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Oral Surgery

Efficiency of Submucosal Versus Intramuscular Injection of Dexamethasone in Reducing Postoperative Complications Following Mandibular Third Molar Surgery: A Ramdomized, Double-blind Clinical Trial

Bagga Jamila[1,2*], Derbel Amine[1,2], Hentati Hajer[1,2], Chokri Abdellatif[1,2], Bouguezzi Adel[1,2], Selmi Jamil[1,2]

[1]Oral Medicine, Oral Surgery Department, University Clinic of Dental Medicine, Monastir, Tunisia
[2]Oral Health and Oro-Facial Rehabilitation Laborotary (LR12ES11), Faculty of Dental Medicine, University of Monastir, Tunisia

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***Corresponding author:** Bagga Jamila

Abstract **Original Research Article**

Objective: To study the efficiency of two different routes of administration of dexamethasone in controlling the main postoperative sequelae after mandibular third molars surgery. ***Patients and methods:*** 44 patients with 60 surgical extractions of impacted lower third molars were enrolled in a randomized, double blind study. Patients either received a submucosal injection of 8mg of dexamethasone and intramuscular injection of saline solution or vice versa. Procedure was carried out under local anesthesia. The assessment of postoperative edema and trismus was based on four facial measurements and the width of mouth opening, taken prior to surgery and on two and seven days, postoperative. To evaluate pain, the number of analgesic (paracetamol) tablets consumed and the visual analog scale score were used. ***Results:*** Due to their inability to complete data collection procedures, six patients were ruled out from the final statistical analysis. The mean surgery duration was 26.93 ± 9.74 minutes. No statistically significant difference was noted between the two groups regarding the three outcomes. ***Conclusion:*** The study findings suggest that the administration of 8mg of dexamethasone via the submucosal route is an effective approach to limit pain, edema and trismus following mandibular third molars surgical extraction.

Keywords: third molar, oral surgery, steroids, postoperative complications, clinical trials.

INTRODUCTION

As an oral surgeon, surgical extraction of lower third molars is a frequently performed operation on daily basis. It is often associated with postoperative discomfort such as facial swelling, pain, and trismus. These postoperative complications may cause dysfunction and affect the patient's quality of life [1, 2].

Corticosteroids have been commonly used to reduce these sequelae due to their role in inhibiting the body's inflammatory response to surgical trauma [3].

Although many studies assessed the effectiveness of steroids in reducing edema, trismus and pain, no clear consensus has been established [4].

This trial aims to study the efficiency of two different routes of administration of 8 mg of dexamethasone, the submucosal (SM) route versus the intramuscular (IM) route, in minimizing the postoperative complications after lower third molars surgery.

PATIENTS AND METHODS

Sample Collection

A randomized, double-blind, parallel-group, single center controlled study performed at the "Oral Medicine, Oral Surgery" department, University Clinic of Dental Medicine, Monastir, Tunisia. This study involved 44 patients, aged between 18 and 36 years. All patients needed surgical extraction of an impacted lower third molar for various reasons.

The local ethic committee had provided its approval to the research protocol. Written informed consent was received from all patients. The trial was carried out in conformity with the protocol and the Declaration of Helsinki and the author vouch for the completeness and accuracy of the data and analyzes.

The age limit was set at 18. Patients must not have any systemic disease. A dental panoramic radiograph was used to classify impacted mandibular third molars. Only Class II or III of Pell and Gregory's third molar classification were included.

Exclusion criteria taken into account were: History of allergic or adverse reactions to test drugs, amoxicillin and paracetamol; Any signs of inflammation or infection at the time of the operation; Antibiotics or anti-inflammatory drugs taken at least 10 days before surgery; If female, pregnancy, lactation or contraceptive pill intake; procedure extending beyond 60 min.

Measurements

Preoperatively, 4 facial distances were measured on the operated side using flexible tape (Figure 1):

- S1: lateral cantus of the eye - mandibular angle.
- S2: ala of the nose - mandibular angle.
- S3: corner of the mouth - mandibular angle.
- S4: pogonion - mandibular angle.

The maximal distance, separating the tips of upper and lower central incisors and considered as the width of the mouth opening, was taken by a clipper.

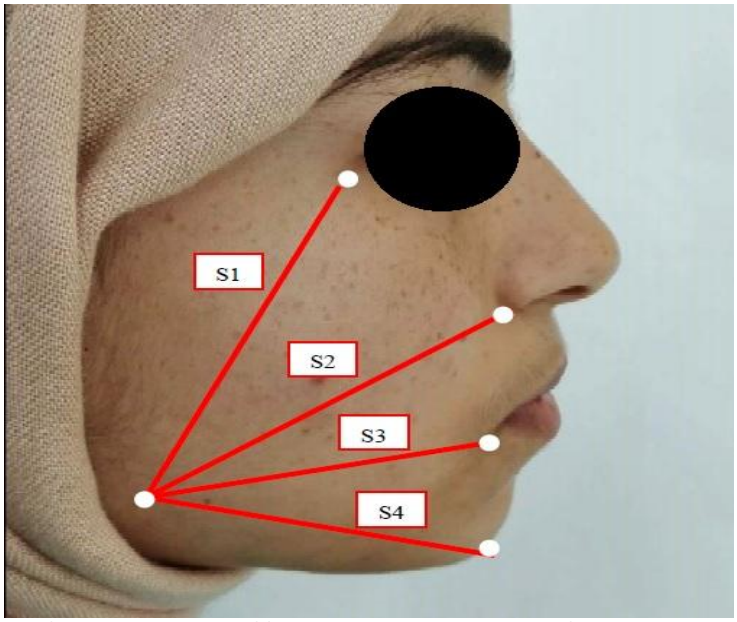

Fig-1: Anatomical distances used for the measurement of facial edema: S1: lateral cantus of the eye-mandibular angle, S2: Ala of the nose-mandibular angle, S3: Corner of the mouth-mandibular angle, S4: pogonion-mandibular angle

Allocation

The randomization was conducted by the surgeon through a computer-generated random number table. Patients were randomly assigned to the submucosal dexamethasone or the intramuscular dexamethasone group in blocks of ten. Then, the assigned treatment was masked using sequentially numbered sealed envelopes.

Blinding

Since we compared the efficiency of dexamethasone in different administration routes, the patients and the operator blinding was done by dummy technique. Each patient received two injections; one group received submucosal injection of 8mg of dexamethasone and intramuscular placebo injection of saline solution, the other one received submucosal placebo injection of saline solution and intramuscular injection of 8mg of dexamethasone.

One of the investigators, who did not take part in the patients' recruitment and evaluation processes, opened the envelope and prepared the two injections in the immediate preoperative period. The operator received two syringes; one with 8mg of dexamethasone and one with saline solution. These syringes were identical in size, shape, color, and appearance, with indicators of each injection location ("S" for submucosal and "I" for intramuscular).

Interventions

In order to keep the variations due to different operators to minimum, all patients were operated by the same surgeon using a standard technique.

Prior to surgery, all patients were submitted to extra-oral antisepsis with povidone iodine 10% and intraoral antisepsis with 0.12% chlorhexidine gluconate for 1 minute. Mepivacaine 3% (Médis®, Nabeul, Tunisia) was used for inferior alveolar nerve block, and mepivacaine 2% (Médis®, Nabeul, Tunisia) with epinephrine 1:100.000 were used for buccal and lingual infiltrations.

Surgical access was done by a standard envelope mucoperiosteal flap with a number 15 scalpel blade. Bone was then removed to expose the tooth. If needed, the tooth was divided and then extracted. The rough bony margin was smoothened; the socket was revised and copiously irrigated with normal saline solution. Then patients received the submucosal injection.

Interrupted 3/0 silk sutures (Vicryl® Ethicon, Somerville, NJ) were used to secure the flap in place. A gauze pad was placed over the site to assure local hemostasis and the standard postoperative instructions were explained to the patients. The surgery duration was measured from the first incision made until completing the last suture. Any cases in which surgery extended beyond 60 min were ruled out.

In the immediate postoperative period, patients had received the intramuscular injection and were instructed to take 1g of amoxicillin every 12 h for seven days, and 500 mg of paracetamol required as "rescue" analgesia and to use a 0.12% chlorhexidine mouth rinse three times per day for ten days.

Data Collection

Facial Edema

The evaluation of facial edema was based on the four facial distances. The preoperative four values were taken at the baseline for the operated side and checked on the second postoperative day (POD2) and the seventh postoperative day (POD7).

Pain

Pain assessment was based on:

- A visual analogue scale (VAS), 10 cm length, that vary from 0 = "no pain" to 10 = "the worst possible pain" on POD2.
- The number of analgesic tablets consumed until the seventh postoperative day (patients were instructed not to take tablets if they did not experience any pain, one or two tablets if they experienced moderate or severe pain respectively every 8 hours).

Trismus

To assess trismus, the width of the mouth opening was measured prior to surgery and on POD2 and POD7.

Data Collection Methods

Data collection was performed using a standard form. Only patients who were present in all follow-up appointments were taken into account in the final data analysis.

Statistical Methods

The significance of differences between the groups was calculated by IBM (SPSS) Statistics, version 18.0 (NY, USA).

The analysis of variance with T Student test was used to estimate the significance of differences among groups. The limit of significance was set at 0.05.

RESULTS

Forty four patients with sixty extracted teeth were enrolled in the study. Six patients were ruled out from the final statistical analysis due to their inability to complete data-collection procedures. Four patients were from the submucosal group and two patients were from the intramuscular one (Figure-2).

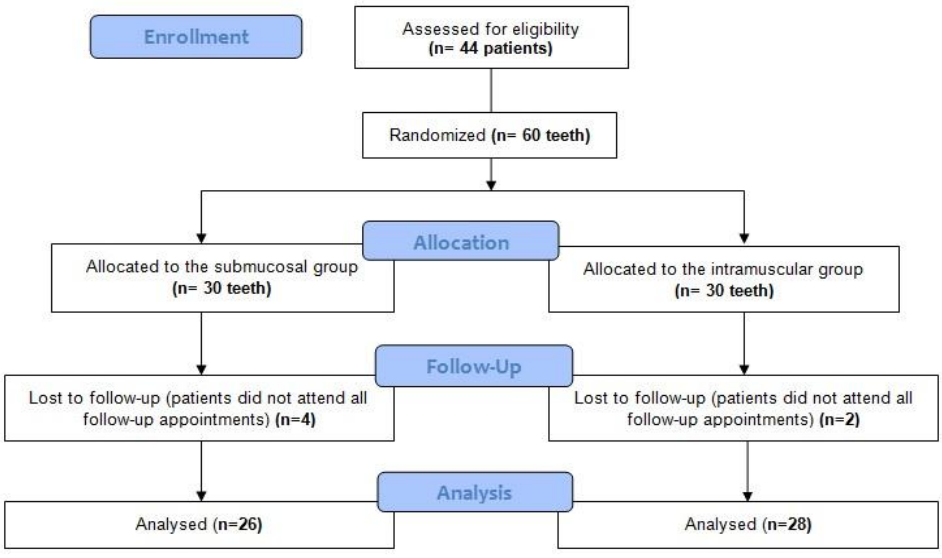

Fig-2: Flow diagram: Screening, enrollment and follow-up of the study patients

The mean surgery duration was 26.93 ± 9.74 min. No significant difference in age, tooth impaction, tooth-ramus relationship and surgery duration between the two groups was noted. On the contrary, gender was considered to be a confounding variable as there was a female predominance (72.2%).

The left mandibular third molar (53.8%) was more extracted than the right one (46.2%) in the submucosal group. Conversely, in the intramuscular group, the right mandibular third molar was (67.9%) more extracted than the left one (32.1%) (Table-1).

Table-1: Baseline data: Clinical and demographic characteristics

Variable	SM group	IM group	Total
Age, mean ± SD, yr	**22.31 ± 3.1**	**23.64 ± 3.53**	**22.22 ± 2.75**
Gender, n			
Male	**3**	**12**	**15**
Female	**23**	**16**	**39**
Impaction depth, n			
A	**17**	**15**	**32**
B	**9**	**10**	**19**
C	**0**	**3**	**3**
Ramus relationship, n			
Class II	**3**	**5**	**8**
Class III	**23**	**23**	**46**

SM: submucosal; IM: intramuscular; SD: standard variation; yr: years

Outcomes

Facial Edema

The four facial distances and their total sum increased on POD2, then decreased on POD7 nearing the preoperative measurement, with no statistically significant difference between the submucosal and intramuscular groups (p>0.05) (Table-2).

Table-2: Edema assessment in the study groups (millimeters): Mean values and differences from preoperative values (total sum)

	SM group Mean (SD)	IM group Mean (SD)	*P*-value
Preoperative	406.30 (23.27)	417.10 (29.22)	0.14
Day 2	417.15 (23.20)	430.60 (28.67)	0.06
Day 7	408.30 (22.40)	419.42 (29.24)	0.12
Differences			
Preoperative - day2	10.84 (9.17)	13.50 (12.46)	0.38
Preoperative - day 7	1.76 (2.99)	1.92 (4)	0.87

SM SM: submucosal; IM: intramuscular; SD: standard variationDay

The four measurements and their total sum were greater in males than in females. No statistically significant difference was detected between the two sides in the distances' augmentation on POD2 and POD7 (p>0.05).

The ">30-min" group had a statistically significant augmentation of the mandibular angle-Ala of the nose distance (S2) and the total sum on POD2 (p=0.04 and p=0.01 respectively).

Pain Evaluation

VAS Score

A not significant difference was noted regarding the mean of VAS score as the "> 30-min" group recorded a higher VAS score than the "≤ 30-min" group (mean VAS=3.26 and mean VAS=4.1 respectively) (p=0.07).

Analgesic Consumption

No statistically significant difference in the amount of analgesic tablets consumed by the submucosal and the intramuscular groups and the female and male groups was found (p=0.55 and p=0.77 respectively).

The mean of analgesic tablets consumed by the "≤ 30-min" and the ">30-min" groups was 9.87 and 16 respectively. The "≤ 30-min" group had consumed less analgesic than the ">30-min" group with a statistically significant difference (p=0.03) (Table-3).

Table-3: Total of analgesic tablets consumed

	Mean	SD	Variance	Median	P-value
SM group	10.85	9.53	90.93	7	
IM group	12.46	10.56	111.51	9	0.55
Female group	11.44	9.28	86.14	10	
Male group	12.33	12.06	145.52	8	0.77
0-30 minutes group	9.87	8.9	79.3	7	
> 30 minutes group	16	11.43	130.8	15.5	0.03*

SM SM: submucosal; IM: intramuscular; SD: standard variation

* P <0.05, statistically significant

No statistically significant difference in the analgesic consumption per day was found between the submucosal and intramuscular groups. It remained evident for the male and female groups.

The ">30-min" group consumed more analgesic per day than the "≤ 30-minute" group on the third and fourth postoperative days with a statistically significant difference (p=0.009 and p=0.04 respectively). For the other days, no difference was noted (p>0.05) (Table-4).

Table-4: Number of analgesic tablets consumed per day by the surgery duration groups

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
≤ 30 minutes group	2.87	2.5	1.84	1.18	0.79	0.47	0.32
> 30 minutes group	3.5	3	2.88	3	1.81	0.75	0.38
P-value	0.19	0.44	0.12	0.009*	0.04*	0.52	0.88

SM SM: submucosal; IM: intra-muscular

* P <0.05, statistically significant

Trismus Measurement

The mouth opening decreased on POD2 day then increased on POD7 and got close to the preoperative measurement. No statistically significant difference was noted between the submucosal and intramuscular groups in the amount of trismus on POD2 and POD7 (p=0.57 and 0.86 respectively).

The amount of trismus was greater in females than in males on POD2 with a statistically significant difference (0.0006).

There was a statistically significant difference between the "≤ 30-minutes" group and the "> 30-minutes" group in the amount of trismus on POD7 (p=0.01) (Table-5).

Table-5: Measurements of mouth opening (millimeters): mean values and differences from preoperative values in the male and female groups

	Male group Mean (SD)	Female group Mean (SD)	*P*-value
Preoperative	40.47 (6.63)	38.85 (4.48)	0.30
Day 2	35.8 (9.18)	27.36 (8.26)	0.002*
Day 7	39.47 (7.71)	36.21 (6.25)	0.11
Differences			
Preoperative - day2	4.67 (6.33)	11.49 (8.29)	0.006*
Preoperative - day 7	1 (2.44)	2.64 (4.77)	0.21

SM SD: standard variation

* P <0.05, statistically significant

DISCUSSION

Corticosteroids are often prescribed after surgical removal of lower third molars to limit postoperative edema. But no clear recommendations regarding different molecules, dosages, time and administration's routes were established. Dexamethasone and methylprednisone are among the most studied corticosteroids [5, 6].

Dexamethasone was first tested in 1965 to reduce postoperative complications in oral surgery. As from then, it has been widely used especially following surgical extraction of third molars due to its potent anti-inflammatory effect and extended half-life [7]. Various routes of administration have been proposed including intravenous, intramuscular, submucosal, endo-alveolar and oral routes [8].

Facial Edema

The main anti-inflammatory effect of Corticosteroids is reducing the fluid transudation and hence edema [3, 9]. In this study, we have focused on the efficiency of two administration routes of 8mg of dexamethasone; the submucosal versus intramuscular. The results showed no significant difference in the reduction of postoperative edema between the two groups on POD2 and POD7. These results are in agreement with the results of Majid et al. who found no significant difference between the submucosal and the intramuscular injection of 4mg of dexamethasone in the reduction of edema. Although, both routes showed a highly significant reduction of edema when compared to the control group [9]. Furthermore, Antunes *et al.*, proved that the dexamethasone in the submucosal route was as efficient as the oral route in reducing edema [10].

Grossi *et al.*, studied the efficiency of different doses of dexamethasone i.e 4mg and 8mg given submucosally immediately after anesthesia. They found no significant difference of edema reduction with the use of a higher dose of dexamethasone and concluded that with an increased dose 8mg no additional benefits were given [11]. On the contrary, Filho *et al*., concluded that rising the dose to 8 mg enhance the effectiveness of dexamethasone in reducing edema after surgical extraction of mandibular third molars [12]. In this study, since we have compared the submucosal with the intramuscular route, the most effective dose of dexamethasone for the two routes which is the 8mg dose was chosen.

Two systematic reviews with meta-analysis of randomized clinical trials were performed aiming to study the effeciency of submucosal injection of dexamethasone to reduce the postoperative complications after surgical extraction of third molars [13, 14]. Maraschini *et al.*, had included 476 patients in their meta-analysis and concluded a moderate level of evidence that dexamethasone administered via the submucosal route is effective in limiting postoperative edema after surgical third molars extraction [13]. The second meta-analysis of Chen *et al*., included 368 patients and showed that dexamethasone significantly reduced edema ($p<0.00001$) [14].

In this study, females were more exposed to postoperative edema than males with no statistically significant difference ($p = 0.09$). This could be explained by the fact that sexual hormone regulate the body fluid and osmotic pressure [15]. Our results were in disagreement with the results of other descriptive studies which aimed to identify the risk factors for postoperative sequelae following surgical removal of third molars. In fact, de Santana-Santos et al. found that edema was greater in females with a statistically significant difference [16].

Contrary to Yuasa *et al*., who noted that males were more exposed to postoperative edema than females [17].

Moreover, we have assessed the influence of the surgery duration on the onset of postoperative edema. In fact, we have concluded that the surgery extend beyond 30 minutes was a risk factor for greater edema on the second postoperative day ($p=0.01$). These results seem to be logical since a longer surgery is usually associated with more surgical trauma, thus with more postoperative complications and are consistent with those of Santana-Santos *et al.*, [16].

It's quite impossible to precisely quantify the postoperative swelling since it involves three dimensional areas with irregularities and convexities.

In this study, edema was assessed using five facial landmarks to evaluate four distances. This method qualifies the changes in soft tissue by numbers. Most of authors used this linear measurement that is directly made onto the skin surface because of its simplicity and reliability [11, 18].

For the timing of edema measurement, we chose POD2 and POD3. As the edema has a peak in the 24-48 postoperative hours, this timing would be informative. Many authors assessed edema on POD1 POD3 and POD7 [9].

Pain

The importance of surgical trauma influences significantly the postoperative pain perception. The effectiveness of corticosteroids in reducing postoperative pain is still a subject of controversy [18].

In this study, we could not make a clear conclusion about this fact since we have no control group without dexamethasone administration.

We found no significant difference between the submucosal and the intramuscular groups in the VAS score ($p=0.99$) and in the number of analgesic tablets consumed ($p=0.55$). Our results were in concordance with the result of other studies that reported no difference between the submucosal and the intramuscular groups in minimizing postoperative pain [9, 19].

Moraschini *et al*., reported a statistically significant lower postoperative pain in favor of the dexamethasone group in comparison to control ($p=0.02$) [13].

No statistically difference between the males and females in pain perception in VAS score ($p=0.99$) and in the number of analgesic tablets consumed ($p=0.77$) was noted. In a review of clinical and experimental studies about the relation between sex and

pain, Fillingim *et al*., found that females perceived more oral pain than males. This could be explained by the influence of sexual hormone in pain perception or in responses to pain treatment [20].

Moreover, we have studied the influence of the surgery duration on the postoperative pain. No significant difference in pain perception was noted when the surgery extended beyond 30 minutes (p=0.07). But the number of analgesic tablets consumed decreased significantly when the surgery duration was less than 30 minutes (p=0.03). These findings seem to be logical, since the more surgical trauma is important the more will be the postoperative pain. De Santana-Santos et al. have drawn the same conclusion that the surgery duration influences significantly the postoperative pain [16].

Trismus

Trismus, measured as a reduction in width of the mouth opening, is a major postoperative complication following mandibular third molars extraction. It is due to fluid accumulation in the fascia of masticatory muscles which compresses the neural structure. This may explain the fact that trismus seems to follow the postoperative edema [13, 18]. The occurrence of trismus may alter the patient's quality of life since it affects basic functions essentially eating and talking [13, 21].

In this study no significant difference in the reduction of trismus between the submucosal and the intramuscular groups on the second and the seventh postoperative days (p=0.57 and p=0.86 respectively) was noted. These results are in agreement with that of Majid *et al*., [9]

When comparing the efficiency of dexamethasone received submucosally with control (no injection or saline solution injection) in the reduction of early and late trismus, the results differ between the studies [11, 13, 14, 22]. In fact, Grossi *et al*., reported no difference in the reduction of trismus between the submucosal injection of 4mg and 8mg of dexamethasone with the control group [11]. However, Warraich *et al*., found a significant limitation in the mouth opening in the control group in comparison to the submucosal group [22].

Moraschini *et al*., reported no statistically significant difference between the two groups (p=0.17) in reducing trismus [13]. In the contrary, Chen *et al*., concluded that that the dexamethasone group had less early and late trismus than the control group (p=0.0003) (p=0.01) [14].

In this study, we have noted that females were significantly affected with trismus than males on POD2 (p=0.006). However, on POD7 no difference was found (p=0.21).

Moreover, we concluded that extend of the surgery beyond 30 minutes did not affect the onset of the trismus on POD2 (p=0.31). But, this is true on POD7 (p=0.01).

The main limitation of this study is that males and females were not equally distributed within the two groups. We noticed a preponderance of females (72.2%).

A split-mouth design should have been adopted. Its main advantage consists in eliminating many of the inter-individual variability from the assessment of the treatment effect [23]. Certainly, this method will increase the power of the study in comparison to parallel group design, but it will hamper the patients' recruitment process as a symmetrical disease patterns is needed [24, 25].

CONCLUSION

In summary, 8mg of dexamethasone injected submucosally is in fact effective in controlling the postoperative complications following third molars surgery and can be a good alternative to the intramuscular route.

The submucosal route is beneficial for the surgeon because the treatment is administered near the operative site and more comfortable for the patient as the drug is injected in an already anesthetized field.

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