Original Article

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Effectiveness of dexamethasone injection in the pterygomandibular space before and after lower third molar surgery

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Background: Previous studies have investigated the effects of dexamethasone injections into the pterygomandibular space and compared them to those of controls; however, the effects of dexamethasone injections before and after lower third molar surgery on postoperative complications have not been studied. This research investigated the postoperative sequelae of dexamethasone injections before and after surgery into the pterygomandibular space. The aim of this study was to evaluate the effects of preoperative and postoperative injections of 4 mg of dexamethasone into the pterygomandibular space on postoperative pain, facial swelling, and the restriction of mouth opening following lower third molar surgical removal.
Methods: Twenty-seven participants with bilateral symmetrical lower impacted third molars were included in this study. Each participant was randomly allocated to one of two groups. Group A received injections of 1 ml dexamethasone (4 mg/mL) and 1 mL placebo into the pterygomandibular space before and after surgery, respectively. Group B received the same doses of placebo before surgery and dexamethasone after surgery.
Results: A significant restriction of mouth opening on the second postoperative day was observed in both groups. Nonetheless, the postoperative restriction of mouth opening, facial swelling, postoperative pain, and analgesic consumption after lower third molar surgical removal were not significantly different in the two groups.
Conclusions: Regardless of the time of administration, dexamethasone injections into the pterygomandibular space resulted in satisfactory control of the postoperative sequelae of the mandibular third molar surgical removal.

Keywords: Dexamethasone; Postoperative Complications; Pterygomandibular space; Surgical Removal; Third Molar.

INTRODUCTION

The surgical extraction of lower impacted third molars (LITMs) is a routine procedure within oral and maxillofacial surgery. Although it is a routine and minor procedure, most patients suffer from several postoperative sequelae such as restricted mouth opening, pain, and facial swelling.

The administration of corticosteroids after the surgical extraction of lower third molars has been widely used to control postoperative sequelae [1,2]. Dexamethasone is a frequently studied and used drug because of its longer duration of action and greater anti-inflammatory potency. When compared with other corticosteroids, it has little to no side effects [3,4].

Several studies have compared the effects of dexamethasone after LITM extraction, as shown in the

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Table 1. The inclusion criteria, exclusion criteria and withdrawal criteria for this study

Inclusion criteria	Exclusion criteria
1. Age of participants between 18 and 30 years 2. Participants with asymptomatic bilateral symmetrical partially or totally impacted lower third molars classified as the inclination according to the Winter classification [20] and position according to the Pell and Gregory classification [21]. 3. This study required flap opening, bone removal, and tooth separation during the operation. 4. The operation site was free from infection and inflammation at the time of operation.	1. Participants with systemic disorders contraindicated the surgical procedure. 2. Facial deformities of the participants that may interfere with the injections during the operation or the evaluation. 3. Smoking, alcoholism, pregnancy or lactation. 4. Allergy to drugs or other substances used in this study. 5. Analgesic intake within the 2 weeks before surgery. 6. Usage of other drugs besides the drugs in this study. 7. Inability to honor the follow-up appointments and refusal to participate in the study. 8. Surgical duration exceeding 60 minutes. 9. Any surgical complications occurred that would render the non-comparable procedures.
Withdrawal criteria	The participants can withdraw from the study at any time.

previous articles [2-19].

However, studies on dexamethasone injections through the pterygomandibular space [10-13,16,17] in LITM surgery are limited.

Therefore, this study was conducted to evaluate the effects of preoperative and postoperative 4 mg dexamethasone injection through the pterygomandibular space on postoperative pain, facial swelling, and restricted mouth opening to determine the best period of administration for LITM extraction.

METHODS

1. The study with ethic approval

This prospective, randomized, split-mouth, crossover clinical study was conducted at the Oral and Maxillofacial Surgery clinic of the Faculty of Dentistry, Mahidol University. It was approved by the Mahidol University Institutional Review Board (MU-IRB) with COA. No. MU-DT/PY-IRB 2018/029.1505.

2. The sample size calculation

The sample size calculation was based on parameters obtained from a previous study using the formula with $\alpha = 0.05$, $\beta = 0.2$. Therefore, this study required a minimum of 26 participants. Considering a 20% compensation for possible loss and withdrawal of cases, the sample size was increased to 31 participants.

Fig. 1. One milliliter of dexamethasone (4 milligrams) or one milliliter of normal saline injected through the pterygomandibular space immediately before and after surgery.

$$n = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2 \sigma^2}{d^2}$$

3. The criteria for patient selection

The inclusion, exclusion, and withdrawal criteria used in this study is illustrated in Table 1.

The participants who met the criteria of this study were informed about the objectives and details. All participants who agreed to participate signed the informed consent document. For each participant, personal data, including name, gender, age, demographic profile, current and previous medical and dental history, were obtained.

The participants had similar bilateral LITMs; therefore, the researcher randomly divided the sides of impaction into two equal groups using a sealed letter containing the

Table 2. The assessment methods for facial swelling, restriction of mouth opening, and pain

Variability	Methods	Unit	Article following
Facial swelling (Fig. 2)	(A): Lateral canthus of the eye to the gonion angle. (B): Tragus to the commissure of the mouth. (C): Tragus to the soft tissue pogonion.	millimeters	Schultze-Mosgau et al. [22] and Antunes et al. [9]
Limitation of mouth opening	The maximum mouth opening taken from the distance between the upper and lower incisal edges of central incisors.	millimeters	Schultze-Mosgau et al. [22] and Antunes et al. [9] and Boonsiriseth [4]
	Pain evaluation		
Visual analog scale (VAS)	The horizontal 100-mm long line starting from 0 on the left-end as "no pain" and 100 on the other right-end as the "worst pain" measured on the day of operation, 2nd and 7th postoperativedays.	millimeters	Katz & Melzack [23] and Sirintawat [24]
Interpretation from VAS to the numeric rating scale (NRS)	no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm) severe pain (75-100 mm)	number	Jensen et al. [25] and Boonsiriseth [4] and Sirintawat [24]
The number of analgesic tablets	The analgesic tablets taken was recorded each day for 7 days postoperatively.	Number of tablets	Boonsiriseth [4]

code for the timing of the injection of 4 mg dexamethasone.

Group A received injections of 1 mL dexamethasone (4 mg/ml) and 1 mL normal saline as placebo in the pterygomandibular space before and after the surgical removal of the LITM, respectively (Fig. 1).

Group B received injections of the same dose of normal saline as placebo before surgery and dexamethasone after surgery into the pterygomandibular space.

Each participant underwent two surgical procedures performed by the same surgeon, with a washout period of four weeks between them.

4. Method of operation

Before the surgical procedure, a single non-operating assistant prepared two identical syringes that contained 1 mL of dexamethasone and normal saline, respectively. Both the surgeon and the participant were blinded to the dexamethasone usage. Local anesthesia was performed by the administration of 4% articaine 1: 100,000 epinephrine to the inferior alveolar nerve, lingual nerve, and buccal nerve block, and objective signs of anesthesia were apparent. All participants received 1 ml of 4 mg dexamethasone or 1 ml normal saline injection depending on their randomly allocated group through the pterygomandibular space at the same site where the inferior alveolar nerve block was performed.

The standard technique of LITM surgical removal was performed subsequently, which involved incision and the reflection of the mucoperiosteal flap followed by bone removal, tooth section, and tooth removal. The remaining soft tissue or dental follicles in the socket were curetted followed by irrigation. The surgical wound was sutured with black silk sutures after adequate hemostasis was secured.

The duration of surgery, in minutes, began from the initial incision and ended at the closing suture. Immediately after the LITM surgical removal, the participant received another 1 mL dexamethasone or normal saline injection through the soft tissue at the same site of the preoperative process.

After the surgical procedure, all participants received routine postoperative instructions. Amoxicillin 500 mg four times daily for 5 days and acetaminophen 500 mg for every 6 hours for pain were prescribed.

5. The evaluation of each measurement methods

All assessments, including evaluations of facial swelling, restriction of mouth opening, and pain, were performed by a single surgeon, as shown in Table 2.

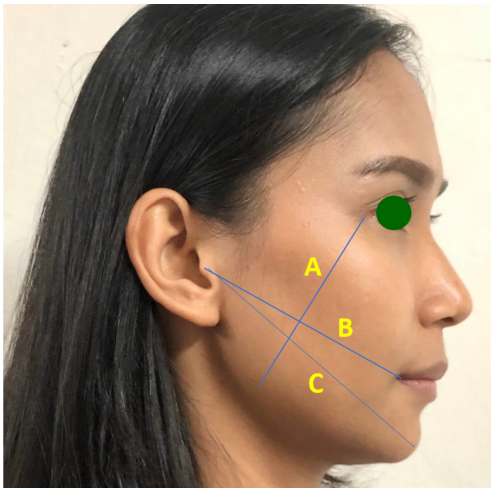

Fig. 2. Three linear facial swelling measurements. Remarks A: Ex-Go, lateral canthus of the eye to the gonion angle; B: Tr-Ch, tragus to the commissure of the mouth; C: Tr-Pg, tragus to the soft tissue pogonion

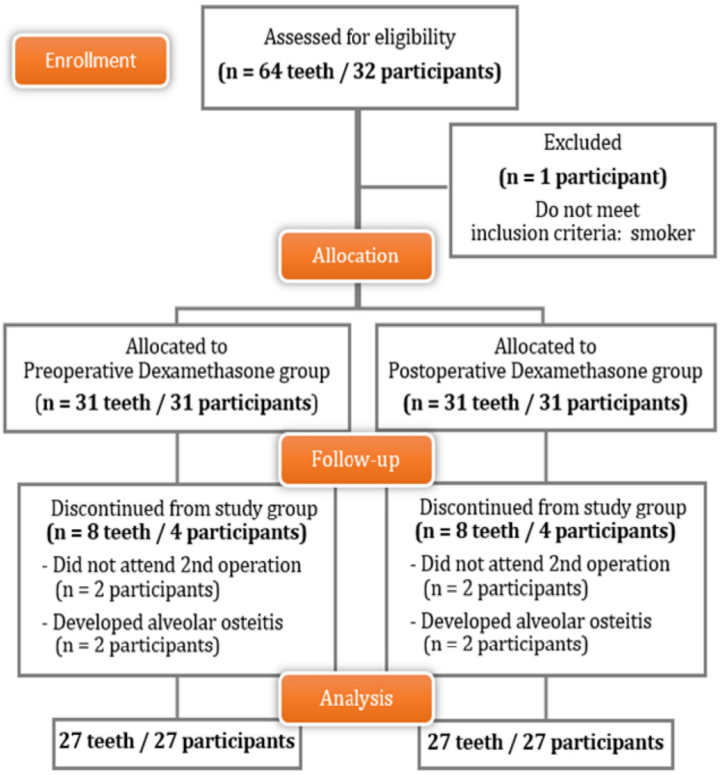

Fig. 3. CONSORT diagram detailing participant recruitment and follow-up in the study

6. Data analysis

All the coded data were inputted into the Microsoft Excel spreadsheet and analyzed using the SPSS Statistical Package for the Social Sciences (SPSS Version 18.0 for Windows, Chicago, IL, USA). The level of significance was set at $P < 0.05$. The significance of the differences between the preoperative and postoperative dexamethasone groups was assessed using paired t-test and Wilcoxon signed rank test. The Friedman two-way analysis of variance was used to analyze the significance of the differences between the dependent variables.

Table 3. Measurements of facial swelling (in millimeters): mean values and differences from preoperative baseline values in the study groups

Distance measurement	Evaluation day	Group A Mean (SD)	Group B Mean (SD)	P-value
Ex-Go	Operation day (preop baseline)	106.61 (5.66)	104.58 (6.01)	0.066
	Second postop day	107.50 (6.76)	106.16 (5.70)	0.371
	Seventh postop day	108.27 (6.09)	105.62 (5.58)	0.106
		Differences		
	Second postop day to baseline	0.89 (4.10)	1.58 (3.74)	0.545
	Seventh postop day to baseline	1.66 (4.67)	1.03 (4.32)	0.654
Tr-Ch	Operation day (preop baseline)	113.18 (8.18)	112.59 (9.03)	0.492
	Second postop day	113.89 (7.79)	114.23 (8.67)	0.730
	Seventh postop day	113.33 (8.07)	112.87 (8.40)	0.569
		Differences		
	Second postop day to baseline	0.71 (2.49)	1.64 (2.31)	0.189
	Seventh postop day to baseline	0.15 (2.39)	0.28 (2.44)	0.846
Tr-Pg	Operation day (preop baseline)	140.11 (10.76)	140.60 (10.34)	0.400
	Second postop day	142.28 (9.38)	142.29 (10.09)	0.943
	Seventh postop day	141.08 (10.03)	140.39 (10.61)	0.429
		Differences		
	Second postop day to baseline	2.17 (3.30)	1.69 (2.36)	0.493
	Seventh postop day to baseline	0.97 (3.42)	-0.21 (2.24)	0.193

Remark: Ex-Go, lateral canthus of the eye to the gonion angle; Tr-Ch, tragus to the commissure of the mouth; Tr-Pg, tragus to the soft tissue pogonion; Group A, preoperative dexamethasone administration; Group B, postoperative dexamethasone administration.

RESULTS

A total of 31 healthy participants were initially enrolled in this study. Two of them did not report for follow up for the second surgery, and two other participants developed alveolar osteitis. Therefore, 4 participants were excluded, and the remaining 27 were included in the study without any withdrawal for data analysis.

The flow chart in Fig. 3 shows the enrolment process for the final participants.

Of the 27 participants, 10 were male (37%) and 17 were female (63%). The age range was 18-29 years with a mean of 22 years.

1. Type of LITM in the study

Fourteen participants had horizontal angulation (52%), 10 had mesial angulation (37%), and 3 had vertical angulation (11%). According to the Pell and Gregory classification and the Winter classification, there were 17 participants with class IA (63%), 2 with class IB (7%), 6 with class IIB (22%), 1 with class IIC (4%), and 1 with class IIIB (4%).

2. Operation time in this study

The mean durations of surgery were 20.24 ± 8.09 minutes for the preoperative dexamethasone group and 20.93 ± 7.97 minutes for the postoperative dexamethasone group, which were not significantly different ($P > 0.5$).

3. The adverse effect from dexamethasone

No adverse events were associated with any of the drugs used in this study. However, two participants experienced alveolar osteitis: one in the preoperative dexamethasone group and another in the postoperative dexamethasone group. However, both of them recovered within two weeks after the surgery; therefore, they were excluded from the data processing (Table 1). Postoperative infection, lower lip paresthesia, and other complications were not observed in either group during the course of the study.

4. Facial swelling measurements

Table 3 shows no significant difference between any of the two-point distances of the swelling measurements

Table 4. Measurements of maximum inter-incisal distances (in millimeters): mean values and differences from preoperative baseline values in the study groups

Evaluation day	Group A Mean (SD)	Group B Mean(SD)	P-value
Operation day (preop baseline)	51.00 (6.60)	51.97 (7.35)	0.173
Postop day 2	43.24 (12.24)	43.83 (11.89)	0.686
Postop day 7	50.50 (7.59)	50.64 (8.59)	0.822
P-value	0.000*	0.000*	
	Differences		
Baseline to postop day 2	7.76 (8.62)	8.14 (8.32)	0.614
Baseline to postop day 7	0.50 (3.65)	1.33 (3.68)	0.212

*Significant, P < 0.05
Remark: Group A, preoperative dexamethasone administration; Group B, postoperative dexamethasone administration; Preop, preoperation; Postop, postoperation.

Table 5. Measurements of VAS pain scores (millimeters): mean values in the study groups

Evaluation day	Group A Mean (SD)	Group B Mean (SD)	P-value
12 hr. postop day	35.75 (25.24)	27.95 (20.84)	0.230
postop day 1	21.92 (23.84)	18.25 (19.08)	1.000
postop day 3	11.48 (17.93)	12.39 (20.44)	0.983
postop day 7	6.30 (10.34)	6.08 (10.47)	0.586
P-value	0.000*	0.000*	

*Significant, P < 0.05
Remark: Group A, preoperative dexamethasone administration; Group B, postoperative dexamethasone administration; Postop, postoperation.

of the preoperative and postoperative dexamethasone groups. Postoperative swelling was not statistically different over time when linked with the preoperative measurements in both groups (P > 0.05).

5. Maximum inter-incisal distances measurements

There was no significant difference between the maximum extents of mouth opening in the preoperative and postoperative dexamethasone groups at any time point (P > 0.05) (Table 4). However, a significant decrease was observed in the maximum mouth opening on postoperative day 2 from the preoperative extent and that on postoperative day 7 in the preoperative dexamethasone group (P = 0.001 and P = 0.000, respectively) and the postoperative dexamethasone group (P = 0.000 and P = 0.019, respectively).

6. VAS pain scores measurements

Regarding pain, there was no significant difference between the VAS scores of the two groups (P > 0.05). Nevertheless, significant reductions in the VAS scores from the day of surgery to the 3rd and 7th postoperative days was observed in the preoperative dexamethasone group (P = 0.001 and 0.000, respectively) and the postoperative dexamethasone group (all P = 0.000). A significant decrease in the VAS scores from the 3rd to the 7th postoperative day (P = 0.001) was also found in both groups, as shown in Table 5.

7. The analgesics taken

The number of analgesics taken did not differ significantly across both groups (P > 0.05). However, significant differences were found between the number of analgesics taken between the day of surgery and the 4th, 5th, and 6th postoperative days in the preoperative dexamethasone group, with P-values of 0.043, 0.022, and 0.004, respectively. Significant differences between the number of analgesics taken between the day of surgery and the 5th and 6th postoperative days were also observed in the postoperative dexamethasone group, with P-values of

Table 6. The number of analgesics taken (tablets): mean values in the study groups.

Evaluation day	Group A Mean (SD)	Group B Mean (SD)	P-value
Operation day	1.30 (0.95)	1.48 (1.09)	0.134
Postop day 1	1 (1.41)	1.07 (1.07)	0.721
Postop day 2	0.85 (1.20)	1.04 (1.43)	0.589
Postop day 3	0.81 (1.52)	0.85 (1.46)	0.905
Postop day 4	0.59 (1.12)	0.67 (1.18)	0.566
Postop day 5	0.56 (1.09)	0.59 (1.05)	0.660
Postop day 6	0.41 (0.69)	0.41 (0.84)	1.000
Total	5.52 (7.12)	6.11 (6.71)	0.329
P-value	0.000*	0.000*	

*Significant, $P < 0.05$
Remark: Group A, preoperative dexamethasone administration; Group B, postoperative dexamethasone administration; Postop, postoperation.

0.047 and 0.003, respectively, as shown in Table 6.

DISCUSSION

Several previous studies have confirmed the anti-inflammatory property of perioperative dexamethasone for controlling the sequelae of LITM extraction with its long-acting action and short-term safety [1-4,19]. In the current study, two participants developed alveolar osteitis and recovered within two weeks postoperatively. Two participants were lost to follow-up for the second surgery.

In previous review articles, the incidence of alveolar osteitis is reported between 1-5% of routine dental extractions, and it may increase to 38% of LITM extractions, which may depend on the severity of tissue injury [26,27]. Female gender and oral contraceptive usage are considered risk factors [28,29]. In the present study, alveolar osteitis (3.33%) developed after two of 60 LITM surgical procedures. Both of the participants were female; one was on regular oral contraception.

Dexamethasone is not indicated for routine use LITM surgical removal; it is used in complicated operations. The difficulty of surgery and the prolonged duration resulted in extensive soft and hard tissue trauma, thus aggravating pain [30]. In this study, the LITM extraction involved bone removal and tooth sectioning, which is a difficult surgical consideration.

Additionally, this split-mouth crossover study on symmetrical bilateral LITM extractions by a single surgeon did not have significantly different durations of surgery in both dexamethasone groups ($P > 0.5$).

Grossi et al. and Arora et al. compared the effects of perioperative submucosal injections of 4 mg and 8 mg dexamethasone and observed that a higher dose of dexamethasone was not superior to the lower dose regimen in reducing postoperative swelling after LITM surgical removal. Thus, the use of a minimal dose of dexamethasone was suggested [6,31]. A previous review by Ngeow and Lim suggested 4 mg of dexamethasone as the lowest therapeutic dose for obtaining an anti-inflammatory effect [2].

To our knowledge, few studies have compared the effects of dexamethasone based on the timing of administration through the pterygomandibular space. The pterygomandibular space was selected as the site of delivery of dexamethasone in this study, given that it is a site for inferior alveolar nerve block injection that is highly enriched in vascular supply. This allows for better drug absorption and convenience for both patients and dental practitioners.

When a preoperative injection of 8 mg dexamethasone into the pterygomandibular space after local anesthesia was administered, Latt et al. found that there was a significant reduction in postoperative pain compared with the control group [10].

Bhargava et al. stated that the co-administration of dexamethasone and a local anesthetic at the same

injection site caused lesser injection pain, shorter anesthetic latency, and prolonged duration of soft tissue anesthesia [11]. Their latter study also reported similar plasma drug concentrations and clinical effects of 4 mg dexamethasone injection through the pterygomandibular space and gluteus muscle [12]. In addition, a study by Bhargava et al. and Singh et al. found that dexamethasone injection through the pterygomandibular space caused similar postoperative clinical effects as administration by the consumption, intravenous, intramuscular, and submucosal routes [13,14].

Based on the findings of the present study, the effect of a preoperative injection of 4 mg dexamethasone through the pterygomandibular space on postoperative pain, facial swelling, and the extent of mouth opening following LITM surgical removal was similar to that of a postoperative injection.

This finding is consistent with the reports in the review by Ngeow and Lim of the comparable effects of corticosteroids irrespective of their preoperative or postoperative administration [2]. However, other previous studies have had different results. Several previous reviews concluded that postoperative anti-inflammatory effects appeared to be greater when dexamethasone was administered before than immediately after LITM surgical removal [19,32,33].

To facilitate early suppression of the effects of inflammatory mediators, dexamethasone should be administered before the onset of the inflammatory process; postoperative administration only prevents further inflammatory progression.

From the results, no significant difference was found between any of the two-point facial swelling measurements of the preoperative and postoperative dexamethasone groups. Postoperative swelling was not significantly different over time compared with the preoperative values of both groups. Consistent with this result, Mojsa et al. found no statistically significant difference between the reductions in postoperative swelling in the preoperative and postoperative dexamethasone groups [17].

In contrast with this study, Al-Shamiri et al. found a greater reduction in postoperative swelling after preoperative than after postoperative administration of 8 mg dexamethasone [18].

Regarding the limitation of mouth opening after LITM surgical removal, this study revealed no significant difference between the maximum inter-incisal distances of the pre- and postoperative dexamethasone groups at any time point. This finding is comparable to that of the previous research by Mojsa et al. [17].

Nevertheless, on postoperative day 2, a significant restriction of mouth opening was observed in both groups. Hence, we assumed that the restriction of mouth opening occurred following LITM surgical removal, regardless of the time of dexamethasone administration. Al-Shamiri et al. found a similar significant reduction in the restriction of mouth opening from baseline to postoperative day 7 in both groups [18].

To assess postoperative pain, the VAS pain score and the number of analgesics taken were recorded by participants in a pain control form. Pain is a subjective perception that varies with individual background, life experience, and the degree of surgical difficulty [23,30]; therefore, the split-mouth crossover design was used in this study to reduce this bias. The maximum VAS scores of the preoperative and postoperative dexamethasone groups were evaluated on the day of surgery with a mean of 35.75 ± 25.24 mm and 27.95 ± 20.84 mm, respectively. We converted the VAS pain score to the numeric rating scale, which was considered as mild pain (5-44 mm) based of the grading by Jensen et al. [25], Boonsiriseth et al. [4], and Sirintawat et al. [24] This study found that the numeric rating scale score decreased with time. Similar to the result of Al-Shamiri et al. [18], this study found no significant difference between the VAS scores of both dexamethasone groups. Our study finding contradicted the report by Mojsa et al. that better pain control was facilitated by postoperative than preoperative submucosal injection of dexamethasone [17]. Furthermore, the current study found significant reductions in the VAS scores from the day of surgery to postoperative

days 3 and 7 in both groups ($P < 0.05$). Al-Shamiri et al. found a significant reduction in the VAS pain score on postoperative day 3 from the day of surgery only in the preoperative group (dexamethasone) [18].

The maximum number of rescue analgesics administered was recorded on the day of surgery in both dexamethasone groups, with a mean of 1.30 ± 0.95 and 1.48 ± 1.09 tablets, respectively; it decreased post-operatively. No statistical difference was found between the groups during the follow-up. This result was similar to that of Mojsa et al. [17].

In conclusion, the effects of preoperative and postoperative injections of 4 mg dexamethasone into the pterygomandibular space after LITM surgical removal were not significantly different. From this study, an injection of 4 mg of dexamethasone into the pterygomandibular space is safe, and it provides a similar control of postoperative pain, facial swelling, and the restriction of mouth opening following LITM surgical removal if administered preoperatively or postoperatively.

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Kalaya Sitthisongkhram: Conceptualization, Data curation, Formal analysis, Investigation, Methodology
Nattisa Niyomtham: Visualization
Teeranut Chaiyasamut: Resources, Supervision, Visualization
Verasak Pairuchvej: Supervision, Visualization
Kumar KC: Visualization, Writing - original draft
Natthamet Wongsirichat: Project administration, Writing - review & editing

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DECLARATION OF PATIENT CONSENT: The authors certify that they have obtained all appropriate patient consent forms. In the forms, the patient have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

ETHICS APPROVAL FOR CLINICAL STUDY: This study was approved by the Institutional Review Board (MU-DT/PY-IRB) of the Faculty of dentistry/Faculty of Pharmacy of Mahidol University with the approval number "COA. No. MU-DT/PY-IRB 2018/029.1505."

CLINICAL TRIAL REGISTRATION: There is no requirement for this in our faculty because clinical research is controlled by the Ethical Committee of Research on Human Beings of the Dentistry and Pharmacy Department of Mahidol University.

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