with a combi-

nation of these agents usually being prescribed. Several randomized controlled trials have indicated that these analgesic combinations act at multiple pain receptor sites resulting in greater pain relief than a single analgesic after third molar surgery.[6-8] Taking analgesics preoperatively or preemptively is a method used to reduce pain postoperatively. The concept of preemptive analgesia was first described by Crile[9] at the beginning of the previous century and was based on clinical observations. The revival of this concept involved a series of animal studies initiated by Woolf and Chong.[10] Preemptive analgesia minimizes postoperative pain by preventing central sensitization of the central nervous system (CNS) before surgery, resulting in a good response to pain.[5,11,12] However, previous studies on the efficacy of preemptive analgesics are controversial[13-16], especially combinations of paracetamol and ibuprofen. Paracetamol and ibuprofen are both cheap, readily available, and widely used in dentistry. The pre- or postoperative administration of either ibuprofen or paracetamol alone does not seem to reduce pain as effectively as the drugs in combination.[8,17,18] The results of two quantitative systematic reviews indicated that the combination of ibuprofen and paracetamol may be effective because of their synergistic effects and fewer side effects[6-8], but these studies focused on only postoperative administration of the drug combination. Currently, few studies exist that described the use of this drug combination as preemptive analgesia in lower third molar surgery. Therefore, the aim of this study was to evaluate the efficacy of ibuprofen 400 mg combined with paracetamol 500 mg as preemptive analgesia after lower third molar surgery.

Materials and Methods

Clinical trial design

A randomized double-blinded clinical trial was conducted on a series of patients admitted for third molar surgery at the Faculty of Dentistry, Prince of Songkla University, from September 2019 to April 2020. The study was approved by the Ethics Committee of the Faculty of Dentistry, Prince of Songkla University, Thailand (EC6204-011). The Thai Clinical Trial Registration number is TCTR20210604006. An estimate for the sample size was calculated using a two-sample comparison of means using data from Kimiaei Asadi H. *et al*.'s 2017 study.[19] The sample size was calculated as 34 patients, using a power of 95% and a type I error rate of 0.05. Patient recruitment was conducted according to the 2010 CONSORT (Consolidated Standards of Reporting Trials) protocol (Figure 1).

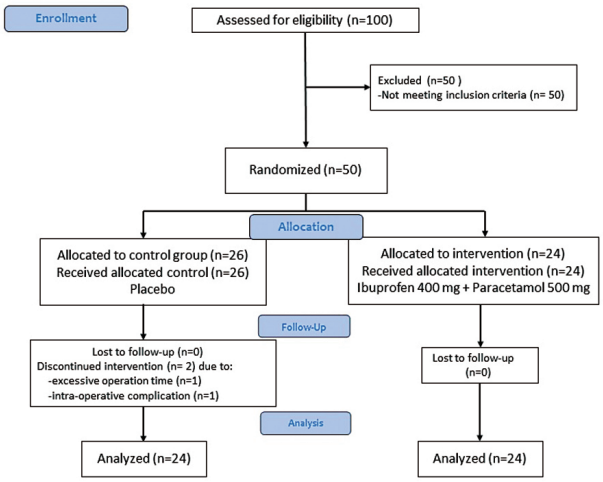

Figure 1: Flowchart of patient recruitment according to the 2010 CONSORT protocol.

The inclusion criteria of this study were: 1) American Society of Anesthesiologists (ASA) classification I and II, 2) age range of 18-30 years, 3) clear indications for removal of lower third molar, and 4) moderate difficulty of lower third molar removal. The indications for lower third molar surgery included: preparation for orthodontic treatment, prevention of pericoronitis, prevention of caries, prevention of periodontitis of adjacent teeth, and prevention of cyst or tumor. All impacted lower third molars were classified as "moderately difficult" using Pederson's difficulty index (score 5-6).[20] Patients who presented with an allergy or hypersensitivity to ibuprofen or paracetamol, had a history of local pericoronitis, systemic infection, cardiovascular disease, smokers, pregnant women, or anyone using medications which might interfere with their perception of pain were excluded from the study. Fifty patients recruited to the study met the criteria for surgical removal of the lower third molar. The position and angulation of the impacted lower third molar were classified by the Pell and Gregory[21] and Winter's[22] classification systems, respectively.

Patient randomization into two groups using blocks of eight was performed by a formal research assistant who also generated the random allocation sequence, enrolled, and assigned patients to receive preemptive drugs or a pla-

cebo. The control group received a placebo resembling the ibuprofen and paracetamol combination and the preemptive group received ibuprofen 400 mg and paracetamol 500 mg. Two groups of drug sachets were prepared. One group was composed of identical tablets of ibuprofen and paracetamol (placebo) prepared by the Faculty of Pharmacy, Prince of Songkla University (Hatyai, Songkla, Thailand); the other group (test drugs) was composed of ibuprofen 400 mg (Ibrofen 400 fc, T.O. Chemical (1979) Ltd., Pathum Thani, Thailand) and paracetamol 500 mg (Tylenol, OLIC (Thailand) Limited, Ayutthaya, Thailand). The sequence number of each patient was labeled on the sachet.

Data collection and operation

Baseline data, including gender, age, weight, and height, were collected from all study participants. The drugs inside the blinded sachet were taken orally one hour prior to surgery. All patients and the operator were blinded to which medications were taken. Surgery was performed by the same surgeon for all participants under local anesthesia with mepivacaine hydrochloride 2% and adrenaline 1:100,000 (Scandonest 2% Special, 20 mg/ml; Septodont UK Ltd.). Injection of the local anesthetic was performed 10 min before surgery and limited to two cartridges. If any subject needed additional local anesthesia during surgery, they were excluded from the study. A triangular flap was created from the distal lower first molar to the lower third molar by blade no. 15. A flap was retracted by molt no. 9. The bone around the impacted tooth was removed with a round carbide bur and then the impacted tooth was sectioned with a cylindrical carbide bur. Finally, the tooth was completely removed. The operation field was irrigated with 0.9% normal saline solution. Wound closure was performed with 3-5 stitches using 3-0 black silk. All patients received instructions for postoperative care.

The duration of each operation (time from the first incision to completion of the last suture) and volume of local anesthetic administered were recorded. The operation time was limited to 1 hour. The pain intensity score was recorded 2 hours after surgery with subsiding local anesthetic effect. Each patient received rescue medications (ibuprofen 400 mg combined with paracetamol 500 mg) together with a form for recording postoperative parameters. Patients were allowed to take rescue medications if they felt pain and were instructed to record the pain intensity and the time at first requirement immediately before taking the medication. The use of other analgesics was not permitted. At the end of 24 hours post-surgery, the total number of tablets of rescue medications were recorded.

Assessment of efficacy

The following primary outcomes were recorded to assess analgesic efficacy: pain intensity at 2, 4, 6, 8, 10, 12, and 24 hours after surgery; overall pain score; number of pain-free patients per group; time at first requirement for rescue medications; number of patients who received rescue medications; and satisfaction with the drug. Patients were asked to rate their pain intensity on a 100-mm visual analog scale (VAS), from which the endpoints were defined as 0, “no pain at all”, and 100, “unbearable pain”.[23] Pain intensity was categorized into four groups: 0-4 mm = no pain, 5-44 mm = mild pain, 45-74 mm = moderate pain, and 75-100 mm = severe pain.[24] Drug satisfaction 24 hours post-surgery was graded from 0 (poor) to 100 (excellent) as a response to the following question: "How would you rate the premedication you received to delay pain?" Facial swelling and mouth opening distance were measured as secondary outcomes pre-operation and on postoperative day 2 and 7. The modified Laskin’s method was used to assess facial swelling by measurement of DHS (the distance, in millimeters, from the most posterior point of the tragus to the midpoint of the symphysis) and DHC (the distance, in millimeters, from the most posterior point of the tragus to the most lateral point on the corner of the mouth).[20] Mouth opening was recorded by measurement of interincisal distance (IID) using a ruler according to the maximum distance between the edge of the upper central incisor and lower central incisors. Symptoms related to adverse drug events such as nausea, vomiting, dizziness, headache, and insomnia were recorded. On the seventh day, the sutures were removed and the postoperative forms were collected.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (ver.23, IBM Corp., Armonk, NY, USA). The differences between the two groups regarding mean pain score, drug satisfaction score, time at first requirement for rescue medications, facial swelling, and mouth opening

were evaluated using Student's t-test for normally distributed variables, otherwise the Mann–Whitney U test was used. The chi-square test was used to evaluate differences between the number of patients who took rescue medications and the number of pain-free patients between groups. Statistical significance was set at $p<0.05$.

Results

Fifty patients were recruited to the study: 26 to the control group and 24 to the treatment group. Two patients from the control group were excluded: one patient had postoperative numbness of the lower lip due to a root of the impacted tooth being close to the inferior dental nerve, and for the other patient the duration of the operation exceeded 1 hour due to difficulty removing the root of the third molar. Therefore, 48 patients were analyzed: 24 in the control group and 24 in the treatment group. There were 31 females and 17 males. Table 1 shows participant characteristics and both preoperative and postoperative data. There were no statistically significant differences in any of these data between the two groups.

Table 2 shows parameters used to evaluate the analgesic efficacy. The only significant difference between the two groups was the time at first requirement for rescue medications, which was significantly longer in the treatment group than in the control group (604.1 vs 287.8 min, respectively; $p=0.003$). Although there was no significant difference in pain intensity at any time between the two groups, the average pain score of patients in the control group was higher than that of the preemptive group in the early postoperative period (first 4 hours). The peak pain score of control group was 17.8 mm in the first 4-hour period postoperatively, while the pain score increased to a peak 15.5 mm after 8 hours in the preemptive group (Figure 2). There was no significant difference in the peak pain intensity scores between the two groups ($p<0.05$).

Six patients did not take the rescue medications: 3 from the control group and 3 from the preemptive group. Among the control group, the average pain score peaked 2 hours post-operation at 17.0, after which the pain intensity gradually decreased until 24 hours post-operation. The average pain score of the preemptive group peaked 12 hours post-operation at 8.67. There was a statistically significant difference in pain intensity between the two groups at 2 and 6 hours post-operation ($p<0.05$); at these time points, the pain intensity was lower among subjects in the preemptive group than subjects in the control group.

In both groups, the mean DHS and DHC increased on postoperative day 2 and decreased on postoperative day 7. The changes in DHS, DHC, and IID were not statistically significant between the two groups ($p<0.05$). The interincisal distance was not significantly different between the two groups at 2 and 7 days postoperatively and neither was the change in IID on both day 2 and 7.

Discussion

Preemptive analgesia is one of the methods used to reduce postoperative pain. The well-known mechanism of preemptive analgesia involves inhibition of central sensitization due to tissue damage during surgical procedures. NSAIDs are commonly used for preemptive analgesia. Numerous studies have investigated preemptive NSAID use after third molar surgery, including the use of flurbiprofen, ketorolac, rofecoxib, celecoxib, etoricoxib, naproxen, diclofenac, and ibuprofen.[14-16,25-28] Ibuprofen is the most common NSAID used by dentists in Thailand. Studies investigating the effect of preemptive analgesia with ibuprofen after third molar surgery are controversial; some studies reported that 400 mg of preemptive ibuprofen could reduce postoperative pain after mandibular third molar surgery[14,26], while others reported no significant to reduce postoperative pain.[15] To improve the efficacy of preemptive analgesia with ibuprofen alone, one study showed that ibuprofen 600 mg combined with dexamethasone 8 mg was superior in preemptive analgesia.[15] Lau *et al*.[3] reported positive results using ibuprofen arginate 400 mg preemptively in third molar surgery, which resulted in effective pain control due to faster onset of action compared with original ibuprofen. Combination ibuprofen and paracetamol is commonly used in the postoperative period and has good efficacy in controlling postoperative pain after third molar surgery[6]; however, there are limited studies reporting the use of this combination in preemptive analgesia. One clinical trial evaluating the combination of paracetamol 600 mg, ibuprofen 400 mg, and caffeine 15 mg as preemptive analgesia after impacted lower third molar surgery showed that the combination could be used effectively to control postoperative pain; however, the study could not represent the true efficacy of ibuprofen combined with paracetamol as preemptive analgesia due to the addition of caffeine.[19] We used ibuprofen 400

Table 1: Participant characteristics and operative data for each group.

Variable	Control (n=24)	Preemptive (n=24)	*p* value
Age, mean ± SD (year)	20.7±1.9	21.1±2.4	0.50
Gender, n (%)			
Men	9 (37.5)	8 (33.3)	0.76
Women	15 (62.5)	16 (66.7)	
Weight, mean ± SD (kg)	59.1±11.9	56.2±10.9	0.39
Height, mean ± SD (cm)	164.0±8.6	161.92±9.2	0.43
Difficulty score, n (%)			
5	13 (54.1)	14 (58.3)	0.77
6	11 (45.8)	10 (41.6)	
Preoperative facial swelling, mean ± SD (mm)			
DSH* at day 0	135.5±19.2	140.9±18.1	0.28
DHC** at day 0	115.1±5.3	117.6±6.1	0.12
Preoperative interincisal distance, mean ± SD (mm)	45.1±6.7	46.0±6.0	0.62
Volume of mepivacaine, mean ± SD (ml)	2.1±0.6	2.2±0.6	0.23
Duration of operation, mean ± SD (min)	19.8±6.4	20.7±5.2	0.47

Note: * DHS, distance in millimeters from the most posterior point of the tragus to the midpoint of the symphysis; ** DHC, distance in millimeters from the most posterior point of the tragus to the most lateral point on the corner of the mouth.

Table 2: Parameters for the evaluation of analgesic efficacy.

Variables	Control group	Preemptive group	*p* value
Pain intensity, mean ± SD (mm)	10.9±8.6	11.9±10.4	0.86
Number of absolute pain-free patients (n)	0	0	-
Number of patients who took rescue medications (n)	21	21	1.00
Time to first rescue medication, mean ± SD (min)	287.81±191.17	604.05±495.93	0.003
Drug satisfaction, mean ± SD	8.47±1.53	8.53±1.39	0.96

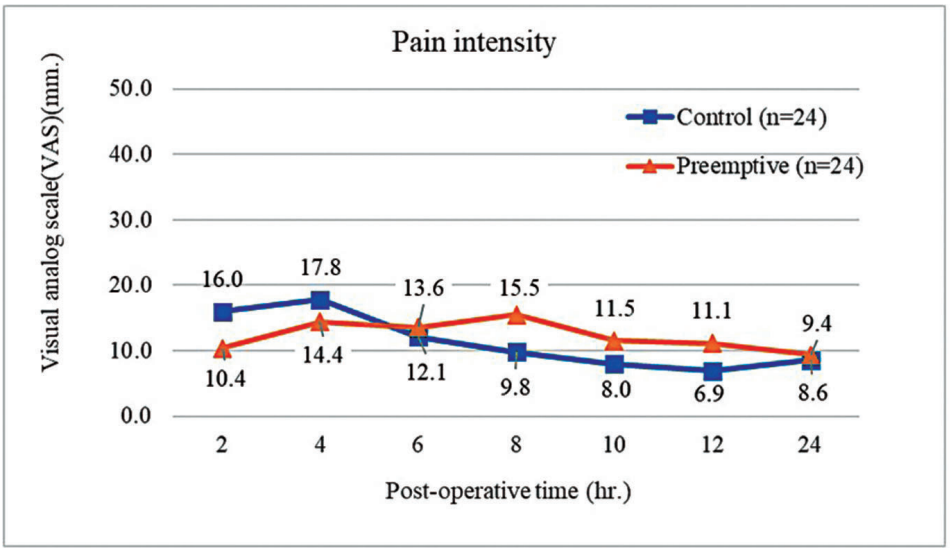

Figure 2: Line graph of pain intensity at each interval for both groups.

mg and paracetamol 500 mg because they act at the two different sites on the COX enzyme and have synergistic properties, thereby providing greater analgesic activity with fewer adverse effects than opioid-containing formulations.[6,8] Additionally, these preparations are widely available in Thailand and most Thai dentists are familiar with these drugs.[29]

The timing of preemptive analgesia varied across studies, ranging from 30 to 90 min before surgery.[14,25-27] In this study, preemptive analgesic drugs were administered 60 min before surgery in all patients because that time period corresponded to the time to peak plasma concentration of ibuprofen and paracetamol, which are 30-120 min and 60-120 min, respectively.[30] Theoretically, the plasma concentration of preemptive drugs should reach maximum levels at the time of surgical incision to reduce the release of inflammatory mediators in both the peripheral and central nervous systems; this not only has immediate analgesic effects, but also blocks the development of central and peripheral hypersensitivity, ensuring prolonged pain reduction after surgery.[31]

This study limited the volume of local anesthetic drug to no more than two cartridges and the results showed no significant difference in this volume between the two groups. This restriction was put in place because higher volumes of local anesthetic drug can cause a longer duration of local anesthesia. This restriction reduced the interference of the local anesthetics on the action of the preemptive analgesics.

In this study, the average pain intensity in the first 24 hours of both groups was lower than the average pain intensity reported in previous studies.[14-16,25-28] The reason for this finding may be that the difficulty of the impacted tooth extraction was not reported in the previous studies.[25,26,28] The difficulty of the impacted tooth extraction in this study may have been lower than in the other studies, resulting in shorter operation time and less postoperative pain.

Although the overall pain intensity in the first 24 hours was not significantly different between the two groups, the pain intensity in the control group was higher than in the preemptive group at 2 and 4 hours after surgery. Additionally, the peak pain intensity in the control group was apparent at 4 hours, while the preemptive group showed a delayed peak at 8 hours. This delayed peak in pain in the preemptive group corresponds with the delayed time at first requirement for rescue medications. The mean time at first requirement for rescue medications among the preemptive group was longer than that of the control group, and the times were longer than those reported in several previous studies.[14-16,25-28] This longer duration may allow the patient to be more comfortable after surgery, especially at the time of peak pain occurrence; furthermore, the prolonged duration helps to reduce unnecessary use of analgesics after surgery, resulting in a decreased risk of side effects. Considering the six patients who did not take any rescue medication, we found that the three patients in the control group presented peak pain intensity at 2 hours, while the peak pain intensity occurred at 12 hours in the preemptive group. These findings suggest that preemptive analgesia with ibuprofen 400 mg combined with paracetamol 500 mg can extend the time to peak pain, especially in the first 8 hours following mandibular third molar surgery.

Regarding the period of time for pain intensity evaluation, there have been a variety of reports in previous studies.[14-16,25-28] Because the maximum intensity of postoperative pain was in the first 12 hours[32], the period of time for pain evaluation used in this study can be considered appropriate for evaluating the efficacy of preemptive analgesia.

In this study, we used paracetamol 500 mg combined with ibuprofen 400 mg as a rescue medication regimen for both groups. Several studies used paracetamol 500 mg only, which was insufficient in controlling moderate pain after third molar surgery.[16,19,25,26,28] Therefore, we combined ibuprofen 400 mg with the paracetamol 500 mg in all cases and all levels of postoperative pain for both groups to ensure the maximum synergistic effect on pain reduction, reduction of side effects, elimination of the bias from analgesic selection of the patient, and also due to ethical concerns.

Drug satisfaction has been assessed by various methods. The Likert scale, which measures a characteristic on an ordinal scale is a common measurement. However, this study used a VAS due to its three major advantages over Likert scale: first, the items are less vulnerable to bias from confounding factors than Likert-scaled items; second, the VAS avoids the ceiling effect better than the Likert scale; and third, the time needed to complete the VAS questionnaire is approximately 28% shorter than the time needed to complete a Likert-scale questionnaire.[33]

This study showed no statistical differences in facial swelling and mouth opening between the two groups. Facial swelling and limited mouth opening are common sequelae after third molar surgery which progress in the first 48 hours and diminish after 72 hours. Ibuprofen has a short half-life (1-2.5 hours) and short duration of effect (4-6 hours)[34], while paracetamol has little to no anti-inflammatory effect.[35] This analgesic combination, therefore, had little effect on reducing facial swelling and trismus. Another possible explanation for these non-significant results may be that the single dose of preoperative ibuprofen was not enough to produce an anti-inflammatory effect. The anti-inflammatory dosage of ibuprofen should be higher than the normal dosage. Pozzi and Gallelli[36] reviewed the effect of ibuprofen at both 1,200 mg daily for 3 days and 2,400 mg daily for 2 days and found that the treatment significantly suppressed edema formation 48 hours after oral surgery. This effect in reducing facial swelling would be increased if ibuprofen was combined with a systemic steroid such methylprednisolone, betamethasone, or dexamethasone.[15,37,38]

For future studies, a standard protocol for clinical trials of preemptive analgesia is needed to represent the true effects of preemptive analgesia. Additionally, verification of the effectiveness of the direct pharmacologic effect of the analgesic drug should be further studied (e.g., measurement of the level of inflammatory mediators).

Conclusions

Preemptive ibuprofen 400 mg combined with paracetamol 500 mg did not improve analgesia, facial swelling, or mouth opening after lower third molar surgery. However, the drug combination prolonged the time to peak pain and the time at first requirement for rescue medications.

Acknowledgments

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Conflicts of interest

The authors declare no conflicts of interest.

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