Original article

The Effects of 4 mg Dexamethasone on Anti-inflammation and Quality of Life after Surgical Removal of The Lower Third Molar: A Split-mouth Triple-blind Randomized Placebo-controlled Study

Laddawun Sununliganon[1], Thachaya Satavuthi[1], Chatchai Pesee[2], Takerngsuk Phetchuay[1], Phensiri Sangroongrangsri[1], Bhakajira Suppateepmongkol[1], Rinruedee Phothinamthong[1], Chatchai Sirirungseero[1]

[1]Discipline of Oral Surgery, College of Dental Medicine, Rangsit University, Pathumthani

[2]Department of mathematics, Kasetsart University, Bangkok

Abstract

Inflammatory complications following third molar surgery are a concern of patients. Dexamethasone, one of the corticosteroids, possesses an anti-inflammatory property that can reduce inflammation. However, there is no consensus on an appropriate administration. This study evaluated the anti-inflammatory outcomes of 4 mg dexamethasone given by pre-operative submucosal injection after the surgical removal of third molars. A split-mouth, randomized, triple-blind, placebo-controlled study was carried out with 17 participants (34 impacted teeth) having bilateral identical lower third molar impaction. Submucosal injection of either 4 mg dexamethasone or placebo was given after anesthetization of the inferior alveolar nerve according to random assignment. The time interval between the first and second operation was a 4week period. Single surgeon, assessor, and data analyst were arranged and they did not know of drug use. Onset and duration of local anesthetic were collected. On postoperative days 1, 2, 3 and 7, pain intensity was recorded using a visual analog scale. At baseline and postoperative days 1, 3 and 7, swelling and maximal mouth opening were measured. No effect of dexamethasone on swelling and mouth opening was detected when compared to control. However, dexamethasone injection group showed significantly less pain than control at every time points, $p<0.05$. The quality of life in the physical domain was better in dexamethasone injection group than control. For third molar surgery, 4 mg dexamethasone did not demonstrate a benefit in anti-swelling or improve mouth opening. However, it significantly reduced pain and improved quality of life.

Keywords: Anti-inflammation, Dexamethasone, Surgical removal of the third molar

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Correspondence to:

Laddawun Sununliganon, Discipline of Oral Surgery, College of Dental Medicine, Rangsit University, 4th Floor, Building 12, 52/347 Muang-Ake, Paholyothin Rd., Pathumthani 12000, Thailand. Tel: 02-997-2200-30 ext. 4319, Fax: 02-997-2200-30 ext 4321, Mobile no. 083-1389119 Email: laddawan.su@rsu.ac.th

Introduction

Pain, swelling, restricted mouth opening and disturbance in quality of life (QOL) are the common unpleasant consequences after the removal of an impacted third molar. However, the surgical removal procedure is necessary, especially in the impacted tooth that may cause infection, cyst, tumor, and jaw fracture.[1] The inflammatory response after surgery derives from releasing chemical inflammatory cytokines of injured tissues. Afterward, vasodilation and an increase in vascular permeability result in leakage of protein and accumulation of fluid in the surgical site. Redness, warmth, swelling, pain, and loss of function commonly occur as classic signs of inflammation.[2-4]

Physical and pharmacological treatment modalities have been used to reduce inflammation. Anti-inflammatory drugs are commonly used and increasing in popularity. Corticosteroids are effective anti-inflammatory therapy. They account for both natural compounds produced by the adrenal cortex and synthetic versions. They affect physiological functions and supply human energy by providing gluconeogenesis.[3] The anti-inflammatory role results from inhibition of phospholipase A2 and arachidonic acid production. Subsequently, inflammatory mediators such as prostaglandins, leukotrienes, and platelet-activating factors are not able to produce. Likewise, corticosteroids are responsible for vasocontraction and provide an immunosuppressive effect, which helps to reduce the inflammation. In humans, the daily release of cortisol ranges from 15–25 mg. However, cortisol level surges in response to stimuli such as stress and trauma, in order to provide the energy and substrate necessary to handle stress-provoking stimuli. Thus, steroids supplement is used to maintain the cortisol level above the amount of physiological release.[5] Nevertheless, consuming supraphysiologic dose of glucocorticoids may result in suppression of the hypothalamic-pituitary-adrenal (HPA) axis by decreasing corticotropin-releasing hormone (CRH) synthesis and secretion. However, HPA axis suppression is likely to develop in patients who receive high doses of glucocorticoids such as more than 20–30 mg hydrocortisone or equivalent, for longer than 3 weeks.[6] Also, steroids may cause gastrointestinal disturbance. Therefore, an effective minimal dose that causes no systemic effect is an aim for the therapy.

Commonly used synthetic corticosteroids are betamethasone, triamcinolone, prednisolone, hydrocortisone, dexamethasone, methylprednisolone, etc.[7] Among these drugs, dexamethasone provides further advantages because it possesses a long duration of action, great glucocorticoid potency, and having minimal mineralocorticoid effect.[8,9] Dexamethasone has a longer duration of anti-inflammatory action (approximately 36 – 72 hours) than common steroids (approximately 24 hours).[8,10] An Additional benefit of dexamethasone is prolonging anesthetic duration when it is used in combination with a local anesthetic.[11] In literature, various dosages, routes, and timings of administration have been proposed for removal of the third molar but there is still no consensus on the most effective application. Recently, a single dose administration of dexamethasone is increasing in popularity.

The inflammatory outcomes following removal of impacted third molar commonly occurs within 1 week. The majority studies reported a peak inflammation between a few hours to postoperative day (POD) 2. Thereafter, the inflammation gradually subsides and recovers within seven days.[12] Various dosages of dexamethasone are used for anti-inflammation in oral surgery. The prescription ranged from 25–156 mg prednisone equivalent and the dose between 50–156 mg prednisone equivalent are claimed to provide effective anti-inflammation without any adverse effects.[13] Based on a reference body weight of 70 kg and 1.73 m^2 body area, Buttgereit *et al.* graded a level of steroid supplement as a prednisone equivalent per day. A low dose referred to less than 7.5 mg prednisone equivalent. An average dose was 7.5-30 mg prednisone equivalent and high dose was more than 30 mg but less than 100 mg prednisone equivalent. A very high dose was more than 100 mg but less than 250 mg while pulse therapy

was more than 250 mg prednisone equivalent.[14] Commonly, 8 mg of dexamethasone is used for anti-inflammation in oral surgery. It's 53.3 prednisone equivalent falls into a high level steroid therapy. Whereas the dose of 4 mg dexamethasone has a 26.7 prednisone equivalent that falls into high level steroid therapy. Therefore, the anti-inflammatory effect of a lower dose of 4 mg of dexamethasone has been further investigated to confirm its clinical benefit. The study by Vivek *et al.* (2017) studied the effects of 8 mg of dexamethasone after the removal of the third molar at immediate postoperation among three routes of administration. They revealed that intravenous injection of dexamethasone significantly reduced pain and swelling on POD 3 when compared to intra-masseteric muscle and submucosal injection. However, they found that the mouth opening was not affected by the routes.[15] Recently, studies of the inflammatory effect of 4 mg of dexamethasone were introduced and compared with 8 mg. However, the clinical outcomes from those studies were not consistent. Laureano Filho *et al.* (2008) conducted a split-mouth randomized control trial of 30 participants who had identical bilateral lower third molar impaction. Dexamethasone at 4 or 8 mg was given via oral route at one hour before surgery and clinical outcomes were monitored at 24 and 48 hours post operation. They found that 8 mg of dexamethasone significantly reduced swelling and improved mouth opening than those had 4 mg. Nonetheless, dexamethasone at both dosages did not provide any benefits in pain control.[16] Dissimilar to a randomized control trial in patients having a single third mandibular molar removal by Grossi *et al.* (2007) and Arora *et al.* (2018). Both studies monitored the outcomes on POD 2 and 7 and supported the use of 4 mg that provides comparable anti-inflammatory results to those received at 8 mg. Grossi *et al.* studied 72 patients and noted that 4 and 8 mg of dexamethasone demonstrated a benefit only on pain reduction on POD 2 but there were no effects on reduction of swelling and mouth opening on PDO 2 and 7. Both dosages of dexamethasone statistically significantly reduced swelling on POD 2 control but the swelling between the dosages were comparable.[17] Whereas Arora *et al.* studied 45 patients and claimed that 4 and 8 mg of dexamethasone similarly reduced swelling and pain which were significantly better than control on POD 2. However, dexamethasone did not improve mouth opening at both time points. Additionally, they found that QOL in aspects of the patient's perception of appearance and ability to chew was statistically significantly affected in control than dexamethasone groups.[12] In brief, the anti-inflammatory effects of 4 mg dexamethasone for surgical removal of the impacted third molar are not conclusive on the outcomes of pain control, anti-swelling, an improvement on mouth opening and quality of life. Therefore, this study aimed to find more evidence on these effects in a split-mouth randomized control triple blinded study.

Materials and Methods

The bilateral surgical removal of the lower third molars in identical positions was conducted in a split-mouth, randomized, triple-blind, placebo-controlled study. Participants seeking the treatment in Discipline of Oral Surgery, College of Dental Medicine, Rangsit University, were registered in the study. This study followed the Declaration of Helsinki on medical protocol and the ethic was granted by The Ethical Committee of Research Institute of Rangsit University (RSEC 68/2560) according to relevant guidelines. The sample size was calculated by using the below formula using results from the study by Laureano Filho, *et al.* (2018).[16] A study power was set at 80 % with a 0.05 level of significance using two tailed tests.

$$n = \frac{2\sigma^2\left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2}{\Delta^2}$$

n = required sample size, σ = standard deviation, and Δ = the difference in effect of two interventions which required $Z_{\frac{\alpha}{2}}$ =1.96 , α = type I error β = type II error, significant level = 0.05. The dropout rate is estimated at 20 % therefore 17 participants (34 impacted teeth) were required for this study. Inclusion criteria were healthy

participants according to The American Society for Anesthesiologists categorized (ASA) I & II who had identical bilateral lower third molar impacted teeth according to Pell & Gregory's classification, aged between 18-40 years, and were free from anti-inflammatory drugs and antibiotics within two weeks before the operation. Exclusion criteria included pregnancy or lactating women, uncontrollable systemic disease, having a history of an adverse effect from drugs used in this study. After the research detail was informed, those granted consents were randomly allocated to the groups. Computer-generated 2 digits randomized table and coin tossing technique were used to allocate the drug and the impacted tooth on the first operation. One fixed-researcher was responsible for this allocation method and prepared drugs used in a blinded-manner. Wash-out period was 4 weeks. The participants, surgeons, and assessor were not known for drug use. A single surgeon operated on each participant. One fixed-researcher assessed the clinical outcomes of all participants and intra-examiner reliability tests were confirmed. After anesthetizing by using 2 % of mepivacaine with epinephrine 1:100,000 (Scandonest special, Septodont, France), either 1 ml of 4 mg dexamethasone (Dexon, General Drug House Co, Ltd., Thailand) or normal saline solution was submucosally injected on buccal mucosa. A standard surgical procedure was performed using full-thickness mucoperiosteal flaps. Bone grinding and tooth sectioning were performed under constant irrigation with sterile normal saline solution. The wound closed with 3/0 black silk suture. Anesthetic onset and duration, as well as operation time, were recorded.

Participants were asked to record pain intensity using visual analog scale (VAS) on POD 1, 2, 3 and 7. The average pain intensity of each day was calculated from those collecting from the period at 7.00–9.00 am 11.00–13.00 am and 8.00–10.00 pm. An oral analgesic drug was given with acetaminophen 500mg/tab (Paragen, Osoth Inter Laboratories Co., Ltd., Thailand) at 1 h after surgery for the first dose and it was prescribed to take 1 tab prn for pain for two days. The participants were informed to record the pain score before taking analgesic drugs. Additional rescue (stronger) analgesic drug was given on the participants' need for severe pain using tramadol hydrochloride 50 mg (volcidol, central poly trading) prn for pain q 6h. No antibiotic was given in our treatment protocol. Facial dimensions (FD) were measured using horizontal lines (H1, H2) and vertical line (V) at pre-operation, POD 1, 3, and 7. Percentage of facial swelling was calculated similarly to the study by Amin and Laksin (1983), as detail described below, Figure 1.[18]

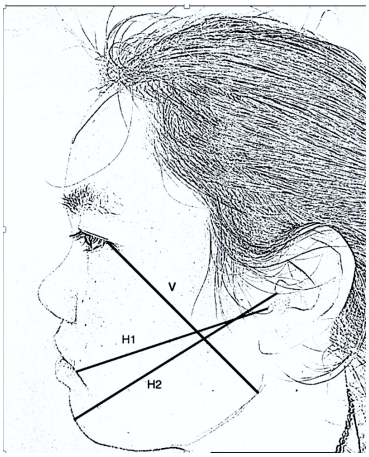

Figure 1 *Diagram shows reference lines which represent facial dimension: H1 refers to a distance from the corner of the mouth to the attachment of the ear lobule. H2 refers to a distance from the tragus to most anterior point of mandibular symphysis (pogonion). Vertical line (V) refers to a distance from the outer canthus of the eyes to the angle of the mandible (gonion).*

$$\text{Average facial dimension (FD)} = \frac{H1+V}{2}$$

$$\text{Percentage facial swelling} = \frac{\text{Postoperative FD} - \text{Preoperative FD}}{\text{Preoperative FD}} \times 100$$

Maximal mouth opening defined as the distance between an incisal edge of the upper and lower central incisors at a mesioincisal point measured with a digital caliper at pre-operation, POD 1, 3, and 7. Participants were required to answer two kinds of QOL questionnaires, modified-OHIP 14 and modified-OIDP on pre-operation and POD 1, 3 and 7. These questionnaires were modified from OHIP14 and OIDP and testified by Cronbach's Alpha

Coefficient which obtained the results at 0.8 and 0.9, respectively. They were attached with this article.[19] The Statistical Package for Social Sciences (SPSS for Windows, version 24.0; SPSS Inc., Chicago, IL, USA) was used. Descriptive statistics was performed, Normality test was confirmed with Korov-Smirnov normality test and paired *t*-test, repeated ANOVA and Bonferoni's multiple comparisons were applied. Comparison of the quality of life from mod-OHIP and mod-OIDP questionaires were conducted using the Wilcoxon Signed-rank test. The significant level was set at 0.05.

Results

Thirty-four impacted teeth from 17 participants aged from 18–25 years (mean 21.9 years) comprising of 3 males and 14 females. Their position included 75 % mesio-angular, 18.75 % horizontal and 6.25 % vertical position. One participant was excluded from data analysis because of postoperative infection causing exaggerated facial swelling. The onset and duration of local anesthetic, as well as the operation time, showed no statistically significant differences ($p>0.05$) between dexamethasone and control, detail shown in table 1. Dexamethasone revealed statistically significant lower pain than control at all healing periods, $p<0.05$. (fig. 2)

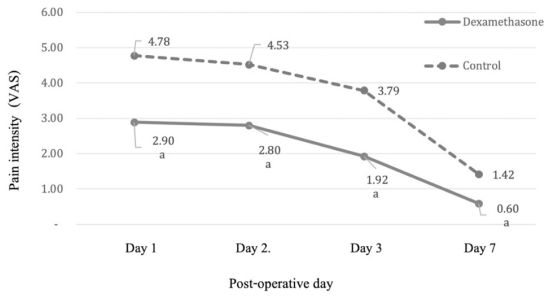

Figure 2 *Comparison of postoperative pain intensity between dexamethasone and control using visual analog scale (VAS) on POD1, 2, 3 and 7, a=p<0.05 using paired t-test.*

Table 1 *Comparison of onset, duration of local anesthetic and operation time (Mean ±SD) between dexamethasone and control. There was no significant difference between onset, duration of local anesthetic and operation time between both groups, p>0.05 using paired t-test.*

Measurements	Dexamethasone (minutes)	Control (minutes)
Onset LA	3.31 ± 1.30	3.88 ± 1.41
Duration of LA	228.75 ± 66.51	237.50 ± 59.93
Operation time	30.19 ± 12.29	28.25 ± 8.54

There were no statistically significant differences in H1 and H2 between both groups, $p>0.05$. Regarding the changes of H1 by time, the H1 of both groups revealed a significant increase from pre-operation to POD 1 (a=$p<0.05$) and pre-operation to POD 3 (b=$p<0.05$). Only the H1 in the control group significantly increased from POD 1 to POD 3 (c=$p<0.05$) but not in dexamethasone. Interestingly, only the H1 in the dexamethasone group significantly decreased from POD 3 to POD 7 (d=$p<0.05$) but not in the control as described in table 2. Maximal facial swelling occurred on POD 3 in both groups. There was no significant difference in the distance V between both groups. However, the distance V was taken into consideration in the evaluation of facial swelling in the above-mentioXXned formula. Likewise, both groups showed no significant difference in facial swelling and maximal mouth opening on POD 1, 3 and 7, $p>0.05$ (table 3).

Pre-operatively, mod-OHIP revealed comparable QOL in both groups while mod-OIDP showed a better QOL in the control group. Subsequently, the QOL was significantly less affected in the dexamethasone group on POD 1 and 3, fig 3. In detail, dexamethasone was less effective on physical pain (mod-OHIP) and physical aspect (mod-OIDP) as compared to the control on POD 1,

$p<0.05$ (fig. 4a, 5a). On POD 3, dexamethasone significantly less affected the QOL on the aspects of functional limitation, psychological disability, social disability, handicap indicated by mod-OHIP and physical aspect indicated by mod-OIDP as compared to control, $p<0.05$ (fig. 4b, 5b). Eventually, the QOL became comparable and almost returned to normal on POD 7 in both groups (fig. 4c, 5c).

Table 2 *Comparison of facial dimensions H1 and H2 (Mean ±SD) between dexamethasone and control There was no significant difference of H1 and H2 between both groups at all time points, p>0.05 using paired t-test.*

Time	Facial dimension (H1)		Facial dimension (H2)	
	Dexamethasone (mm)	Control (mm)	Dexamethasone (mm)	Control (mm)
Pre-operation	120.46 ± 3.86[a,b]	121.36 ± 4.03[a,b]	149.61 ± 8.44	149.45 ± 8.54
POD 1	123.06 ± 4.24	124.05 ± 4.67[c]	151.95 ± 9.11	151.33 ± 8.14
POD 3	124.02 ± 5.00[d]	125.53 ± 4.61	150.60 ± 12.39	152.21 ± 8.28
POD 7	122.40 ± 4.21	122.66 ± 3.56	150.85 ± 8.63	150.69 ± 8.66

Note: Within group comparison revealed a=p<0.05, Pre-op to POD1; b=p<0.05, Pre-op to POD 3; c=p<0.05, POD 1 to POD 3; d=p<0.05, POD 3 to POD 7 using repeated ANOVA and Bonferrroni multiple comparison tests.

Table 3 *Comparison of facial swelling (%) and maximal mouth opening (Mean±SD) between dexamethasone and control at pre and post-operation day (POD) 1, 3, and 7. There was no significant difference on facial swelling and maximal mouth opening between both groups at all time points, p>0.05 using paired t-test.*

Time	Facial swelling (%)		Maximal mouth opening	
	Dexamethasone (mm)	Control (mm)	Dexamethasone (mm)	Control (mm)
Pre-operation	115.10 (±3.47)	114.99 (±2.25)	43.42 ± 4.97	45.66 ± 5.78
POD 1	1.85 (±1.39)	2.19 (±1.38)	34.81 ± 8.04	32.78 ± 7.89
POD 3	2.52 (±1.45)	3.35 (±2.07)	35.65 ± 7.02	35.09 ± 8.67
POD 7	1.51 (±1.78)	1.15 (±1.30)	40.44 ± 7.56	41.08 ± 7.85

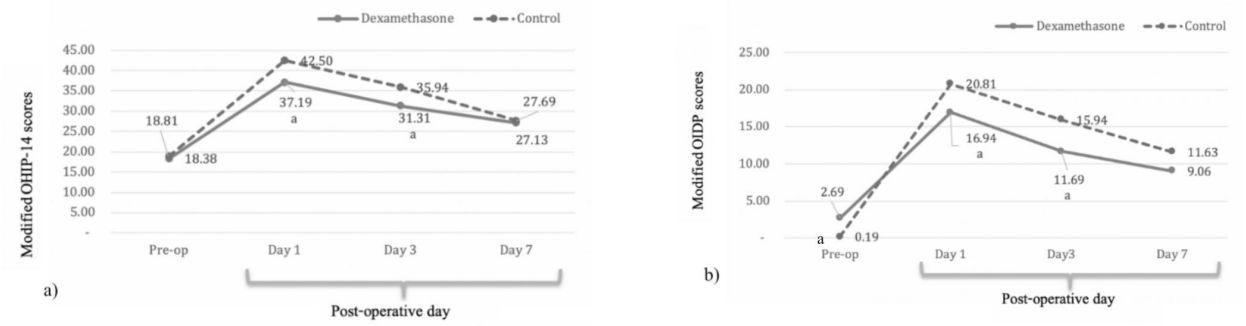

Figure 3 *Diagram demonstrates comparison of changes in the quality of life (QOL) at pre and post-operation between dexamethasone and control. From a) comparison of modified OHIP-14 scores; a=p<0.05. b) comparison of modified OIDP score; a=p<0.05 using Wilcoxon signed rank test.*

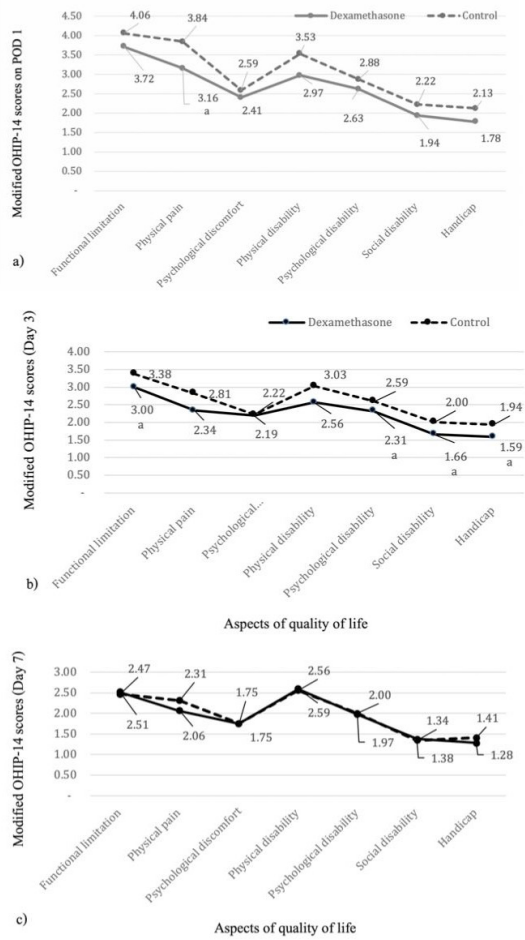

Figure 4 *Comparison of detail aspects of the quality of life from modified OHIP-14 scores between dexamethasone and control on (a) post-operative day 1, a=p<0.05; (b) post-operative day 3, a= p<0.05 and (c) post-operative day 7, p>0.05 using Wilcoxon signed rank test.*

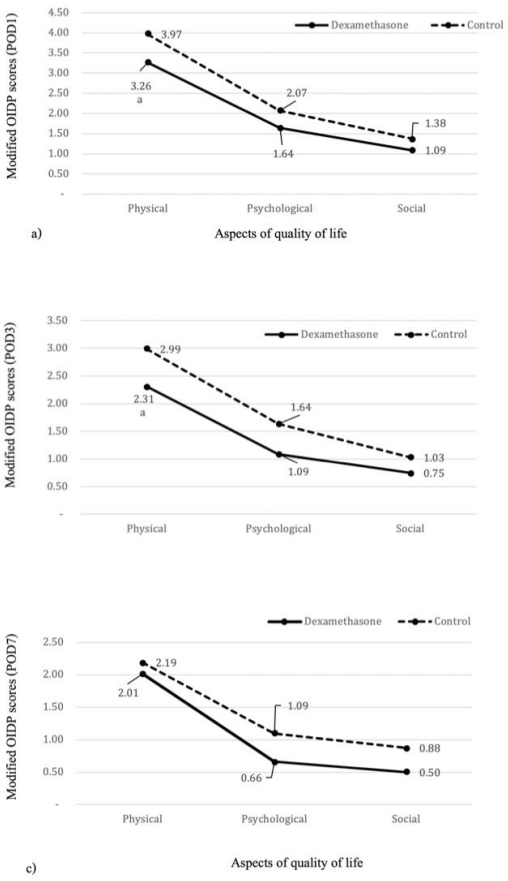

Figure 5 *Comparison of detail aspects of the quality of life from modified OIDP scores between dexamethasone and control on (a) post-operative day1, a=p<0.05; (b) post-operative day 3, a=p<0.05 and (c) post-operative day 7, p>0.05 using Wilcoxon signed rank test.*

Discussion

Steroids are chosen as a personal preference or in situations when NSAIDS provide less benefit. Steroids are commonly used for nonherpetic mucosal lesions such as an aphthous ulcer or lichen planus, surgical or local anesthetic-induced nerve trauma, phlebitis, prophylaxis of surgical swelling, endodontic over instrumentation, and prophylaxis of postoperative nausea and vomiting. For surgery, they are used to reduce the magnitude of swelling after surgery while NSAIDs are used to relieve moderate to severe pain.[3,21] Though, some studies reported a reduction of pain by steroids and a reduction of swelling by NSAIDs. In comparison to NSAIDS, dexamethasone, one of the steroids, provides a stronger anti-inflammatory property. Importantly, dexamethasone provides a much longer duration of action than NSAIDs that can cover a peak inflammation period after surgery with a single administration dose. In clinical practice, the combined use of steroids and NSAIDs may be considered if severe postoperative inflammation is expected.[3]

The side effects of dexamethasone depend on dose and duration of administration. The steroid use for anti-inflammation in dentistry usually apply as a single dose or a short-course is unlikely to produce any harm. Short-course use of glucocorticoids such as between 5-7 days in dental practice is unlikely to cause considerable side effects. A short-term elevation of blood glucose level and blood pressure may occur during treatment which is an unharmful rare consequence. However, the relative contraindications for even a short-term use include poor control diabetes, immunocompromised, active peptic ulcer, osteoporosis, and active herpetic or fungal infections. Besides, may influence mood and behavior. Therefore, high dosages should not be used in patients who have psychoses or other similar disorders.[3] Moreover, a single steroid therapy given for anti-inflammation for various kinds of surgery in patients without high risk of delayed wound healing showed no effect on the development of postsurgical infection.[21]

In general, clinicians attempt to make the patients feel safe and comfortable with the surgery. Atraumatic and painless surgery, as well as minimal unpleasant sequelae from surgery, are the targets. Regarding the route of drug administration, submucosal injection technique is noninvasive, simple and safe. Also, injection on the anesthetized area after long buccal nerve block causes no additional pain. Dexamethasone has a potent anti-inflammatory property, long duration of action, and safe from an adverse effect. The least dose that has been introduced to reduce inflammation for surgical removal of impacted tooth procedure is 4 mg. Though there are a certain number of studies investigated its effects, the methodology was varied and the benefit on anti-swelling, pain reduction and improve mouth opening were not consistent. Likewise, a recent systematic review and meta-analysis by Chen *et al.* (2017) suggested collecting more and stronger evidence for the conclusion of these effects.[22]

First of all, we evaluated the effect of dexamethasone on the onset and duration of local anesthetic. Dexamethasone did not show any effect on both onset and duration. In contrast to the study by Bhargava *et al.* (2013). They conducted a study of 20 patients with bilateral impacted mandibular molar in a split-mouth cross-over study. In a test group, a mixture of 1.8 ml of 2 % lignocaine with 1:200,000 epinephrine and 1 ml of 4 mg dexamethasone were injected into pterygomandibular space for nerve block. Whereas 2 % lignocaine with 1:200,000 epinephrine and 1 ml of normal saline solution were injected in a control group. They claimed that intra-pterygomandibular space injection of dexamethasone provided statistically significant shorter onset and longer duration of local anesthesia than control. The anesthetic onset significantly shorter in the control (76±7.62s) than the test group (51±17.5s). The duration of local anesthesia was significantly longer in the control (176 ±15.6s) than the test group (301±60s), (p<0.0001). They explained these effects as dexamethasone shorten the onset as a result of an alteration of a pH. Also, prolongation of the duration might cause from the vasoconstriction effect of dexamethasone or its effect on inhibition of nociceptive C-fibers.[23] However, these effects were claimed as a result from perineural administration of dexamethasone. Oliveira *et al.,* (2015) explained that these effects possibly caused by inhibiting the activity of potassium channel on unmyelinated c-fibers which brings nociceptive information; a slow absorption of a local anesthetic agent from vasoconstriction property; and decreasepostoperative pain from inhibit the release of anti-inflammatory mediators.[24] Nevertheless, the studies by Desmet *et al.* (2013) and Choi *et al.* (2014) discovered that not only perineural route but also intravenous route administration of dexamethasone could prolong the durationof the local anesthetic in interscalene and brachial plexus nerve block.,[25,26] Hence, the mechanism related to local anesthetic remains unclear and it was not evidence in our study.

Importantly, the expected anti-inflammatory benefits from dexamethasone are the reduction of swelling and improve mouth opening after third molar surgery.[27] Nonetheless, we could not detect these effects in our study. Instead, pain intensity in dexamethasone

was statistically lower than control at every time points (p<0.05). Regarding the analgesic effect, dexamethasone is recently used as adjuvant pain relief from either surgery and guideline for palliative care therapy[28,29] Even though some studies could detect the effect of dexamethasone on pain reduction.[30]

In previous studies, different time points were used to evaluate the effects of 4 mg dexamethasone following removal of the third molar which results were also inconsistent. The intense clinical inflammatory responses after surgical removal of the third molar occur within 1-3 days and it may persist to 7 days. Likewise, the quality of life was reported to be affected up to 5 days.[31] In our study, we provided the first dose of the oral analgesic drug at 1 h after surgery that covered postoperative immediate pain period. Subsequently, the clinical inflammatory responses were evaluated on POD 1, 2, 3 and 7 healing periods. A self-reported record of pain intensity was done at all above mentioned periods. While the rests of outcomes were evaluated by the researcher in the clinic on POD 1, 3 and 7. These periods were adequate to cover a peak inflammation and normal recovery period. Naire *et al.* (2013) reported that dexamethasone significantly reduced swelling on POD 2 but there was no effect on pain and mouth opening as compared to control.[32] Ehsan *et al.* (2014) found a significant reduction in swelling and improvement of mouth opening in the dexamethasone group on POD 2 but they did not evaluate the effect on pain.[33] Warraich *et al.* (2013) supported a significant benefit of 4 mg dexamethasone on pain, swelling and mouth opening as compared to control.[34] While Mojsa *et al.* (2017) compared the effects among pre, post-operative dexamethasone, and placebo given by submucosal injection. They found that dexamethasone given at both timings significantly reduced pain, swelling, and improved mouth opening when compared to placebo.[35] Recent systematic review and meta-analysis by Chen *et al.* (2017) claimed that dexamethasone tended to reduce swelling and also improve mouth opening at an early stage. Still, they concluded that the additional supports are required because inadequate evidence was obtained from the previous studies.[22]

The oral health impact profile (OHIP) and oral impacts on daily performance (OIDP) questionnaires are the widely used instruments to evaluate an individual's perception of oral health and the influences on daily activities. They were confirmed as a precise, valid and reliable instrument for evaluation of oral health-related QOL in adult patients.[36] The OHIP-14 questionnaire is "a comprehensive measure of self-reported dysfunction, discomfort, and disability attributable to oral conditions".[36] The OIDP questionnaire evaluates the behavioral impacts on performance. These questionnaires were modified to suit the type of research and participants.[19] Both questionnaires confirmed a similar impact of dexamethasone on patients' QOL. OHIP-14 provided more detail of aspects affected the QOL. In general, third molar surgery leads to in a negative effect on the QOL during POD 1–-5. Subsequently, it returned to normal on POD 6–7.[37] In our study, two kinds of questionnaires were used to assess and confirm their effects on the QOL. At baseline, the QOL in both groups were comparable from assessing with mod-OHIP 14 and better from assessing with mod-OIDP in control group. In detail, the physical aspect, functional limitation, psychological disability, social disability, and handicap aspects were mostly relieved in the dexamethasone group. These effects might result from a significant pain reduction with dexamethasone use. Subsequently, they might contribute to improvement in the QOL of patients. Eventually, wound recovery took place in one week and the QOL became comparable on POD 7 in both groups. Our study could not detect evidence supporting anti-swelling and improved mouth opening after submucosal injection of 4 mg dexamethasone. Therefore, further studies are required to draw a conclusion on these properties. During follow-up periods,. participants informed the researcherthat they felt more comfortable with one surgery over another without knowing the kind of drug used in each operation.

Conclusion

Our study could prove that 4 mg dexamethasone given before the operation via submucosal injection significantly reduced pain at all time points (POD 1, 2, 3, and 7), $p<0.05$. However, it did not show significant benefit for anti-swelling or mouth opening following third molar surgery. Both mod-OHIP-14 and mod-OIDP questionnaires confirmed a significant better QOL on POD 1 and 3 in dexamethasone than control group. Pre-operative submucosal injection of 4mg dexamethasone can be routinely used for third molar surgery on selected cases. With the absence of the relative or absolute contraindications, this safe and simple method can improve the QOL of patient after surgery.

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References

1. Santosh P. Impacted mandibular third molars: Review of literature and a proposal of a combined clinical and radiological classification. ***Ann Med Health Sci Res*** 2015;5(4):229–34.

2. Scallan J, Huxley V, Korthuis R. Capillary fluid exchange: Regulation, functions, and pathology. San Rafael (CA). Morgan & Claypool Life Sciences; 2010.

3. Becker DE. Basic and clinical pharmacology of glucocorticosteroids. ***Anesth Prog*** 2013;60(1):25–32.

4. Kim K, Brar P, Jakubowski J, Kaltman S, Lopez E. The use of corticosteroids and nonsteroidal antiinflammatory medication for the management of pain and inflammation after third molar surgery: a review of the literature. ***Oral Surg Oral Med Oral Pathol Oral Radiol Endod*** 2009;107(5):630–40.

5. Chugh A, Singh S, Mitta Y, Chugh V. Submucosal injection of dexamethasone and methylprednisolone for the control of postoperative sequelae after third molar surgery: a randomized controlled trial. ***Int J Oral Maxillofac Surg*** 2018;47(2):228–33.

6. Alexandraki K, Kaltsas G, Chtousos G. Adrenal Suppression. in Endotext [Internet], South Dartmouth (MA), MDText.com, Inc., 2018.

7. Koçer G, Yuce E, Tuzuner OA, Dereci O, Koskan O. Effect of the route of administration of methylprednisolone on oedema and trismus in impacted lower third molar surgery. ***Int J Oral Maxillofac Surg*** 2014;43(5):639–43.

8. Steven HK. Adrenal Cortico Steroids. In: Drug Facts and Comparisons; 1997:122-–8.

9. Shanmugapriyan PD, Balakrishnan VE, Elumalai M. Dexamethasone for third molar surgery- A review. ***Int J Pharma and Bio Sci*** 2013;4(4):9–13.

10. Herrera-Briones FJ, Sánchez EP, Botella CR, Capilla MV. Update on the use of corticosteroids in third molar surgery: a systematic review of the literature. ***Oral Surg Oral Med Oral Pathol Oral Radiol*** 2013;116(5):e342–51.

11. Chong MA, Berbenetz NM, Lin C, Singh S. Perineural versus intravenous dexamethasone as an adjuvant for peripheral nerve blocks: A systematic review and meta-analysis. ***Reg Anesth Pain Med*** 2017;42(3):319–26.

12. Arora SS, Phull T, Kumar I, Kumar A, Kumar N, Singh H. A comparative study of the effect of two dosages of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective randomized study. ***J Oral Maxillofac Surg*** 2018;22(2):225–30.

13. French-Speaking Society of Oral Medicine and Oral Surgery 2008: Recommendation for prescription of oral anti-inflammatory agent in oral surgery in adults. JOMOS 2008;14(3):129–159. Available from: http://societechirorale.com/ documents/Recommandations /recommandations_anti-inflammatoires-EN.pdf)

14. Buttgereit F, Burmester GR, Lipworth BJ. Optimised glucocorticoid therapy: the sharpening of an old spear. ***Lancet*** 2005;365(9461),801–3

15. Vivek GK, Vaibhav N, Shafath A, Imran M. Efficacy of intravenous, intramassetric, and submucosal routes of dexamethasone administration after impacted third molar surgery: A randomized, comparative clinical study. ***J Adv Clin Res Insights*** 2017;4(1):3–7.

16. Laureano Filho JR, Maurette PE. Allais M, Cotinho M, Fernandes C. Clinical comparative study of the effectiveness of two dosages of dexamethasone to control postoperative swelling, trismus and pain after the surgical extraction of mandibular impacted third molars. ***Med Oral Patol Oral Cir Bucal*** 2008;13(2):129–32.

17. Grossi GB, Maiorana C, Garramone RA, Borgonovo A, Beretta M,

Farronato D, *et al.* Effect of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective study. ***J Oral Maxillofac Surg*** 2007;65(11):2218–26.
18. Amin MM, Laskin DM. Prophylactic use of indomethacin for prevention of postsurgical complications after removal of impacted third molars. ***Oral Surg Oral Med Oral Pathol*** 1983;55(5):448–51.
19. Sununliganon L, Janthrrat C, Chanchamcharoon Y, Siripan P, Parisuthiman D. Anti-inflammatory effect of Andrographis paniculata after third molar impaction removal: clinical and quality of life assessment. Pathumthani: Sponsored by the National Research Council of Thailand; 2009. Code 35218040100641. Faculty of Dentistry, Thammasat University, Thailand.
20. Sortino F, Cicciù M. Strategies used to inhibit postoperative swelling following removal of impacted lower third molar. ***Dent Res J (Isfahan)***. 2011;8(4):162–171.
21. Polderman JA, Farhang-Razi V, Van Dieren S, Kranke P, DeVries JH, Hollmann MW, *et al.* Adverse side effects of dexamethasone in surgical patients. ***Cochrane Database Syst Rev*** 2018;11:CD011940.
22. Chen Q, Chen J, Hu B, Feng G, Song J. Submucosal injection of dexamethasone reduces postoperative discomfort after third-molar extraction: A systematic review and meta-analysis. ***J Am Dent Assoc*** 2017;148(2):81–91.
23. Bhargava D, Sreekumar K, Rastogi S, Deshpande A, Chakravorty N. A prospective randomized double-blind study to assess the latency and efficacy of twin-mix and 2 % lignocaine with 1:200,000 epinephrine in surgical removal of impacted mandibular third molars: a pilot study. ***J Oral Maxillofac Surg*** 2013;17(4):275–80.
24. Oliveira J. Does the addition of dexamethasone to local anesthetic used for peripheral nerve block prolong analgesia In the surgical patient?. University of New England DUNE: DigitalUNE.[Online]. 2015 Available from: http://dune.une.edu/na_capstones /3.
25. Desmet M, Braems H, Reynvoet M, Plasschaert S, Van Cauwelaert J, Pottel H, *et al.* I.V. and perineural dexamethasone are equivalent in increasing the analgesic duration of a single-shot interscalene block with ropivacaine for shoulder surgery: a prospective, randomized, placebo-controlled study. ***Br J Anaesth*** 2013;111(3) :445–52.
26. Choi S, Rodseth R, McCartney CJ. Effects of dexamethasone as a local anaesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis of randomized trials. ***Br J Anaesth*** 2014;112(3):427–49.
27. Messer EJ, Keller JJ. The use of intraoral dexamethasone after extraction of mandibular third molars. ***Oral Surg Oral Med Oral Pathol.*** 1975;40:594–8.
28. Meng Jian, Lin Li. The efficiency and safety of dexamethasone for pain control in total joint arthroplasty: A meta-analysis of randomized controlled trials. ***Medicine (Baltimore)*** 2017;96(24):e7126.
29. Barghi K, Edmonds KP, Ajayi TA, Atayee RS. Prescribing Trends of Palliative Care Team's Use of Dexamethasone for Cancer-Related Pain. ***J Pain Palliat Care Pharmacother*** 2018;32(1):37–43.
30. Deo SP. Single-dose of submucosal injection of dexamethasone affects the post operative quality of life after third molar surgery. ***J Maxillofac Oral Surg*** 2016;15(3):367–375.
31. Deepti C, Rehan HS, Mehra P. Changes in quality of life after surgical removal of impacted mandibular third molar teeth. ***J Maxillofac Oral Surg*** 2009;8(3):257-60.
32. Nair RB, Rahman NM, Ummar M, Hafiz KA, Issac JK, Sameer KM. Effect of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective study. ***J Contemp Dent Pract*** 2013;14(3):401–4.
33. Ehsan A, Ali Bukhari SG, Ashar Manzoor A, Junaid M. Effects of pre-operative submucosal dexamethasone injection on the postoperative swelling and trismus following surgical extraction of mandibular third molar. ***J Coll Physicians Surg Pak*** 2014;24 (7):489–92.
34. Warraich R, Faisal M, Rana M, Shaheen A, Gellrich NC, Rana M. Evaluation of postoperative discomfort following third molar surgery using submucosal dexamethasone - a randomized observer blind prospective study. ***Oral Surg Oral Med Oral Pathol Oral Radiol*** 2013;116(1):16–22.
35. Mojsa IM, Pokrowiecki R, Lipczynski K, Czerwonka D, Szczeklik K, Zaleska M. Effect of submucosal dexamethasone injection on postoperative pain, oedema, and trismus following mandibular third molar surgery: a prospective, randomized, double-blind clinical trial. ***Int J Oral Maxillofac Surg*** 2017;46(4):524–30.
36. Lawal FB, Taiwo JO, Arowojolu MO. Comparison of two oral health-related quality of life measures among adult dental patients. ***Oral Health Prev Dent*** 2015;13(1):65-74.
37. Deepti C, Rehan HS, Mehra P. Changes in quality of life after surgical removal of impacted mandibular third molar teeth. ***J Maxillofac Oral Surg*** 2009;8(3):257–60.