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นิพนธ์ต้นฉบับ
Original Article

การศึกษาเทียบผลการลดความเจ็บปวดของการให้ยาไอบูโพรเฟนก่อนการผ่าตัดฟันกรามล่างซี่ที่สาม

Comparison of postoperative pain reduction with preoperative ibuprofen administration before mandibular third molar surgery

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บทคัดย่อ **การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบการลดความเจ็บปวดหลังจากรับประทานยาไอบูโพรเฟน 400 มก. ก่อนการผ่าตัดฟันกรามคุดล่างซี่ที่สาม 1 ชั่วโมงและการรับประทานยาทันทีก่อนการผ่าตัด โดยทำการทดลองทางคลินิกแบบสุ่มและมีกลุ่มควบคุมที่มีการปกปิด 2 ทาง ในอาสาสมัครจำนวน 31 คน อายุระหว่าง 18-35 ปี มีฟันกรามคุดล่างซี่ที่สามทั้ง 2 ข้าง ที่มีความยากตามดัชนีของ Pederson ระดับปานกลาง โดยอาสาสมัครจะได้รับประทานยาไอบูโพรเฟนก่อนการทำหัตถการ 1 ชั่วโมง หลังจากนั้นจึงรับประทานยาหลอกก่อนการทำหัตถการทันทีในข้างที่เป็นกลุ่มควบคุม ส่วนอีกข้างอาสาสมัครจะได้รับประทานยาหลอกก่อนการทำหัตถการ 1 ชั่วโมง จากนั้นจึงรับประทานยาไอบูโพรเฟนก่อนทำหัตถการในทันทีเป็นกลุ่มทดลอง ทำการบันทึกข้อมูล เพศ อายุ ตำแหน่งฟันกรามล่างซี่ที่สาม ระยะเวลาการผ่าตัด จำนวนยาชาที่ใช้ การแบ่งฟัน ภาวะแทรกซ้อนจากการผ่าตัด นอกจากนี้อาสาสมัครต้องทำแบบประเมินความวิตกกังวลก่อนการทำหัตถการ และทำการบันทึกค่าระดับความเจ็บปวดหลังทำหัตถการชั่วโมงที่ 0, 2, 4, 6, 8, 24, 48 และ 72 รวมทั้งจำนวนและเวลาที่อาสาสมัครรับประทานยาแก้ปวดไอบูโพรเฟนหลังผ่าตัด ผลการศึกษาพบว่าการ**

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รับประทานยาไอบูโพรเฟน 400 มก. ก่อนการผ่าตัด 1 ชั่วโมง กับการรับประทานยาทันทีก่อนการผ่าตัดฟันกรามคุดล่างซี่ที่สามไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติที่ระดับความเชื่อมั่น 95% (p >0.05) จึงอาจสรุปได้ว่าไม่มีความจำเป็นที่ต้องรับประทานยาไอบูโพรเฟนก่อนการผ่าตัดฟันกรามคุดล่างซี่ที่สามเป็นเวลานาน 1 ชั่วโมง เพื่อลดระยะเวลารอก่อนการผ่าตัดฟันกรามล่างซี่ที่สาม

คำสำคัญ : การให้การระงับปวดก่อนที่จะเกิดความเจ็บปวดขึ้น ฟันกรามคุดล่างซี่ที่สาม หัตถการขนาดเล็ก ยาไอบูโพรเฟน ความเจ็บปวดที่เกิดขึ้นหลังการทำหัตถการ

Abstract The objective of the study is to compare postoperative pain reduction after the administration of ibuprofen 400 mg between 1 hour and immediately before the surgical removal of lower impacted third molar. This experiment was a double-blind, randomized clinical trial. Thirty-one patients, age between 18-35 years old, who had bilateral mandibular impacted third molars with moderate difficulty level according to Pederson's index, were included in this study. The patients taking a 400 mg of ibuprofen 1 hour before surgery followed by placebo immediately before surgery were designated as the control group, whereas the patient taking a placebo 1 hour before surgery followed by 400 mg of ibuprofen immediately before surgery were designated as the experimental group. A demographic data, including gender, age, tooth number, position of mandibular third molar impacted, operative time, an amount of anesthetic agent, tooth sectioning and complication, were recorded. Furthermore, the anxiety score(HAM-A), visual analog scale (VAS) at 0, 2, 4, 6, 8, 24, 48 and 72 hours postoperatively, amount and time of postoperative ibuprofen were recorded in each subject. For the result, there was no statistically significant difference between 1 hour preoperative and immediately preoperative administration 400 mg of ibuprofen at 95% confidence level (p > 0.05). For the conclusion from this study, there was not necessary to administrate ibuprofen 1 hour preoperatively to reduce the waiting time before the operation.

Keywords : preemptive analgesia, lower impacted third molar, minor surgery, ibuprofen, postoperative pain reduction

Introduction

The most common complication in surgical removal of impacted third molar is pain. Pain is an unpleasant sensory or experience associated with the damaged tissue.[1,2] Pain signals enter to the dorsal horn of the spinal cord, that causes more release of mediators especially prostaglandin which is the important pain mediator. Then, pain signals are sent to the brain via spinothalamic tract.[3] The different brain areas interpret the signals from the body and determine the meaning and importance of the signals, results in a unique individual experience of pain. An effectively postoperative pain control is the beneficial way for both patients and operators. From the previous studies, the

way that reduces postoperative pain is to administer the analgesic drug before the operation, the preemptive analgesia which produces more benefit results than postoperative administration. Preemptive analgesia is the analgesic administration before the injury.[4] The three goals of preemptive analgesia are : firstly, to reduce pain resulted by the activation of inflammatory mechanisms from the surgical incision; secondly, to hinder the pain memory response of the central nervous system; and thirdly, to control of postoperative pain in order to avoid the development of chronic pain.[5]

In 1913, Crile[6] firstly introduced preemptive theory. His patient was sedated with morphine and ether inhalation then local infiltration of cocaine was preoperatively administered before the surgery. There is no single agent alone but through selection and combination of anesthetics that aim to attain the anesthesia. He reported that a marked reduction in morbidity and mortality had dropped to 1.8%.The preemptive concept is to reduce postoperative pain by blocking nociceptive stimuli from operative injury. Thus, preemptive is defined as anti-nociceptive treatment that is preoperatively attribution that affectes to nociceptive transmission. Once any tissue injury would release cyclooxygenase-2 (COX-2), thereafter, COX-2 induces prostaglandin activity to activate peripheral nociceptors and then induce the inflammatory symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandins and activates the peripheral and central sensitization.[7,8] Besides, the mechanism of action affects at both the site of injury and within the central nervous system. Therefore, NSAIDs was increasingly studied in this concept. In Thailand, ibuprofen is widespread traditionally prescribed in any minor surgery as surgical removal of impacted tooth to reduce postoperative pain. However, some studies did not support the preemptive concept such as Aznar-Arasa et al. in 2012[9], which compared the analgesic and anti-inflammatory effects of 1 hour preoperative and postoperative administration of 600 mg ibuprofen after the surgical removal of impacted lower third molars. The preoperative intake of ibuprofen did not seem to reduce pain, facial swelling and trismus after impacted lower third molar removal when compared to its postoperative administration. Moreover, the preemptive concept has to wait for the onset of ibuprofen, about 30-60 minutes. This will waste the time to patients and dental team. Consequently, we required studying whether the immediately preoperative administration of ibuprofen could reduce the postoperative pain as the preemptive concept.

The objectives of this study were to compare the analgesic effect of 1 hour preoperative and immediately preoperative administration of 400 mg ibuprofen before surgical removal of mandibular third molar and to evaluate the correlation between the patient's anxiety and postoperative pain of impacted third molar surgical removal.

Materials and methods

A randomized double-blind split mouth, placebo-controlled clinical trial was performed. Thirty-one patients (17 women and 14 men) between ages of 18 to 35 years old who had undergone the surgical removal of bilateral impacted lower third molar in same difficulty index (moderate difficult of Pederson's scale) were included in this study. The exclusion criteria were patients who had acute infection on surgical area, allergic to ibuprofen or articaine, systemic diseases (gastrointestinal disorder, bleeding disorder, renal and liver diseases, and asthma), pregnancy or breast feeding, ASA III or IV (American Society of Anesthesiologist 2014), and on medications interacting with articaine or

ibuprofen.

Preoperative and postoperative assessments

The study was ethically approved by the Human Ethic Committee of Rangsit University. The objectives, data collections (including visual analog scale (VAS), amount and timing of postoperative analgesic drug), and possible complications of this clinical trial were explained to all patients before their enrollment. Informed consent form was done before surgery. The researchers were responsible to clinical trial, including financial compensation and complications.

A panoramic radiograph was taken and the classification of impacted tooth by Pell & Gregory was assessed. The Hamilton Anxiety Rating Scale (HAM-A) was used to assess patients' anxiety before the operation (Fig.1). The impacted teeth were distributed into 2 groups by simple random sampling technique. One side, the patient received 400 mg preoperative ibuprofen 1 hour prior, after that the placebo was taken immediately before the operation, as the control group. The another side, the patient received the placebo 1 hour prior and then 400 mg ibuprofen immediately before the operation, as the experimental group.

All surgeries were performed by one surgeon at Surgery Clinic of the Faculty of Dental Medicine of Rangsit University. The operation was performed under local anesthesia with 4% articaine with 1 : 200,000 epinephrine. All patients received inferior alveolar nerve block and buccal infiltration, then surgery was initiated. The surgical procedure was standardized, including creating mucoperiosteal flap followed by bone removal. Tooth sectioning was done if necessary. After complete removal of impacted tooth, the wound was rinsed with sterile solution of physiological saline, followed by local hemostasis and black silk sutures.

Patients were administered with amoxicillin 500 mg 20 caps, 1 cap tid pc, as antibiotic prophylaxis. In case of allergic to amoxicillin, clindamycin 300 mg 20 caps, 1 cap tid pc, were prescribed. All groups received ibuprofen 400 mg as a rescue medication on the patient request, with minimum 6-hour redosing interval. The time that patients requested analgesic drug and the rescue medication intake were recorded. The subjects were instructed to measure the intensity of the postoperative pain in the different visual analogue scales (VAS) of 10 cm (0 = no pain, 10 = worst pain). Pain was assessed at 0, 2, 4, 6, 8, 24, 48 and 72 hours postoperatively. Demographic data and visual analog scale were analyzed.

Results

Thirty-four patients were participated into this study, but three of them withdrawn from the study because they did not attend to the continued treatment. Then the results were based the analysis of thirty-one participants (Table 1).

The gender, age, difficulty index (Pederson's scale), surgery duration, postoperative analgesics, rescue medication time, anesthetic volume, tooth sectioning and HAM-A were recorded (Table 1). This difference of age was considered to be extremely statistically significant, the most patients were in the range of age 21-25 years. But the remaining of all data were not statistically different.

The VAS score of two groups increased during the 4th-8th hour after surgery. The highest VAS score at the 6th hour were similarly between 2 groups. (Fig. 2)

The comparison of average VAS scores at 0, 2, 4, 6, 8, 24, 48 and 72 hours between control and experimental group showed no statistically significant difference. (Mann-Whitney U test, $p > 0.05$) (Table 2)

Most of the patients in both control and experimental groups, more than 90%, were in mild level of

รูปที่ 1 *แบบประเมินความวิตกกังวลของแฮมิลตัน*

Fig. 1 *Hamilton Anxiety Rating scale (HAM-A).*

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = not present, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe

1. Anxious mood ☐0 ☐1 ☐2 ☐3 ☐4

Worries, anticipation of the worst, fearful anticipation, irritability.

2. Tension ☐0 ☐1 ☐2 ☐3 ☐4

Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.

3. Fears ☐0 ☐1 ☐2 ☐3 ☐4

Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.

4. Insomnia ☐0 ☐1 ☐2 ☐3 ☐4

Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.

5. Intellectual ☐0 ☐1 ☐2 ☐3 ☐4

Difficulty in concentration, poor memory.

6. Depressed mood ☐0 ☐1 ☐2 ☐3 ☐4

Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

7. Somatic (muscular) ☐0 ☐1 ☐2 ☐3 ☐4

Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

8. Somatic (sensory) ☐0 ☐1 ☐2 ☐3 ☐4

Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

9. Cardiovascular symptoms ☐0 ☐1 ☐2 ☐3 ☐4

Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.

10. Respiratory symptoms ☐0 ☐1 ☐2 ☐3 ☐4

Pressure or constriction in chest, choking feelings, sighing, dyspnea.

11. Gastrointestinal symptoms ☐0 ☐1 ☐2 ☐3 ☐4

Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

12. Genitourinary symptoms ☐0 ☐1 ☐2 ☐3 ☐4

Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.

13. Autonomic symptoms ☐0 ☐1 ☐2 ☐3 ☐4

Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

14. Behavior at interview ☐0 ☐1 ☐2 ☐3 ☐4

Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

Scoring

Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0-56, where <17 indicates mild severity, 18-24 mild to moderate severity and 25-30 moderate to severe.

anxiety (Table 3). To determine whether VAS score was correlated on HAM-A score using Pearson correlation analysis, both groups had no correlation between VAS and HAM-A scores. ($p > 0.05$) (Table 3 and Fig. 3)

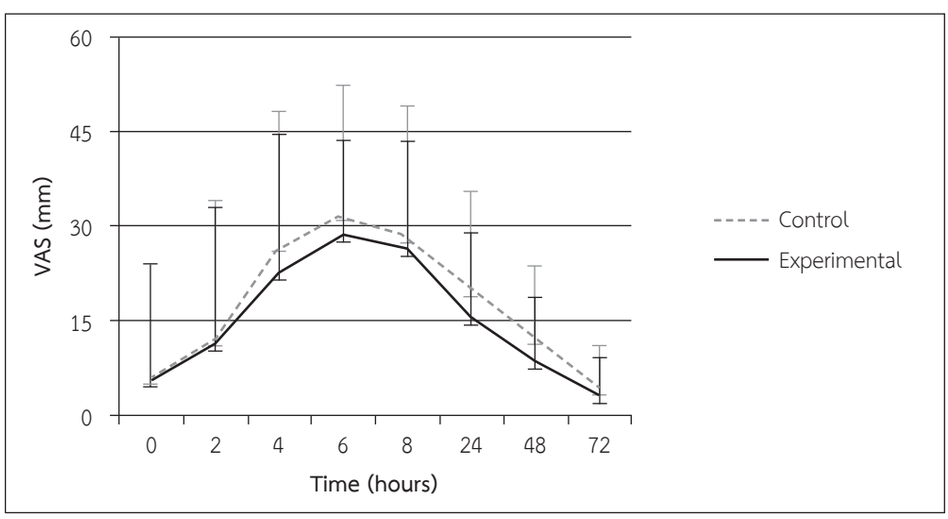
Discussion

Preemptive analgesic is an antinociceptive treatment which decreases the postoperative pain. It has been performed for a long time by initiated adminis-

ตารางที่ 1 ข้อมูลของกลุ่มตัวอย่าง

Table 1 The information of patients

		Control group	Experimental group	*p*-value
Gender	Male	14 (45.2%)		0.59
	Female	17 (54.8%)		0.59
Age	≤20 years	6 (19.4%)		0.001
	21-25 years	20 (64.5%)		0.001
	26-30 years	4 (12.9%)		0.001
	30-35 years	1 (3.2%)		0.001
Difficulty index (Pederson's scale)	5	21 (67.7%)	23 (74.2%)	0.056
	6	9 (29.0%)	3 (9.7%)	0.056
	7	1 (3.2%)	5 (16.1%)	0.056
Surgery duration (mins)		18.10	18.13	0.848
Postoperative analgesics (tablets)		4	4	0.937
Rescue medication time (mins)		403.67	344.22	0.848
Anesthetic volume (ml)		3.19	2.82	0.077
Tooth sectioning	Yes	27 (87.1%)	29 (93.5%)	0.390
	No	4 (12.9%)	2 (6.5%)	0.390
HAM-A		5.13	6.11	0.946



รูปที่ 2 *เปรียบเทียบวิชวลแอนะล็อกสเกล (วีเอเอส) ของอาการปวด ระหว่างกลุ่มควบคุมและกลุ่มทดลอง*

Fig. 2 *Comparison of visual analog scale (VAS) between control and experimental groups.*

tration of analgesia before surgical procedure in order to prevent peripheral and central sensitizations in the pain pathway. In our study, we choose ibuprofen because it has not only been frequently used in minor surgery of dentistry but it is also effective and inexpensive. All patients have to get 30-60 minutes preoperative ibuprofen for the highest peak plasma concentration before starting the operation. The waiting time of ibuprofen onset is wasted, so the objective of our study is to decrease preoperative time of both

ตารางที่ 2 ค่าเฉลี่ย ± ค่าเบี่ยงเบนมาตรฐานของวีเอเอสที่แสดงระดับอาการปวดหลังผ่าตัด

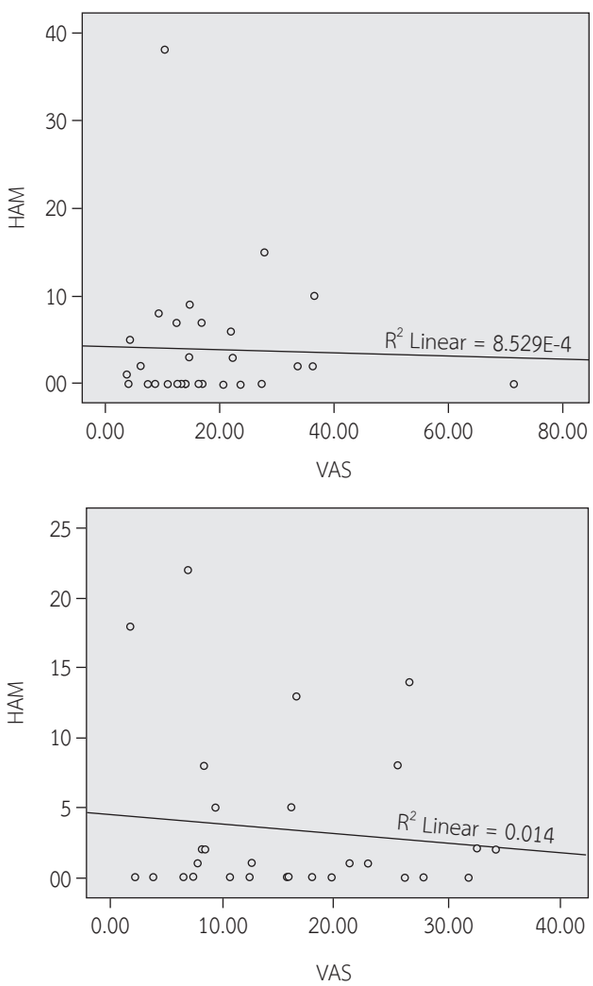
Table 2 Mean ± SD of postoperative VAS pain scores

Time (hours) / Group	0	2	4	6	8	24	48	72
Control	6.13±17.95	12.10±21.80	27.06±21.13	31.77±20.48	28.26±20.64	19.74±15.68	12.35±11.23	4.19±6.73
Experimental	5.39±18.53	11.23±21.65	22.68±21.82	28.48±15.01	26.26±17.09	15.48±13.37	8.42±10.16	3.00±6.09
p-value	0.084	0.736	0.278	0.751	0.849	0.402	0.063	0.168

ตารางที่ 3 จำนวนและร้อยละของค่า เอชเอเอ็ม-เอ ในแต่ละระดับของความปวด

Table 3 Number and percent of HAM-A on each level of severity

Group / Level	Control (n=31)	Experimental (n=31)
<17 (mild)	30 (96.8 %)	29 (93.5 %)
18-24 (mild to moderate)	-	2 (6.5 %)
25-30 (moderate to severe)	-	-
>30 (severe)	1 (3.2 %)	-



รูปที่ 3 *ค่าสหสัมพันธ์ของเพียร์สันระหว่างค่าเอชเอเอ็ม-เอ กับวีเอเอสของกลุ่มควบคุม (รูปบน) และกลุ่มทดลอง (รูปล่าง)*

Fig. 3 *Pearson correlation between HAM-A and VAS of the control (upper) and the experimental group (lower)*

operator and patient.

We found that the mean VASs were no statistically different between the control group (1 hour preoperative of ibuprofen then immediately preoperative of placebo administration) and the experimental group (1 hour preoperative of placebo then immediately preoperative of ibuprofen administration), which was correspondent with many studies. In 1992, Vogel et al[10] studied in 60 patients who had periodontal surgery treatment and found that the group who received postoperative analgesic medication had lower postoperative pain. This study has also been shown that was no statistically significant difference among pretreatment, posttreatment and placebo administration of ibuprofen. Due to that study supposed that the onset of ibuprofen would delay the intensity of postoperative pain similarly to our study. In 2005, Jung et al.[11] studied in 80 patients undergoing surgical removal of impacted third molar that were divided into 3 groups, preoperative analgesic administration, postoperative analgesic administration and no medication intake group. They found that postoperative analgesic administration group had the lowest postoperative

pain as compared to preoperative and no medication intake. In 2012, Aznar-Arasa et al.[9] found that the administration of 600 mg ibuprofen 1 hour before surgery was no statistically significant difference of postoperative pain as compared to the administration immediately before surgery. In 2012, Liporaci[12] reported that selected 13 patients underwent surgical removal of bilateral third molar in 2 separate procedures and received oral ketoprofen 150 mg every 12 hours for 2 days, before and after the procedure. On the other side, a control (placebo) was used similarly. The results in this study showed no significant difference of postoperative pain between 2 groups.

In our study, postoperative pain between 2 groups were not significantly different. As shown in results, maximum operating time was 40 minutes and the average duration of the surgical procedure was 18.10 minutes in the control group and 18.13 minutes in the experimental group which were not long span minor surgery. By the way, Savage and Henry[7] revealed that the maximum concentration of prostaglandins around damaged tissue were obtained approximately 1 hour after injury. Jones et al.[13] showed that the maximum plasma peak after the PO administration of 400 mg of ibuprofen occurred after 32 minutes. From those two previous studies, the anti-nociceptive effect of NSAIDs extended into initial postoperative period while onset and duration of ibuprofen occurred before the peak of prostaglandins. It would reduce perception of pain. Therefore, the effects on VAS of both groups were not significantly different.

In 2013, Yamaguchi and Sano.[14] revealed that the surgical removal of impacted tooth was moderately difficult operation with less tissue damage and postoperative pain. Pain from the surgical removal of third molar impaction was activated from peripheral sensitization of postoperative inflammation more than direct central sensitization during the operation. Thus, the mechanism of preemptive analgesia which reduced peripheral and central sensitizations resulted from direct trauma was still controversial. Along with local anesthetic agent injection before the operation reduced local nociceptor that occurred during the operation, conformed to the study of Liporaci[12] which used local anesthesia (2% lidocaine and 4% articaine) and preoperative administration of NSAIDs (ibuprofen, corticosteroids or long lasting local anesthetics) and found that the local anesthesia affected in reduction of postoperative pain, whereas the NSAIDs were not the main factor for the preemptive analgesic effect.

The surgical removal of impacted tooth was minor surgery, using shortly operating time and small surgical area, which caused minor tissue damage and postoperative pain compared to major operation which caused severe tissue damage, such as thoracic and abdominal surgeries, as well as orthognathic surgery or tumor surgery in head and neck region. In major surgery or long span operating time procedure, the effect of preemptive analgesia on VAS should be significant. According to most studies of preemptive analgesia in major surgery, administration of preoperative analgesia could reduce postoperative pain, similar to the study of Harshel[15], which showed that preemptive analgesia prior to major surgery significantly decreased the postoperative pain and rescued analgesic requirement.

The study of Sharma et al. in 2015,[16] about the relationship between pain and anxiety in patients who had required extraction due to orthodontic treatment, reported the significant correlation between VAS and anxiety score. In the other hand, there was no significant correlation between VAS and HAM-A in our study meant that patient's anxiety did not affect the postoperative pain. HAM-A scores were also no statistically

different in both control and experimental groups. HAM-A scores in most of the patients were in mild level resulted from many factors such as high reliability of the faculty and surgeon. Moreover, the patient known that they got the medicine for pain relief before surgery. The study of Locker et al. in 1996[17] found that the patient who had negative dental experience always came with high level of anxiety. Most of the patients in this study had no any bad experience about dental procedure, so they had mild anxiousness.

Our study showed that the surgical removal of impacted third molar was in moderate difficulty level. All surgeries were performed by an expert surgeon accompanied by cooperative patients. Consequently, the preemptive analgesia was not necessary to our study. We suggest that administration of analgesic drug immediately before the surgical removal of third molar impacted tooth without waiting for 1 hour following the preemptive analgesia theory is efficient, but the analgesic drug should be administrated before the onset of pain to reduce the pain and anxiety of the patient. For the further studies, major surgery or long timing operation should be included in the study, in order to confirm the effectiveness of preemptive analgesia.

Conclusion

This study provides valuable information concerning the analgesic effect of ibuprofen given immediately or 1 hour before operation has no significantly different. This suggests that for the best effect of ibuprofen and convenience of patient and dentist, this drug can be easily given right before the operation.

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