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"JÚLIO DE MESQUITA FILHO"
Instituto de Ciência e Tecnologia
Campus de São José dos Campos

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Effectiveness of three different local routes of dexamethasone administration on postoperative sequelae following mandibular third molar surgery. A prospective randomised single-blind clinical study

Eficácia de três diferentes vias locais de administração de dexametasona em sequelas pós-operatórias após cirurgia de terceiros molares inferiores. Um estudo clínico prospectivo randomizado simples-cego

Mohamed Ihab MOSLEH[1]

1 - Beni-Suef University, Department of Oral and Maxillofacial Surgery. Beni-Suef, Egypt.

ABSTRACT

Objective: The aim of this study was to provide evidence for comparing the effectiveness of three different routes of local administration of Dexamethasone on the postoperative pain, edema and trismus following surgical removal of impacted mandibular third molar. **Material and Methods:** Forty-five patients underwent surgical removal of impacted lower third molars and were randomly allocated postoperatively into 3 groups: 8 mg of dexamethasone injected into the submucosa of the vestibule near the surgical site (group I), 8 mg of dexamethasone injected into the pterygomandibular space (group II) and 10 mg of dexamethasone powder applied to the extraction site, after bleeding control (group III). Facial swelling and maximal interincisal opening were measured at preoperatively. Pain was measured by the patient response to a visual analogue scale. Pain perception, Facial edema and trismus were evaluated for one week postoperatively. **Results:** There was no significant difference between the three groups concerning pain after 1, 2, 5, 7 days of follow up. However, group II showed less pain at 3 and 4 days. The difference between edema measurements was not significant in the three groups at 1, 5, 7 days, though in group I and II edema subsided from day 2. As for trismus, group I and III showed statistically significant lower maximum interincisal opening measurement than group II after two days. **Conclusion:** Local administration of Dexamethasone through three different routes is beneficial in decreasing postoperative sequelae following third molar surgery. Pterygomandibular space injection of Dexamethasone resulted in earlier resolution of pain, and less facial edema and trismus at the second postoperative day compared to the submucosal injection and transalveolar application. However, at one week the difference in measurements of the three variables between the groups was not significant.

KEYWORDS

Dexamethasone; Local routes of administration; Mandibular third molar; Surgery.

RESUMO

Objetivo: O objetivo deste estudo foi fornecer evidências para comparar a eficácia de três diferentes vias de administração local de dexametasona na dor pós-operatória, edema e trismo após a remoção cirúrgica do terceiro molar inferior impactado. **Material e Métodos:** Quarenta e cinco pacientes foram submetidos à remoção cirúrgica de terceiros molares inferiores impactados e distribuídos aleatoriamente no pós-operatório em 3 grupos: 8 mg de dexametasona injetados na submucosa vestíbular próximo ao local da cirurgia (grupo I), 8 mg de dexametasona injetados no espaço pterigomandibular (grupo II) e 10 mg de pó de dexametasona aplicados no local da extração, após o controle do sangramento (grupo III). Edema facial e abertura interincisal máxima foram medidos no pré-operatório. A dor foi medida pela resposta do paciente a uma escala visual analógica. Percepção de dor, edema facial e trismo foram avaliados por uma semana de pós-operatório. **Resultados:** Não houve diferença significativa entre os três grupos em relação à dor após 1, 2, 5, 7 dias de acompanhamento. No entanto, o grupo

II mostrou menos dor em 3 e 4 dias. A diferença entre as medidas de edema não foi significativa nos três grupos em 1, 5, 7 dias, embora nos grupos I e II o edema cedeu a partir do dia 2. Quanto ao trismo, os grupos I e III apresentaram medida de abertura interincisal máxima inferior estatisticamente significativa do que o grupo II depois de dois dias. **Conclusão:** A administração local de dexametasona por três vias diferentes é benéfica na redução das sequelas pós-operatórias após a cirurgia do terceiro molar. A injeção de dexametasona no espaço pterigomandibular resultou na resolução mais precoce da dor e menos edema facial e trismo no segundo dia de pós-operatório em comparação com a injeção submucosa e a aplicação transalveolar. No entanto, em uma semana, a diferença nas medidas das três variáveis entre os grupos não foi significativa.

PALAVRAS-CHAVE

Dexametasona; Rotas locais de administração; Terceiro molar inferior; Cirurgia.

INTRODUCTION

Surgical extraction of impacted third molars is the most common procedure in oral and maxillofacial surgery, and it's considered as a minor surgical procedure done mostly on an outpatient basis under local anesthesia. Patients undergoing the surgical removal of impacted third molar teeth usually experience significant postoperative pain, swelling and trismus that may have a biological and social impact and can cause distress to the patient affecting their daily activities and quality of life after surgery. Oral surgical procedures differ greatly in difficulty and in the degree of trauma caused to the surrounding tissues. The greater the amount of tissue injury, the more increased amount of inflammation in the perisurgical area and the intensity of acute and long-term postoperative complications.

Postoperative swelling and edema may be due partly to the conversion of phospholipids into arachidonic acid by phospholipase A_2, and the resultant synthesis of prostaglandins, leukotrienes, or thromboxane related substances acting as vasoactive substances and mediators of the inflammatory response [1,2] which lead to a state of increased peripheral sensitivity to noxious stimuli. This peripheral sensitization causes an afferent barrage of nociceptive activity that can lead to central sensitization [3]. These symptoms are not observed immediately after surgery but rather begin gradually, peaking two days after the surgery [4].

Oral surgeons have routinely prescribed corticosteroids, non-steroidal anti-inflammatory drugs (NSAID), and narcotic analgesics to manage these postoperative sequelae. The arachidonic acid release is inhibited and so the synthesis of leukotrienes and prostaglandins is suppressed by corticosteroid. Corticosteroids are successful in controlling acute inflammation by interfering with the multiple signaling pathways involved in the inflammatory response [5,6]; thus, reducing neutrophils accumulation and diminishing fluid transduction and swelling [7,8] as a an advantage over nonsteroidal anti-inflammatory drugs. This surgical procedure causes an inflammatory response translated into a sequelae of clinical triad; edema, trismus, and pain, with variable degree, and possibly other complications. Pain after surgery begin when the effect of local anesthesia subsides and reaches its maximum intensity during the first 12 hours postoperatively and may last for at least two days [9,10].

Swelling may be particularly significant when the surgery is prolonged and when large amounts of tissues are manipulated through elevation and retraction. It represents fluid accumulation in the interstitial area due to transduction from injured blood vessels and fibrin obstruction of lymph drainage [11]. Therefore, careful surgical technique is effective in limiting tissue damage and swelling. Edema is usually maximal at 48 hours after surgery and may completely resolve in 5-7 days [12].

limitations of mouth opening or Trismus after surgery is attributed to edema, hematoma, and pain associated with the surgical trauma. Restriction of mouth opening is reported to be due to the physiological splinting action of the investing muscles in an attempt to avoid painful movement and reduce discomfort after surgery [13] rather than to inflammation widespread involving the muscles of mastication with edema preventing its flexibility [13,14]. It usually reaches its maximum about 16 hours postoperatively, eventually more marked on the second day and improves through seven to ten days postoperatively [15-17].

Corticosteroids such as dexamethasone have been extensively used in varying regimen and routes to reduce postoperative inflammatory sequelae

due to its high potency in decreasing morbidity after oral surgery and long half-life [2,6,18-22]. Corticosteroids are usually administered as a single dose just before the procedure or given as a single dose immediate postoperatively. Both short term and single dose treatment have been found effective in reducing postoperative inflammation in many patients without producing side effects which also justifies their usage in minor surgical procedures. Dexamethasone is a long-acting glucocorticoids with long half-life more than 36 hours of duration, with the potentiality to hinder the physiological process of inflammation due to low sodium retaining capacity [23,24]. However, the clinical use of this type of drugs should be vigilant and reasonable for limited time and dose, because according to endocrinology analysis, after the 5th day of use, the therapy begin to produce immunosuppression, delayed healing and HPA axis suppression condition that in some patients may take up to 9 months to return to normal levels [25].

The majority of surgeons use corticosteroids to manage the surgery consequences with different protocols regarding the time and route of administration [19,20,25,26], but researchers still unable to find a consensus on the most effective dosage and administration method to reduce post-operative discomfort. Five well known routes are used for administering dexamethasone: oral, submucosal, intramuscular whether local or systemic, intravenous and endoalveolar [27-32]. Local routes of dexamethasone administration showed comparable effect to systemic routes [30]. It could be performed intra-operative or postoperative or both with all routes; however, trans-alveolar route postoperative use is applied immediately before wound closure [31,32].

The preoperative submucosal injection of dexamethasone compared to intramuscular injection was found to be beneficial in amending the patient postsurgical experience [24], and proved to be even more effective than intramuscular injection [33]. Submucosal injection does not require experience and is effective with significant decrease in swelling and trismus and improvement of quality of life [34-40]. This was further emphasised in many studies [29,41-45] where Submucosal injection of Dexamethasone after third molar surgery produced similar effects to intravenous, extraoral intramuscular route, oral administration and local intramuscular injection. A meta-analysis study conducted by Moraschini et al. [46] in 2016 on the effect of submucosal injection proved a statistically significant difference in reducing pain and edema after third molar surgery in comparison to placebo group. Further studies [42,47] have proven that postoperative submucosal injection of dexamethasone demonstrated better results in controlling pain when compared to preoperative injection. On the other hand, the preventive effect of 4 mg Dexamethasone injected into the masseter muscle on swelling, trismus and pain after removal of impacted mandibular third molars showed about 50% reduction of postoperative swelling and trismus and 30% reduction of postoperative pain [48]. On the contrary, a further recent study reported that it does not affect pain [49]. Furthermore, Latt et al [50] reported that the preoperative injection of 8mg Dexamethasone in the pterygomandibular space has effectively reduced the postoperative pain and other postoperative sequalae.

Several studies [31,32] have been conducted on comparing topical endoalveloar application of Dexamethasone and submucosal injection. Graziani et al. [32] concluded that no statistically significant differences were observed, both submucosal and endoalveolar administration of Dexamethasone are effective in reducing postoperative sequelae of surgical removal of lower wisdom teeth. On the opposite, Pappalardo et al. [31] concluded that a satisfactory results were obtained from endoalveolar route compared to non-satisfactory ones from the submucosal injection of Dexamethasone.

Concerning the Dexamethasone dose, no statistically significant difference was reported when two different doses of dexamethasone (4 mg and 10 mg) were used upon submucosal injection [30], increasing the dose provided no further benefit. Recently this was furtherly emphasized in a systematic review conducted by Larsen et al. [51] in 2018.

The aim of the present study was to provide evidence for comparing the effectiveness of three different routes of local administration of dexamethasone on the postoperative pain, edema and trismus following surgical removal of impacted mandibular third molar.

PATIENTS AND METHODS

This Prospective randomised clinical study included patients who required surgical

removal of a single impacted mandibular third molar under local anaesthesia. The study was approved by the local institutional academic ethics committee according to the Declaration of Helsinki in ethical issues relevant guidelines. Patients were randomly divided into three study groups in which Dexamethasone was locally administered by three different routes namely submucosal, pterygomandibular space injection and trans-alveolar application. Neither the patients nor the surgeons were blinded to the use of corticosteroids. A Nonprobability consecutive sampling technique was used to select the required sample. A sample size of 45 patients was planned to improve the power of study and enhance its internal validity. Inclusion criteria included partial bony impacted mandibular third molars with similar anatomical position, and similar surgical difficulty, free of pericoronitis and infection at the time of surgery, no allergies to the drug used or medicines prescribed postoperatively, non-smoking and non-medically compromised patients. Patients with periapical pathologies, pregnant or lactating females, patients having a recent history of long-term steroid therapy or currently taking anti-inflammatory drugs, antibiotic, or narcotic analgesics and patients who refused being involved in the study or those who could not attend the follow-up visits were excluded. All relevant demographic information of each patient was assessed by complete history, clinical and radiographic examination for eligibility to participate in this study. Patients were divided randomly into three equal groups including 15 patients each. Randomization was achieved using the sealed envelope method. A brief overview regarding the steps of surgery, medications and the required follow-up was explained to them and a written consent was obtained from each subject to participate in the study after explaining the potential sequalae and complications of the procedure.

The baseline data were recorded by an independent blinded examiner through preoperative assessment of facial width or contour and interincisal distance in mm. Facial contour was measured with flexible measuring tape from tragus of ear to corner of mouth, outer canthus of eye to gonion angle and from corner of the mouth to gonion angle on the operated side. Each of the three lines represents the distances between two fixed anatomical points as described by Neupart et al. [20]. Maximum interincisal opening MIO was assessed by recording the interincisal distance between the upper and lower right central incisor along the midline at maximum mouth opening. The measurements were taken with the patient seated in an upright position and the teeth in rest position. The arithmetic mean of these preoperative values (in millimeters) were taken as the baseline data. Pain was measured by the patient response to a visual analogue scale.

Surgical procedure

A standardised surgical procedure was performed on all patients by the same surgeon under similar conditions. Local anesthesia containing 2% lidocaine and 1:100.000 adrenaline was given to block the inferior alveolar, lingual and buccal nerve. Surgical access routinely achieved buccally through a triangular full thickness mucoperiosteal flap. The flap was repositioned and sutured back using simple interrupted sutures. Group I received 8mg dexamethasone (Dexa-Allvoran®, TAD Pharma GmbH, Legmo, Germany) as submucosal injection into the buccal vestibule near the surgical site and group II received 8 mg dexamethasone as pterygomandibular space injection similar to the inferior alveolar nerve block technique without touching bone. All injections were given immediately after surgery and wound closure. In group III trans-alveolar 10mg of dexamethasone sodium phosphate powder (Decadron fosfato, Merck Sharp & Dohme S.p.A, Roma, Italy) was applied incrementally into the extraction socket, after bleeding is controlled, followed by careful packing using a small plastic spoon to avoid spreading of the powder, immediately before suturing the wound edges onto it. All the subjects were prescribed a 5 days course of antibiotic and an analgesic for 3 days as well as a rescue analgesic to be used as needed /PRN in the event of aggravated uncontrolled pain episode. Surgical procedures and drug administration were done by the same surgeon to minimize the difference from inter-operator variability.

Postoperative Facial swelling and trismus were measured at the second, fifth and seventh post-operative day. Assessment of postoperative pain intensity was done on daily basis. Post-operative pain scoring was evaluated subjectively using a visual analog scale (VAS), ranging from 0 = 'no pain' to 10 = 'the worst possible pain' and objectively by counting the number of rescue analgesic tablets used. Patients were

instructed to report the number of rescue analgesic tablets required on the day of surgery and on each subsequent day of follow-up for the first post-operative week. All postoperative measurements were done by the same independent blinded examiner.

Statistical analysis

Numerical data were explored for normality by checking the distribution of data and using tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). Edema and maximum interincisal opening data showed normal (parametric) distribution while pain and percentage changes in all variables data showed non-normal (non-parametric) distribution. Parametric data were presented as mean, standard deviation (SD) and 95% Confidence Interval (95% CI) values. Non-parametric data were presented as median and range values. Repeated measures ANOVA test was used to compare between mean edema as well as maximum inter-incisal opening (MIO) in the three groups as well as to study the changes by time within each group. Bonferroni's post-hoc test was used for pair-wise comparisons when ANOVA test is significant. For non-parametric data, Kruskal-Wallis test was used to compare between the three groups. Friedman's test was used to study the changes by time within each group. Dunn's test was used for pair-wise comparisons. Qualitative data were presented as frequencies and percentages. The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

RESULTS

The study included forty five patients their age ranged between 25-32 years (mean 28.5 years), including 21 male and 24 female requiring surgical removal of the lower third molar. Group I included 6 males and 9 females, group II included 8 males and 7 females, and group III included 7 males and 8 females. No side effects, no discomfort, nausea, vomiting, headache, epigastric discomfort, gastrointestinal irritation concerning the drug used or rescue analgesics intake were reported by the patients in all groups; and all patients were able to resume their normal activities on the second day after surgery.

Pain (VAS) scores

There was no statistically significant difference between pain scores in the three groups after 1 day ($p = 0.270$), 2 ($p = 0.176$), 5 ($p = 0.303$) as well as 7, ($p= 0.688$); while after 3 days ($p = 0,042$) as well as 4 days ($p = 0.038$); the difference between pain scores in the three groups was statistically significant. Pair-wise comparisons between the groups revealed that there was no statistically significant difference between median pain scores in Groups I and III; both showed statistically significant higher score than Group II (Table I, Figure 1). Regarding the changes by time, there was a statistically significant change in pain scores by time in the three groups. In group I, Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in median pain scores after 2 days, from 2 to 3, 3 to 4 as well as from 4 to 5 days. From 5 to 7 days; the change was not statistically significant ($p < 0.001$). In Group II, Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in median pain scores after 2 days, from 2 to 3 as well as from 3 to 4 days, though from 4 to 5 as well as 5 to 7 days; the change was not statistically significant ($p < 0.001$). In Group III, Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in median pain scores after 2 days followed by non-statistically significant change from 2 to 3 days. The decrease in pain scores from 3 to 4, 4 to 5 as well as 5 to 7 days was statistically significant ($p < 0.001$).

Edema measurement (mm)

There was no statistically significant difference between edema measurement in the three groups pre-operatively ($p= 0.772$), after 1 day ($p= 0.944$), 5 days ($p= 0.610$) as well as 7 days ($p=0.839$). As regards the changes by time in Groups I, II and III there was a statistically significant change in edema measurement by time. In group I and II; Pair-wise comparisons between the time periods revealed that there was a statistically significant increase in mean edema measurement after 2 days followed by a statistically significant decrease in edema measurement from 2 to 5 days. From 5 to 7 days; the change in mean edema measurement was not statistically significant. In Group III, Pair-wise comparisons between the time periods revealed that there was a statistically significant

Table I - Descriptive statistics and results of Kruskal-Wallis test for comparison between pain scores in the three groups and Friedman's test for the changes by time within each group

Time	Group I (n = 15)		Group II (n = 15)		Group III (n = 15)		*P*-value	*Effect size (Eta Squared)*
	Median	Range	Median	Range	Median	Range		
1day	6 ^{D}	2.5-10	5 ^{D}	3-8	7 ^{D}	3-10	0.270	0.052
2 days	5 ^{E}	2-10	4 ^{E}	2-6	4 ^{E}	3-10	0.176	0.123
3 days	4 ^{AF}	0-9	2 ^{BF}	0-6	4 ^{AE}	2-7	0.042*	0.360
4 days	2 ^{AG}	0-8	0 ^{BG}	0-6	2 ^{AF}	1-5	0.038*	0.377
5 days	0 ^{H}	0-6	0 ^{G}	0-6	1 ^{G}	0-5	0.303	0.033
7 days	0 ^{H}	0-3	0 ^{G}	0-4	0 ^{H}	0-2	0.688	0.104
P-value (Changes by time)	<0.001*		<0.001*		<0.001*			
Effect size (w)	0.605		0.795		0.943			

*Significant at P ≤ 0.05. A, B, C superscripts in the same row indicate statistically significant difference between groups; D, E, F, G, H superscripts in the same column indicate statistically significant changes by time

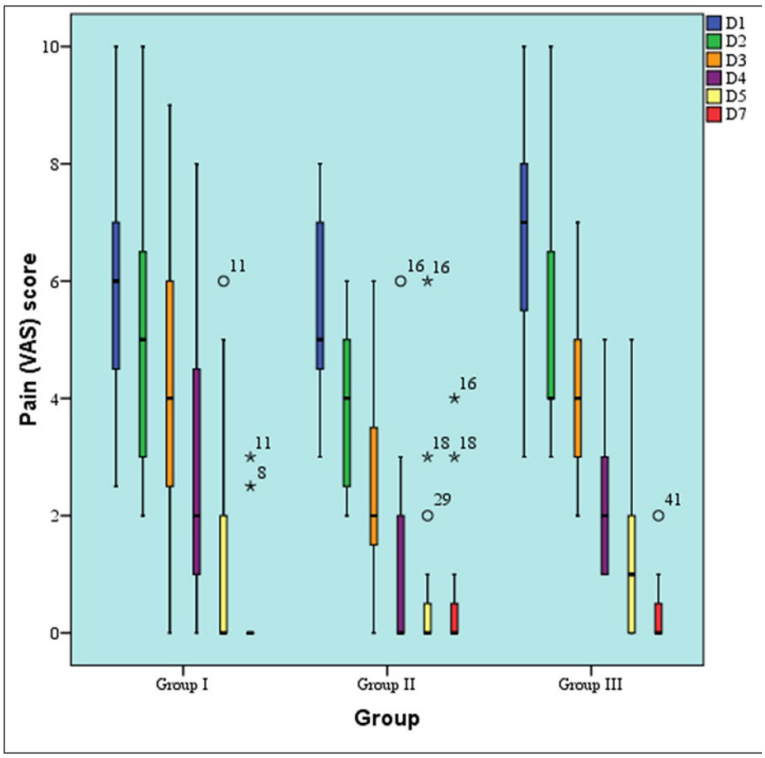

Figure 1 - Box plot representing median and range values for pain scores in the three groups (Circles and stars represent outliers).

increase in mean edema measurement after 2 days followed by a statistically significant decrease in edema measurement from 2 to 5 as well as from 5 to 7 days. The mean edema measurement after 7 days in the three groups showed non-statistically significant difference from pre-operative measurement ($p < 0.001$) (Table II, Figure 2).

Maximum Inter-Incisal Opening (MIO) (mm)

There was no statistically significant difference between MIO measurement in the three groups pre-operatively, after 5 ($p = 0.273$) as well as 7 days ($p = 0.971$). After 2 days, there was a statistically significant difference between MIO measurements in the three groups ($p = 0.046$). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between mean MIO measurements in Group I and Group III; both showed statistically significant lower mean MIO measurement than Group II. At one week, the maximum interincisal opening was not different from preoperative measurements in the group I, II and III. As regards the changes by time in Groups I, II and III, there was a statistically

Table II - Descriptive statistics and results of repeated measures ANOVA test for comparison between edema measurement in the three groups and the changes by time within each group

Time	Group I (n = 15)		Group II (n = 15)		Group III (n = 15)		*P*-value	*Effect size (Partial Eta Squared)*
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI		
Pre-operative	37.41 (2.48) ^{B}	36.32-38.49	37.21 (1.47) ^{B}	36.13-38.3	36.87 (2.16) ^{C}	35.78-37.95	0.772	0.012
2 days	38.69 (2.51) ^{A}	37.53-39.84	38.72 (1.49) ^{A}	37.57-39.87	38.47 (2.48) ^{A}	37.31-39.62	0.944	0.003
5 days	37.92 (2.55) ^{B}	36.66-39.18	37.05 (2.31) ^{B}	35.79-38.31	37.61 (2.39) ^{B}	36.35-38.87	0.610	0.023
7 days	37.29 (2.51) ^{B}	36.19-38.4	37.13 (1.43) ^{B}	36.03-38.24	36.84 (2.26) ^{C}	36.35-38.87	0.839	0.008
P-value (Changes by time)	<0.001*		<0.001*		<0.001*			
Effect size (Partial Eta Squared)	0.653		0.721		0.718			

*Significant at P ≤ 0.05. A, B, C superscripts in the same column indicate statistically significant changes by time. SD: standard deviation; CL: Confidence level.

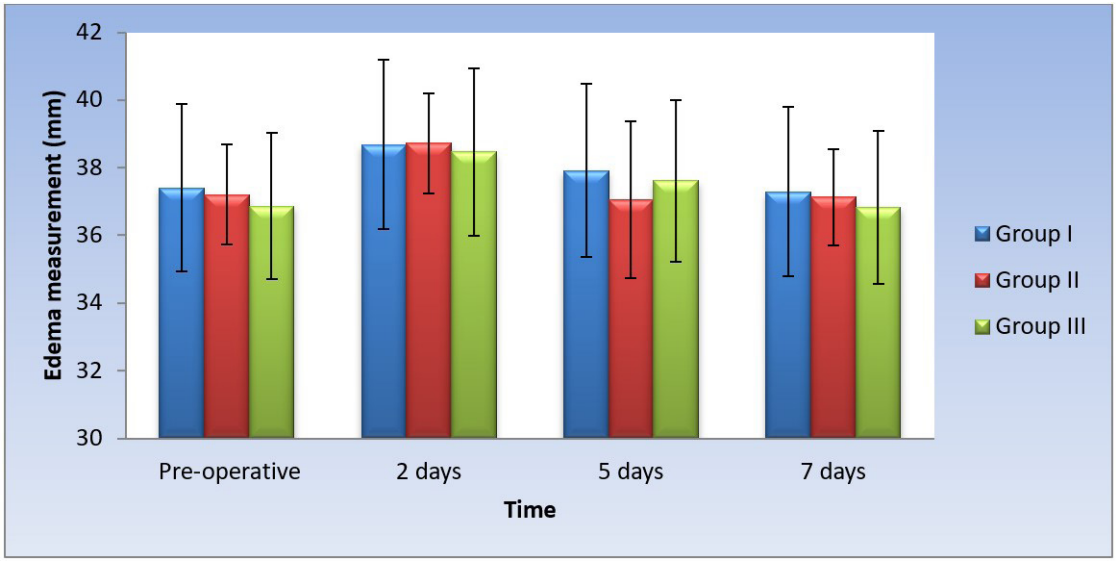

Figure 2 - Bar chart representing mean and standard deviation values for edema measurements in the three groups.

significant change in MIO measurement by time. Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in mean MIO measurement after 2 days followed by a statistically significant increase in MIO measurement from 2 to 5 as well as 5 to 7 days ($p < 0.001$). The mean MIO measurement after 7 days showed non-statistically significant difference from pre-operative measurement (Table III, Figure 3).

Percentage changes in different variables (Table IV)

Pain (VAS) scores

There was no statistically significant difference between percentage changes in pain scores in the three groups after 2, 3, 4, 5 as well as 7 days.

Edema measurement

There was no statistically significant difference between percentage changes in edema measurements in the three groups after 2 as well as 7 days. After 5 days; there was a statistically significant difference between percentage changes in edema measurements in the three groups ($p = 0.011$). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between median percentage increase in edema measurements in Groups I and III; both showed statistically significant higher percentage increase in edema measurement than Group II.

MIO measurement

There was a statistically significant difference between percentage changes in MIO measurements in the three groups after

Table III - Descriptive statistics and results of repeated measures ANOVA test for comparison between MIO measurement in the three groups and the changes by time within each group

Time	Group I (n = 15)		Group II (n = 15)		Group III (n = 15)		*P*-value	*Effect size (Partial Eta Squared)*
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI		
Pre-operative	40 (6.36) ^{D}	36.88-43.12	41 (6.27) ^{D}	37.88-44.12	40.4 (5.26) ^{D}	37.28-43.52	0.900	0.005
2 days	27.27 (6.92) ^{BF}	24.1-30.44	32.67 (5.07) ^{AF}	29.5-35.84	28.33 (6.13) ^{BF}	25.16-31.5	0.046*	0.136
5 days	34.93 (7.14) ^{E}	31.55-38.32	38.6 (5.79) ^{E}	35.22-41.98	35.67 (6.49) ^{E}	32.28-39.05	0.273	0.060
7 days	39.8 (5.93) ^{D}	36.68-42.93	40.33 (6.39) ^{D}	37.21-43.46	40.07 (5.65) ^{D}	36.94-43.19	0.971	0.001
P-value (Changes by time)	<0.001*		<0.001*		<0.001*			
Effect size (Partial Eta Squared)	0.771		0.541		0.746			

*Significant at P ≤ 0.05. A, B, C superscripts in the same row indicate statistically significant difference between groups; D, E, F, G superscripts in the same column indicate statistically significant changes by time.

Table IV - Descriptive statistics and results of Kruskal-Wallis test for comparison between percentage changes in different variables in the three groups

Variable	Time	Group I (n = 15)		Group II (n = 15)		Group III (n = 15)		*P*-value	*Effect size (Eta Squared)*
		Median	Range	Median	Range	Median	Range		
Pain	2 days	-20	-80-133	-33.3	-75-66.7	-25	-57.1-33.3	0.377	0.004
	3 days	-33.3	-100-100	-50	-100-20	-50	-62.5-33.3	0.312	0.028
	4 days	-66.7	-100-100	-100	-100-20	-66.7	-87.5-0	0.125	0.179
	5 days	-100	-100-100	-100	-100-20	-83.3	-100- -33.3	0.269	0.052
	7 days	-100	-100-0	-100	-100- -20	-100	-100- -66.7	0.700	0.107
Edema	2 days	3.16	0.5-7.59	4.05	2.6-6.94	4.05	1.39-7.79	0.473	0.042
	5 days	1.33 ^{A}	0-5.06	0.56 ^{B}	-15.62-5.19	1.6 ^{A}	0.52-5.19	0.011*	0.584
	7 days	0	-2.7-1.27	0	-1.33-0	0	-1.01-1.33	0.912	0.151
MIO	2 days	-29.8 ^{A}	-57.1- -11.1	-16.7 ^{B}	-43.6- -6.3	-29.3 ^{A}	-51.4- -13.3	0.006*	0.677
	5 days	-14.3 ^{A}	-28.6-0	-5.4 ^{B}	-19.1-0	-11.4 ^{A}	-26.3- -2.7	0.009*	0.614
	7 days	0	-5.8-2.7	0	-16.7-0	0	-6.3-2.7	0.524	0.059

*Significant at P ≤ 0.05. A, B, C superscripts in the same row indicate statistically significant difference between groups.

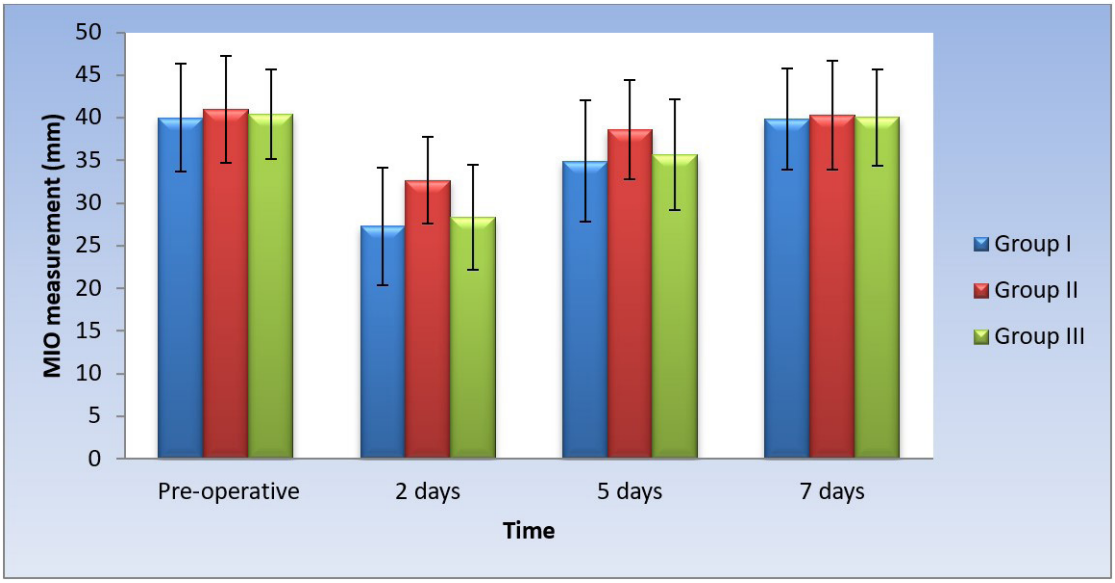

Figure 3 - Bar chart representing mean and standard deviation values for MIO measurements in the three groups.

2 (p = 0.006) as well as 5 days (p = 0.009). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between median percentage decrease in MIO measurements in Groups I and III; both showed statistically significant higher percentage decrease in MIO measurement than Group II. After 7 days; there was no statistically significant difference between percentage changes in MIO measurements in the three groups (p = 0.524)

DISCUSSION

The surgical removal of third molars is often associated with severe postoperative discomfort, and patients usually suffer from trismus, pain and facial swelling even when teeth are removed using a gentle atraumatic surgical technique. Prevention and management of such consequences is an essential part and a major area of interest in clinical practice; thus, many attempts have been made to reduce the post-operative sequelae by using the anti-inflammatory drugs. The anti-inflammatory efficacy of corticosteroids has led to their widespread use when third molars are removed to limit the intensity of complications, shorten the duration of the postoperative course and provide more comfort for the patient though it was reported that corticosteroids should only be used in selected cases [51]. In this study, to minimize the effect of many variable factors, patients were selected according to specific criteria, also surgery was performed using a standardized technique and done by the same operator. All other factors were unified including surgical difficulty, flap design, postoperative instructions and medications, though a number of researchers reported no association or statistically significant positive correlation between postoperative sequalae and demographic variables [52]. Time consuming surgical procedures play an important role in postoperative morbidity. The operation time may be a significant risk indicator for postoperative complications, and extended operation time has been related to postoperative pain and a long recovery period after third molar surgery [53]. Time factor in this study did not have an impact on or correlation with swelling, pain and trismus as all cases were operated by the same surgeon.

Concerning the use of corticosteroids after third molar surgery, several doses and routes have been suggested [19,20,27,30,31,42-44,51,54]. Much have been reported about the parental use of corticosteroids in oral surgery [2,42] but little have been published on the intraoral local route of administration though direct application of steroids in the traumatized tissues was documented to reduce the inflammatory-related events in previous studies [44,45,47]. Local administration of corticosteroids after third molar surgery is a painless procedure as it is more comfortable for patients to receive the injection in the region close to the already anesthetized operative field. The desirable anti-edematous effect seems to be dose dependent; however, different dosages of corticosteroids and administration routes revealed contrary results indicating that administration of a higher dosage of corticosteroids do not necessarily cause a proportionally decrease in facial swelling, pain and trismus [51]. In this study a dose of 8 mg Dexamethasone is used in group I and II. Swelling measurements and pain scores showed improvement with this small dose of Dexamethasone, which coincides with the results of further studies [30,38-42,47]. A dose of 10mg dexamethasone powder in group III was used as according to Graciani et al. [32]; an endoalveolar dose of 10 mg showed a greater reduction in postoperative edema compared to 4mg.

Local injection of Dexamethasone around the site of surgery is expected to provide a repository or sustained effect in term of less complications, slow absorption and prolonged duration of action. In addition, it does not require clinicians expertise or additional armamentarium and does not depends on patient compliance and repeated doses to maintain adequate blood levels during the postoperative period which is considered an advantage over the intravenous and intramuscular parental routes of administration [40].

Post-surgical facial edema is hard to quantify accurately because it involves 3 dimensions of measurements each representing the distance between two fixed anatomical points with an irregular, convex surface and can manifest itself internally as well as externally. The method used in this study to measure facial swelling, trismus and pain is simple, non-invasive, cost-effective, valid and time-saving method which provides numeric data for determination of parameters changes. In this study, the highest mean pain intensity score VAS was recorded in the first day after surgery in the three groups. This finding coincides with other previous studies [9,13].

Although some reduction of postoperative pain generally accompanies a reduction of edema; the role of corticosteroids in preventing post-surgical pain is controversial. Corticosteroids alone do not seem to have a clinically significant analgesic effect, as it was reported that PGE2 responsible for peripheral pain response is not adequately suppressed by Dexamethasone to prevent the sensitization of peripheral nociceptors [2]. Furthermore, the investigators proposed that Dexamethasone inhibits COX-1 associated with Thromboxane-B2 (TXB2) production in certain cell types and has little effect on inhibiting COX-1 and PGE2 production in other cell types [25]. Though, it has been reported that steroids can be related to a reduction in the number of analgesic tablets consumed after surgical extractions [55] as Dexamethasone in particular appears to decrease pain after surgery [16]. This appears to be widely in agreement with this study which showed a statistically significant decrease in mean VAS by time after surgery in group I, II and III through all periods of follow up. It was reported that Dexamethasone exerts its action at virtually every step in the inflammatory process, which leads to decreasing capillary dilatation, decreasing circulating lymphocytes and inhibiting prostaglandins and leukotrienes [16]. Moreover, group II showed less pain scores at day 3 and 4 compared to group I and III which could be attributed to the high potency, rapid onset upon local injection of Dexamethasone into the pterygomandibular space leading to reduction of edema developing in the medial pterygoid muscle and consequently good control of early postoperative pain. On the other hand, the mean % decrease in VAS from the first day to the seventh day between the three groups throughout the follow up periods proved to be statistically non-significant which could be due to the small sample included in the study.

Edema and Swelling was at a maximum on the second postoperative day in the three groups and lasted for 2-5 days this result coincides with further studies [22,52]. In group I and III edema was still evident till day 5, while in group II edema started to resolve after day 2 and subsided completely after one week in all groups. The early resolution of edema in group II occurred because the pterygomandibular space comprises loose areolar tissue, has high vascularity, and is adjacent to the operation area. Thus, injection of the drug into this space after local anesthesia ensures better absorption of the drug and sustained prolonged duration of action [49], compared to when Dexamethasone is applied submucosally or directly in the extraction socket. The data on reduction of swelling in this study resemble the results reported by others [25,49,51]. The results of this study confirm the observation of Dionne et al [25] who indicated that the greater analgesic effect with the peripheral route is due to achieving a higher effective drug concentration at the site or confines of injured tissues without loss due to its diffusion to other compartments and planes or the onset absorption and elimination. This was further emphasized in a recent meta-analysis [44] and a review [56] which reported Dexamethasone as the drug of choice in third molar surgeries since having similar results as intramuscular injection when given perioperatively than postoperative.

The time course for trismus described in the current study is in agreement with findings that indicated that trismus is maximum at day 1 or 2 postoperatively and generally resolve by day 7 [14-16,21-23,26]. Since steroids do not exert any direct effects on muscle contraction, trismus reduction would be secondarily due to the decrease of the local inflammatory-related events as edema, haematoma and pain. Therefore, trismus in group II was less than group I and III at the second day after surgery which could be due to direct injection into the vicinity of the muscle and better distribution of Dexamethasone in the traumatized region when given in the pterygomandibular space than when administered submucosally or transalveolar in the socket.

CONCLUSIONS

From this study we can conclude that the local use of Dexamethasone is effective in reducing postoperative pain, edema and trismus at the local site of action. It is convenient for both the surgeon and the patient, simple, safe, painless, cost effective therapeutic option, and improves postoperative quality of life after third molar surgery. Pterygomandibular space injection of Dexamethasone resulted in earlier resolution of pain, edema and less trismus at the second postoperative day compared to the submucosal and transalveolar routes. However, the difference between the groups proved to be non-significant at one week postoperative.

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Conflict of Interest

There are no conflict of interest to declare.

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Regulatory Statement

The study was approved by university ethical committe and i confirm have read the Helsinki Declaration and followed guidelines in this research work. The approval code of this study: FDBSUREC/0907202.

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Mohamed Ihab Mosleh
(Corresponding address)
Beni-Suef University, Department of Oral and Maxillofacial Surgery, Beni-Suef, Egypt.
Email: mohamed_mosle7@hotmail.com, mohamed_mosleh@dent.bsu.edu.eg

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