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EFFICACY OF SUB-MUCOSAL, INTRA-MASSETERIC AND INTRA-MUSCULAR ROUTES OF DEXAMETHASONE ADMINISTRATION ON POST-OPERATIVE COMPLICATIONS FOLLOWING IMPACTED MANDIBULAR THIRD MOLAR SURGERIES, COMPARATIVE CLINICAL TRIAL

Nermine Ramadan Mahmoud*

ABSTRACT

Purpose: The aim of the current study was to compare the efficacy of dexamethasone injection submucosally, intra-masseteric and intramuscular in surgical removal of mandibular third molars on post-operative swelling, mouth opening and pain.

Patients and Methods: forty five patients with impacted mandibular third molars were selected to undergo surgical removal of mandibular third molars. Patients were randomly divided into three groups of fifteen each. **Group I**, taking sub-mucosal dexamethasone injection, **Group II**, taking Intra-masseteric dexamethasone injection and **Group III**, taking intramuscular dexamethasone injection, all patients were injected pre-operatively Assessment of swelling, mouth opening, and pain was done at intervals of 1st, 3rd, and 7th post-operative days.

Results: our study showed no statistically significant difference between mean MMO as well as VAS in Group I and II; both showed statistically significant higher mean MMO and VAS than Group III. Significant reduction in pain and swelling in both sub-mucosal, intra-masseteric and intra-muscular but a greater immediate effect on trismus was seen in sub-mucosal and intra-masseteric routes

Conclusion: It can be concluded that pre-operative dexamethasone injection is an effective pharmacological agent to reduce post-surgical third molar removal sequelae such as pain, swelling and trismus.

KEYWORDS: Antibiotics, corticosteroid, dexamethasone, post-surgery swelling, third molar extraction

* Lecturer oral and Maxillofacial Surgery, Oral Surgery Department, October 6 University

INTRODUCTION

Surgical removal of impacted third molar representing one of most commonly performed dento-alveolar procedures. These are associated with postoperative sequelae, such as pain, trismus and swelling. The sequelae of the postoperative complications depends on various factors such as patients related factors and surgical procedures, varying physiological inflammatory response, the degree of tissue trauma and the extent of bone manipulation [1].

A surgical trauma in the oral cavity always causes tissue injury characterized by hyperemia, vasodilatation, increased capillary permeability with liquid accumulation in the interstitial space and granulocyte and monocyte migration, [2,3] due to the increased osmotic pressure in capillaries (Starling law). Edema is the expression of exudates or transudation, and in surgery, probably both the events occur.[4–6] Transudation in fact is secondary to blood flow slowing (i.e. hyperemia, vasodilatation, stenosis, etc.), while a superimposed infection is responsible for exudates.[4]

Extension of incision as well as tissue manipulation and length of surgery could affect the entity of swelling. According to previous published data, postoperative swelling and pain are significantly lower following a smaller incision. [5,7–10]

When impacted third molars are removed, post-surgery is characterized by limitation in the mouth opening, pain, reduced masticatory capability and swelling of variable degree. The latter represents a serious issue as it affects the ability of the patient to interrelate and to return to the routine working life, especially during the first 3 days following oral surgery. [11–14]

This explain swelling, pain and difficulty in opening the mouth after surgical removal of third molars which can affect quality of life of patient, steroids with their anti-inflammatory action can be quite useful in preventing the discomfort associated with such procedures [15].

PHARMACOLOGIC STRATEGIES

Pharmacologic management of inflammation mainly includes blocking formation or inhibiting the action of inflammatory mediators [16]. Steroids, non-steroidal anti-inflammatory agents, enzymes are some of them. The initial phase of the inflammatory process is marked by production of vasoactive substances, such as prostaglandins and leukotriene, corticosteroids act by suppressing their production, thereby reducing fluid transudation and consequent edema [17].

Corticosteroids

Most surgeons utilize corticosteroids based on the recognized efficacy to control surgery outcomes and to yield a comfortable post-surgery period. [18] However, there are no definite protocols relative to different molecules or regimens, time and route of administration.

Corticosteroids are known to reduce inflammation, fluid transudation and edema. [18, 19] They represent the most efficacious anti-inflammatory agents and to this purpose can be used in several different conditions. [20]. The mechanism of action of corticosteroids has been largely reviewed by several authors, [21, 22] and those are preferentially utilized in dentoalveolar surgery include dexamethasone (administered orally), dexamethasone sodium phosphate (IV or IM), dexamethasone acetate (IM), methylprednisolone (orally), methylprednisolone acetate and methylprednisolone sodium succinate (IV or IM). In the past, betamethasone has been used as well. [23-25]

Dexamethasone given as an intra-masseteric injection is seen to reduce complications following third molar surgeries [26].

Dexamethasone is a long acting corticosteroid and has minimal mineralo-corticoid activity and

maintains a therapeutic plasma level throughout immediate postoperative period. [27]

Milles and Desjardins [28] obtained good results with administration of methylprednisolone (16 mg, orally, 12 h before; and 20 mg, IV, immediately before surgery) against placebo administration as one oral tablet 12 h preoperatively. They also suggested continuing administration of methylprednisone for at least 3 days following surgery.

Tiwana et al. [29] reported their study on patients undergoing surgery for extraction of four impacted molars. Patients were divided in two groups: the first group was administered with 8 mg dexamethasone IV and the second one with 40 mg methylprednisolone IV. It was concluded that preoperative administration of corticosteroids IV has a better outcome, even in absence of antibiotic therapy, as suggested by 8% of patients with slight swelling versus 28% in control untreated group.

However, by evaluating the swelling by ultrasonography and CT, ***Esen et al.*** [30] observed a significant reduction with preoperative administration of 125 mg methylprednisolone IV, and 500 mg penicillin orally, for 5 days following surgery.

In the same study, adrenal activity was analyzed by measuring plasma cortisol concentrations before surgery and 2 and 7 days post-surgery, leading to the conclusion that corticosteroid therapy was well tolerated if no absolute contraindications were present, did not affect adrenal activity for short period administration, and showed the ability to reduce edema by 42%. However, it is recommended not to exceed the dose of 125 mg and to avoid long-term treatment to preserve adrenal function. Likewise, ***Bystedt and Nordenram*** [31] suggested avoiding very high dosages, and maximum 5-day therapy. In contrast, ***Helhag et al.*** [32] suggested that 10 mg dexamethasone, two times a day, reduces the plasma cortisol levels.

A significant 62% reduction of edema has been reported after orthognathic surgery when 1 mg/kg methylprednisolone was administered IV for 24 h. [33]

Efficacy of preoperative administration of 1.5 mg/kg methylprednisolone sodium succinate IV versus that of 3 mg/kg followed post-surgery by 2 million IU oral penicillin V, plus acetaminophen 500 mg, was evaluated in patients operated for extraction of lower third molars bilaterally. [34] No significant differences were observed in inflammation, pain and swelling between the two dosage regimens.

Good results were also obtained with 32 mg methylprednisolone and 400 mg ibuprofen administered 12 h before and 12 h after surgery respectively.[35]

Postoperative edema can also be controlled with dexamethasone administered in the submucosa. [36] Submucosal administration of 4 mg dexamethasone 1 h before surgery has been compared with that of 8 mg dexamethasone plus 2 g amoxicillin/clavulanic acid two times a day. Both dosages improved swelling versus untreated groups, but no differences were observed between the two dosage regimens.

However, ***Laureano Filho et al.***[37] reported that in patients undergoing removal of impacted third molars, administration of 8 mg dexamethasone 1 h before surgery, followed by 750 mg paracetamol every 6 h for 4 days produced a better control of swelling when compared to treatment with 4 mg dexamethasone. Dexamethasone has also been administered 1 h before surgery (4 mg orally) and 12 h after surgery (4 mg IV), along with analgesic agents (30 mg ketorolac IV), when pain was present.[28].

Elhag et al.[32] reported that administration of 10 mg dexamethasone IM, 1 hour before surgery and 10–18 h later together with antibiotic therapy (400 mg oral metronidazole, administered pre- and post-surgically), significantly reduces swelling when compared to only postoperative treatment, without corticosteroids.

Although a significant reduction (50%) of swelling was observed 2 days after surgery in patients treated with 4 mg dexamethasone IM, no effect was present after 7 days.[38] However, when 4 mg dexamethasone administered IV 5–10 min before surgery, no effects in controlling edema when no antibiotic therapy was associated with it.[39]

A review of the literature has been reported by ***Markiewicz et al.***[40] in which all corticosteroids have been compared to methylprednisolone. The effect of treatments administered either immediately or later after surgery has been analyzed. Data obtained report a reduction of 0.6 mm and of 0.5 mm of swelling at 1–3 and 7 days, respectively. However, no significant difference was observed due to the high standard deviations, leading the authors to conclude that corticosteroid administration causes only a slight reducing effect on edema.

In a different study,[41] patients were divided into three groups: untreated or treated after surgery with 25 mg prednisolone IM or 25 mg prednisolone IM together with diclofenac. Both treatments produced a reduction of swelling on the 2nd day post-surgery.

Vegas-Bustamante et al. [42] reported that following extraction of mandibular impacted third molar, a single treatment of methylprednisolone, 40 mg IM, through intrabuccal injection in the masseter muscle, together with amoxicillin 750 mg, every 8 h for 7 days, and 575 mg metronidazole, orally, every 6 h for 3 days, significantly reduced postoperative swelling when compared to control, untreated group.

The intramasseteric muscle injection has also been studied by ***Montgomery et al.***[43] The authors did not report any advantage of this versus systemic administration.

Graziani et al.[44] analyzed 43 patients undergoing surgery for removal of bilateral impacted lower third molars and administered with (i) dexamethasone, 4 mg endoalveolar; (ii) dexamethasone, 10 mg endoalveolar; and (iii) dexamethasone, 4 mg in the oral submucosa. Amoxicillin and clavulanic acid, 1 g every 12 h, were added for 5 days. The best control of edema was observed in the group treated with 4 mg dexamethasone endoalveolar.

The investigated studies showed how the effectiveness of the corticosteroid administration before surgery could not be considered as a predictable therapy in order to control the postoperative swelling and edema of the surgical area. However, corticosteriod administration during the surgeries or in the postoperative period seems to give a great benefit for reducing postoperative swelling and edema.

Antibiotics

Antibiotic therapy to treat established infection or as prophylactic strategy in order to prevent infection or to control postoperative discomfort in third molar surgery is today a broadly accepted indication with documented efficacy. [45] However, the great variability in the pharmacologic administration related to parameters like time and way of administration, chemical structure seems to influence the effectiveness of the postoperative discomfort.[46,47]

In a study reported by ***Halpern et al.,***[48] reduction of both alveolar osteitis and inflammation was observed in patients treated with penicillin (15,000 UI/kg, IV) or clindamicin (600 mg in patients allergic to penicillin), 1 h before surgery versus placebo-treated control patients.

Administration of amoxicillin (2 g orally), 1 h before surgery, did not result in any improvement in the postoperative period versus untreated controls. [49] According to ***Martin et al.***,[50] parenteral antibiotic prophylaxis should be applied only in the case of osteotomy, whereas oral surgeons are suggested to limit the use of second and third generation antibiotics in maxillo-facial surgery and systemic pathologies.[51] In patients treated with amoxicillin/

clavulanic acid (1 g, twice a day, for 5 days before surgery), no significant differences were observed versus patients treated with the same drug for 5 days following surgery.[52]

Several authors discussed the effectiveness of antibiotic prophylaxis, and it seems to be highly recommended for patients who present with a high risk of infection or when traumatic surgical procedures have been performed. [53–57] Antibiotics are largely used in the postoperative period. [58, 59] They can be applied topically or administered systematically, but the efficacy of antibiotic treatment in the preoperative period is also highlighted. According to some authors, to obtain results with antibiotic treatment, they must be administered preoperatively to act when the bacterial infection starts. [58]

Topical endoalveolar application of minocyclin [10 mg in bioresorbable poly (D, L-lactide-co-glycolide) lactide sustained-release microspheres] following extraction of third molars, significantly reduces the risk of postoperative infection.[60]

In contrast, no significant difference as regards to pain, swelling and trismus was reported in a study which compared patients treated without antibiotic therapy and others with administration of clindamycin 300 mg three times a day, for 5 days, and amoxicillin/clavulanic acid 1 g, two times a day, for 5 days.[59]

Sekhar et al.,[61] using metronidazole, 1 g, 1 h before surgery, and 400 mg every 8 h for 5 days after surgery, reported that antibiotic treatment is not efficacious either in the pre- or postoperative period.

However, topical application of covomicyn D resulted in a good control of postoperative swelling in a study carried out in the same patients treated for extraction of the impacted third molars with or without antibiotic therapy.[62]

According to the literature review, the use of the antibiotics before surgery could be considered a predictable procedure to avoid and control the possible infection related to the surgery. If infection and inflammation are present in the surgical area, an antibiotic therapy seems to give a better clinical compliance of the tissues undergoing surgery. The antibiotic administration before, during and after surgery seems to be a better therapeutic choice for controlling the infection arising in the postoperative period.

Surgical techniques

Different surgical strategies have been reported in the literature to reduce the postoperative discomfort after the third molar surgeries. They can be used either separately or in association with pre- or postoperative strategies. Different kinds of flaps have been used during extraction of impacted third molars, specifically to assess whether a marginal flap could control postoperative swelling better than a para-marginal one.[63] No significant difference in the entity of swelling was observed after using the two kinds of flaps. However, there were no significant differences between the marginal and para-marginal flaps in terms of swelling.

In contrast, ***Kirk et al.*** [64] reported significant differences, particularly for swelling and pain, during the 2nd day post-surgery between a group with a buccal flap and a group with a triangular flap modified by Szmyd.[65] In the latter case, an increased swelling was observed.

Based on hypothesis that the flap shape could affect postoperative swelling, the response to surgery was analyzed in same patient undergoing germectomy of the third molars and treated with a triangular marginal and a paramarginal flap.[66] However, no significant difference between the two treatments was observed.

In other studies, ***Pasqualini et al.***[67] have compared 100 patients treated with tight suture with 100 patients sutured after removal of 5–6 mm of mucosa distally to second molar to allow draining. Using this procedure, postoperative swelling was

reduced especially on days 2 and 4, while in the group treated with tight suture, the peak of swelling was observed on day 3.

According to several authors, [68–70] tight closure favors edema formation by creating a unidirectional valve that allows fragments of food to reach the cavity, but not to leave it easily. This can be the origin of local infection, inflammation, edema and potential alveolar osteitis and pain for difficult draining.[71]

However, different factors such as edema, pain and trismus that follow extraction of impacted third molars can be related to suture technique and to surgery length, and the use of a draining tube can be helpful in reducing or preventing postoperative swelling. This has been confirmed in study specifically designed to compare postoperative responses in two groups, one treated with suture and the other with draining. [72,73]

Rakprasitkul and Pairuchvej [74] they reported reduced swelling with suture in the presence of a draining tube when compared to the primary suture.

In a different study, the effect of draining has been compared with methylprednisone treatment. [75] Although no significant differences were reported, pharmacological treatment reduced swelling and was better tolerated by patients. It is then reasonable to conclude that most authors prefer secondary healing and/or draining rather than primary closure.

Different surgical procedures have also been related to postoperative swelling. Osteotomy through piezo-surgery has given positive results on time factor compared to traditional techniques. However, the studies analyzed did not involve extraction of impacted third molars, but general osteotomy of the jaws.[76–78]

Cryotherapy

Therapeutic effects of ice applied on a surgery wound are due to changes of hematic flow and consequent vasoconstriction and reduced metabolism.[79,80] In surgery and orthopedics, in fact, the main function of ice on the treated area is to produce vasoconstriction and to control bleeding, resulting in reduced metabolism and control of bacterial growth.[81–83]

Ice applied on area such as the jaw angle produces rapid chilling in cutaneous layer, but the effect is much lesser and occurs much later in deep tissues such as bone. [84–86] The application of ice does not have to be too long as this may be responsible for tissue death due to prolonged vasoconstriction, ischemia and capillary thrombosis. [87]

The first physiological response of tissues to cryotherapy is reduction of local temperature that causes reduced cellular metabolism. In this way, cells consume less oxygen and resist longer to ischemia.[88] In treatment of impacted third molars, the use of ice shows a good efficacy in reducing post-surgery swelling and pain as demonstrated by several authors. [79,85,88]

In contrast, ***van der Westhuijzen et al.*** [83] state that there is no scientific evidence to support the use of icepack in oral and maxillo-facial surgery and report that slight, but not significant difference in swelling was observed in patients in whom ice was applied continuously for 24 h after extraction of third molars compared to untreated controls. Similar lack of efficacy has also been reported by other authors. [89]

Moore et al. [90] reported that the application of ice pack following surgery of impacted third molars causes a reduction of 3°C in oral mucosa, while **Nusayr** [91] underlines in his study the importance of right length of time of cold application.

It is interesting to note that low laser dosage (4 J cm^2), applied soon after surgery, produces a good control of swelling, especially in patients treated with 4 mg dexamethasone IM. [92]

Aim of study: The aim of the current study was to compare the efficacy of dexamethasone injection

submucosally, intra-masseteric and intramuscular in surgical removal of mandibular third molars on post-operative swelling, mouth opening and pain.

PATIENTS AND METHODS

Forty five patients requiring surgical removal of impacted mandibular third molars that met the inclusion crieteria and were enrolled in randomized clinical study.

They were divided into three groups of fifteen each.

Group I, taking sub-mucosal dexamethasone injection. **Group II**, taking Intra-masseteric dexamethasone and **Group III**, taking intramuscular dexamethasone injection. All patients were injected pre-operatively.

Inclusion criteria

- Patients in the age group - 18 to 45 years
- Patients free from any systemic diseases.

Exclusion criteria

- Patients with existing active infections
- Patients with systemic disorders
- Patients on steroids therapy.
- Pregnant and lactating women.

Surgical technique

Initial pre-operative assessment was done for all patients. All the patients were operated on by a single surgeon. Following standard surgical and aseptic protocols, the patients were prepared for the surgical procedure. Classical inferior alveolar nerve block along with lingual nerve block was administered.

Group I, was injected sub-mucosal dexamethasone, [Figure 1] Group II, Intra-masseteric dexamethasone was administered [Figure 2] Group III , taking intra-muscular dexamethasone injection.

A standard Ward's incision was utilized to gain access, and the tooth was delivered after adequate bone cutting and tooth splits as was deemed necessary. Care was taken to ensure minimal trauma to the tissues.

Post-extraction, the socket was copiously irrigated using 5% povidone-iodine solution diluted with equal parts of normal saline. The flap was sutured back with 3-0 silk sutures using two interrupted sutures.

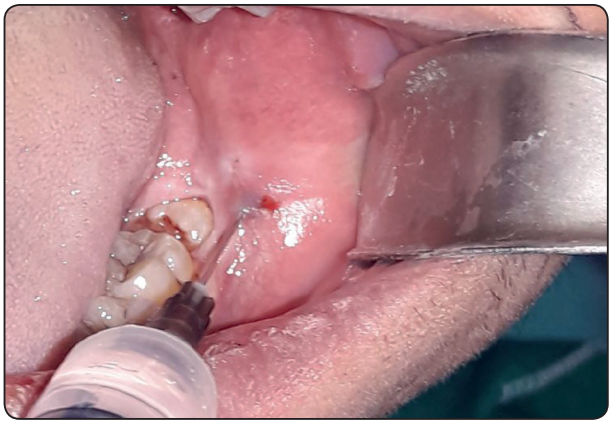

Fig. (1): Clinical photograph showing submucosal dexamethasone injection in group I

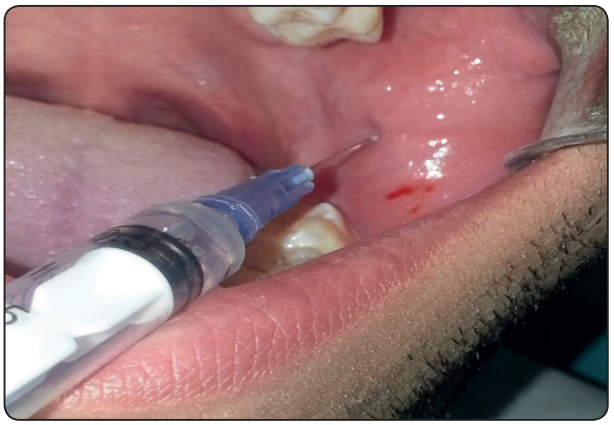

Fig. (2): Clinical photograph showing intramasseteric dexamethasone injection in group II

The patients were given standard post-operative instructions and were told to apply an ice pack on the region intermittently for the next 6 h. All patients were put on 500 mg of amoxicillin thrice daily for 5 days and paracetamol (500 mg) combination thrice

a day for 3 days. All patients were followed up at intervals of 1st, 3rd, and 7th post-operative days. Suture removal was done on the 7th post-operative day if the healing was deemed to be satisfactory.

The following were assessed:

• **Swelling evaluation:** by a modification of tape measuring method described by ***Schultze-Mosgau et al.***[93] Two measurements were made between three reference points: Tragus, pogonion, and the corner of the mouth [Figure 3,4].

• **Pain evaluation:** Post-operative pain was evaluated using a visual analogue scale (VAS) that ranged from 0 = "no pain" to 10 = "the worse possible pain." Figure (5)

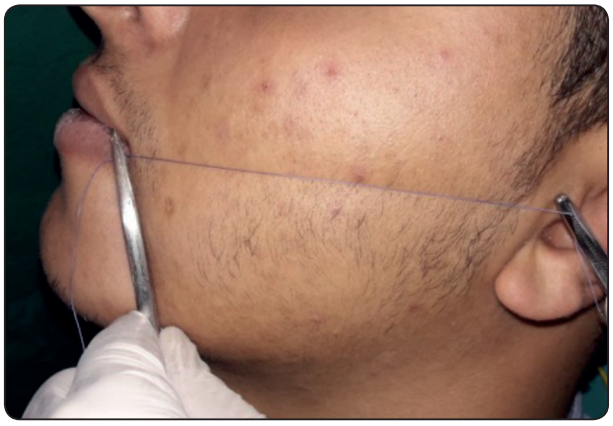

Fig. (3): Pre-operative clinical photograph showing method of assessing swelling according to Schultze-Mosgau et al. [93] from tragus to corner of mouth in group I=13.5 cm

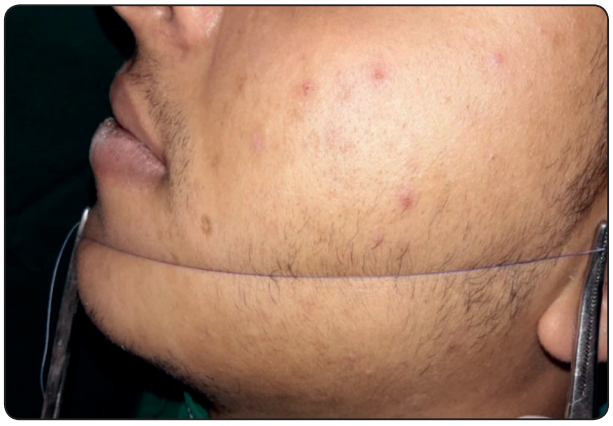

Fig. (4): Pre-operative clinical photograph showing method of assessing swelling according to Schultze-Mosgau et al. [93] from tragus to progonion in group I=18.5 cm

• **Trismus evaluation:** Measured as the difference in maximal mouth opening (taken as the distance between upper and lower central incisors) before and after operation. Figure (6)

RESULTS

Follow up

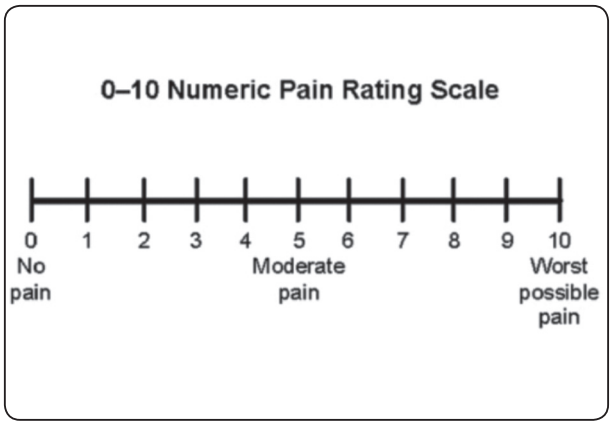

Fig. (5): Showing numeric pain rating scale, visual analogue scale (VAS)

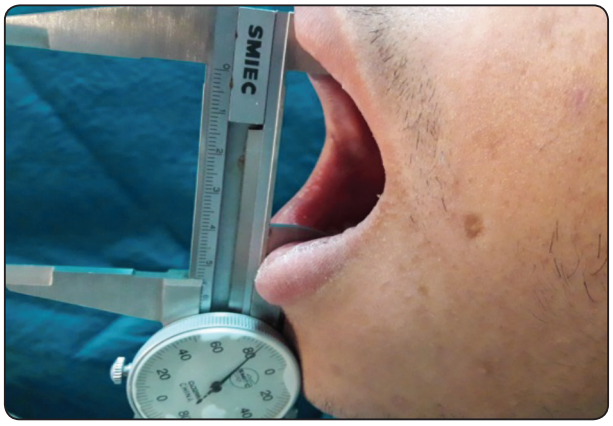

Fig. (6): Post-operative clinical photograph showing the inter-incisal opening to assess degree of trismus in group I = 56 mm

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). Age, Maximum Mouth Opening (MMO) and edema measurements data showed normal (parametric) distribution while pain scores

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. For parametric data, one-way ANOVA test was used to compare between mean age values in the three groups. Repeated measures ANOVA test was used to compare between mean MMO and edema measurement values 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. Chi-square test was used for comparisons between the groups.

The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM® SPSS® Statistics Version 20 for Windows

Demographic data

There was no statistically significant difference between mean age values in the three groups. There was also no statistically significant difference between gender distributions in the three groups.

I- Maximum Mouth Opening (MMO)

Pre-operatively, there was no statistically significant difference between MMO in the three groups (*P*-value = 0.816, Effect size = 0.010).

After 1 day, there was a statistically significant difference between MMO in the three groups (*P*-value <0.001, Effect size = 0.339). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between mean MMO in Groups I and II; both showed statistically significantly higher mean MMO than Group III.

After 3 days, there was a statistically significant difference between MMO in the three groups (*P*-value <0.001, Effect size = 0.437). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between mean MMO in Groups I and II; both showed statistically significantly higher mean MMO than Group III.

After 7 days, there was a statistically significant difference between MMO in the three groups (*P*-value = 0.009, Effect size = 0.200). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between mean MMO in Groups I and II; both showed statistically significantly higher mean MMO than Group III.

TABLE (1): Mean, standard deviation (SD), frequencies (n), percentages and results of one-way ANOVA and Chi-square tests for comparisons of demographic data of the three groups

	Group I (n = 15)	Group II (n = 15)	Group III (n = 15)	***P*-value**
Age (Years)				0.530
Mean (SD)	27.6 (4.8)	29.8 (5.2)	28.5 (5.9)	
Gender [n (%)]				0.910
Male	10 (66.7)	9 (60)	9 (60)	
Female	5 (33.3)	6 (40)	6 (40)	

****: Significant at P ≤ 0.05***

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® SPSS, Inc., an IBM Company.

As regards the changes by time in Group I, there was a statistically significant change in MMO by time (*P*-value <0.001, Effect size = 0.793). Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in MMO after 1 day. From 1 day to 3 days as well as from 3 to 7 days, there was a statistically significant increase in mean MMO. The mean MMO after 7 days showed non-statistically significant difference from pre-operative MMO measurement.

Similarly in Group II, there was a statistically significant change in MMO by time (*P*-value <0.001, Effect size = 0.772). Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in MMO after 1 day. From 1 day to 3 days as well as from 3 to 7 days, there was a statistically significant increase in mean MMO. The mean MMO after 7 days showed non-statistically significant difference from pre-operative MMO measurement.

While for the changes by time in Group III, there was a statistically significant change in MMO by time (*P*-value <0.001, Effect size = 0.928). Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in MMO after 1 day. From 1 day to 3 days as well as from 3 to 7 days, there was a statistically significant increase in mean MMO. However; the mean MMO after 7 days showed statistically significantly lower mean value compared to pre-operative MMO measurement.

TABLE (2): Descriptive statistics and results of repeated measures ANOVA test for comparison between MMO in the three groups as well as 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)***
Pre-operative					
Mean (SD)	46.5 (4.3) ^{D}	47.5 (4.6) ^{D}	47.1 (4.9) ^{D}	0.816	0.010
95% CI	44.1 – 48.9	45.1 – 49.9	44.7 – 49.4		
1 day					
Mean (SD)	37.4 (3.8) ^{AF}	39 (4.9) ^{AF}	31.6 (4.9) ^{BG}	<0.001*	0.339
95% CI	35 – 39.8	36.6 – 41.4	29.2 – 34		
3 days					
Mean (SD)	41.4 (3.7) ^{AE}	43.5 (4.5) ^{AE}	34.7 (5) ^{BF}	<0.001*	0.437
95% CI	39.1 – 43.7	41.2 – 45.8	32.4 – 37		
7 days					
Mean (SD)	45.6 (3.9) ^{AD}	46.7 (4.2) ^{AD}	41.8 (4.9) ^{BE}	0.009*	0.200
95% CI	43.3 – 47.9	44.5 – 49	39.5 – 44.1		
***P*-value (Changes by time)**	<0.001*	<0.001*	<0.001*		
Effect size (Partial Eta Squared)	0.793	0.772	0.928		

**: Significant at P ≤ 0.05 A,B,C Superscripts in the same row indicate significant differences between groups D,E,F,G Superscripts in the same column indicate significant changes by time*

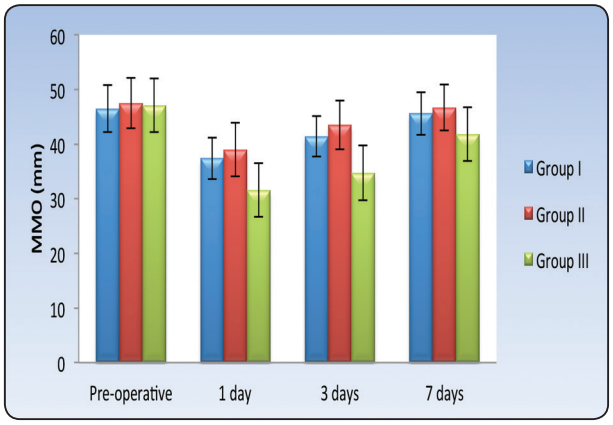

Fig. (7): Bar chart representing mean and standard deviation values for MMO in the three groups

II- Pain (VAS scores)

After 1 day, there was a statistically significant difference between pain scores in the three groups (*P*-value = 0.001, Effect size = 0.195). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between median pain scores in Groups I and II; both showed statistically significantly lower median pain scores than Group III.

After 3 days, there was a statistically significant difference between pain scores in the three groups (*P*-value = 0.014, Effect size = 0.155). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between median pain scores in Groups I and II; both showed statistically significantly lower median pain scores than Group III.

After 7 days, there was a statistically significant difference between pain scores in the three groups (*P*-value <0.001, Effect size = 0.310). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between median pain scores in Groups I and II; both showed statistically significantly lower median pain scores than Group III.

As regards the changes by time in Group I, there was a statistically significant change in pain scores by time (*P*-value <0.001, Effect size = 0.970). Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in pain scores from 1 day to 3 days as well as from 3 to 7 days.

TABLE (3): Descriptive statistics and results of Kruskal-Wallis and Friedman's tests for comparison between pain scores in the three groups as well as 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)*
1 day					
Median	4 ^{BD}	4 ^{BD}	6 ^{AD}	0.001*	0.195
Range	2 – 7	2 – 7	4 – 9		
3 days					
Median	2 ^{BE}	3 ^{BE}	4 ^{AE}	0.014*	0.155
Range	0 – 5	0 – 5	2 – 5		
7 days					
Median	0 ^{BF}	1 ^{BF}	2 ^{AF}	<0.001*	0.310
Range	0 – 2	0 – 4	0 – 4		
***P*-value (Changes by time)**	<0.001*	<0.001*	<0.001*		
Effect size (H)	0.970	0.851	0.900		

****: Significant at P ≤ 0.05 A,B,C Superscripts in the same row indicate significant differences between groups D,E,F Superscripts in the same column indicate significant changes by time***

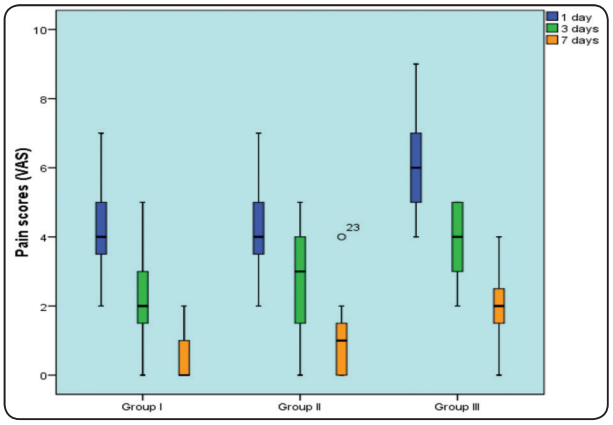

Fig. (8): Box plot representing median and range values for pain (VAS) scores in the three groups (Circle represents outlier)

Similarly in Group II, there was a statistically significant change in pain scores by time (*P*-value <0.001, Effect size = 0.851). Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in pain scores from 1 day to 3 days as well as from 3 to 7 days.

Same results were obtained in Group III, there was a statistically significant change in pain scores by time (*P*-value <0.001, Effect size = 0.900). Pair-wise comparisons between the time periods revealed that there was a statistically significant decrease in pain scores from 1 day to 3 days as well as from 3 to 7 days.

III- Swelling

A) Tragus-corner of the mouth measurement:

Pre-operatively, there was no statistically significant difference between tragus-corner of the mouth measurements in the three groups (*P*-value = 0.304, Effect size = 0.055).

After 1 day, there was a statistically significant difference between tragus-corner of the mouth measurements in the three groups (*P*-value <0.001, Effect size = 0.397). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between mean tragus-corner of the mouth measurements in Groups I and II; both showed statistically significantly lower mean value than Group III.

After 3 days, there was a statistically significant difference between tragus-corner of the mouth measurements in the three groups (*P*-value = 0.008, Effect size = 0.207). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between mean tragus-corner of the mouth measurements in Groups I and II; both showed statistically significantly lower mean value than Group III.

After 7 days, there was no statistically significant difference between tragus-corner of the mouth measurements in the three groups (*P*-value = 0.097, Effect size = 0.105).

As regards the changes by time in Group I, there was a statistically significant change in tragus-corner of the mouth measurement by time (*P*-value <0.001, Effect size = 0.492). Pair-wise comparisons between the time periods revealed that there was a statistically significant increase in tragus-corner of the mouth measurement after 1 day. From 1 day to 3 days, there was no statistically significant change in mean tragus-corner of the mouth measurements. From 3 to 7 days, there was a statistically significant decrease in mean tragus-corner of the mouth measurement. The mean tragus-corner of the mouth measurements after 7 days showed non-statistically significant difference from pre-operative tragus-corner of the mouth measurement.

As regards the changes by time in Group II, there was a statistically significant change in tragus-corner of the mouth measurement by time (*P*-value <0.001, Effect size = 0.692). Pair-wise comparisons between the time periods revealed that there was a statistically significant increase in tragus-corner of the mouth measurement after 1 day. From 1 day to 3 days as well as 3 to 7 days, there was a statistically significant decrease in mean tragus-corner of the

mouth measurements. The mean tragus-corner of the mouth measurements after 7 days showed non-statistically significant difference from pre-operative tragus-corner of the mouth measurement.

While in Group III, there was a statistically significant change in tragus-corner of the mouth measurement by time (*P*-value <0.001, Effect size = 0.869). Pair-wise comparisons between the time periods revealed that there was a statistically significant increase in tragus-corner of the mouth measurement after 1 day. From 1 day to 3 days as well as 3 to 7 days, there was a statistically significant decrease in mean tragus-corner of the mouth measurements. However; the mean tragus-corner of the mouth measurement after 7 days showed statistically significantly higher mean value compared to pre-operative tragus-corner of the mouth measurement.

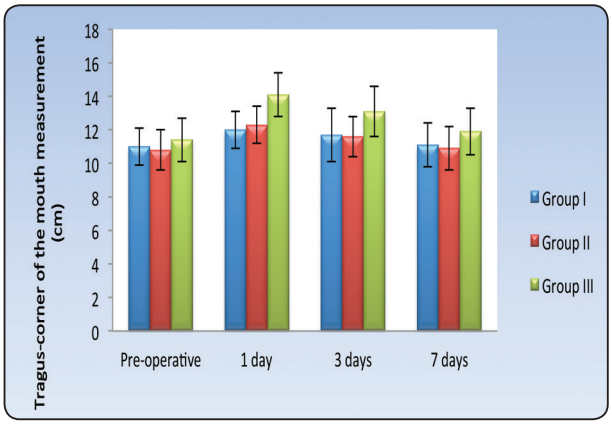

Fig. (9): Bar chart representing mean and standard deviation values for tragus-corner of the mouth measurements in the three groups

TABLE (4): Descriptive statistics and results of repeated measures ANOVA test for comparison between tragus-corner of the mouth measurements in the three groups as well as 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)
Pre-operative				0.304	
Mean (SD)	11 (1.1) ^{E}	10.8 (1.2) ^{F}	11.4 (1.3) ^{G}		0.055
95% CI	10.3 – 11.6	10.1 – 11.4	10.8 – 12.1		
1 day				<0.001*	
Mean (SD)	12 (1.1) ^{BD}	12.3 (1.1) ^{BD}	14.1 (1.3) ^{AD}		0.397
95% CI	11.4 – 12.6	11.7 – 12.9	13.5 – 14.7		
3 days				0.008*	
Mean (SD)	11.7 (1.6) ^{BD}	11.6 (1.2) ^{BE}	13.1 (1.5) ^{AE}		0.207
95% CI	10.9 – 12.4	10.8 – 12.3	12.4 – 13.9		
7 days				0.097	
Mean (SD)	11.1 (1.3) ^{E}	10.9 (1.3) ^{F}	11.9 (1.4) ^{F}		0.105
95% CI	10.5 – 11.8	10.3 – 11.6	11.3 – 12.6		
P-value (Changes by time)	<0.001*	<0.001*	<0.001*		
Effect size (Partial Eta Squared)	0.492	0.692	0.869		

: Significant at P ≤ 0.05 A,B,C Superscripts in the same row indicate significant differences between groups D,E,F,G Superscripts in the same column indicate significant changes by time

B) Tragus-Progonion measurement

Pre-operatively, there was no statistically significant difference between tragus-Progonion measurements in the three groups (*P*-value = 0.641, Effect size = 0.021).

After 1 day, there was a statistically significant difference between tragus-Progonion measurements in the three groups (*P*-value = 0.002, Effect size = 0.260). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between mean tragus-Progonion measurements in Groups I and II; both showed statistically significantly lower mean value than Group III.

After 3 days, there was a statistically significant difference between tragus-Progonion measurements in the three groups (*P*-value = 0.041, Effect size = 0.141). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between mean tragus-Progonion measurements in Groups I and II; both showed statistically significantly lower mean value than Group III.

After 7 days, there was no statistically significant difference between tragus-Progonion measurements in the three groups (*P*-value = 0.169, Effect size = 0.081).

As regards the changes by time in Group I, there was a statistically significant change in tragus-Progonion measurement by time (*P*-value <0.001, Effect size = 0.549). Pair-wise comparisons between the time periods revealed that there was a statistically significant increase in tragus-Progonion measurement after 1 day. From 1 day to 3 days as well as 3 to 7 days, there was a statistically significant decrease in mean tragus-Progonion measurement.

TABLE (5): Descriptive statistics and results of repeated measures ANOVA test for comparison between tragus-Progonion measurements in the three groups as well as 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)***
Pre-operative				0.641	
Mean (SD)	14.8 (1.5) ^{F}	14.7 (1.4) ^{F}	15.1 (1.3) ^{G}		0.021
95% CI	14 – 15.5	13.9 – 15.4	14.4 – 15.9		
1 day				0.002*	
Mean (SD)	16 (1.7) ^{BD}	16.3 (1.4) ^{BD}	17.9 (1.3) ^{AD}		0.260
95% CI	15.2 – 16.7	15.6 – 17.1	17.2 – 18.7		
3 days				0.041*	
Mean (SD)	15.5 (1.6) ^{BE}	15.4 (1.4) ^{BE}	16.7 (1.6) ^{AE}		0.141
95% CI	14.7 – 16.3	14.6 – 16.2	15.9 – 17.5		
7 days				0.169	
Mean (SD)	14.9 (1.6) ^{F}	14.8 (1.4) ^{F}	15.7 (1.5) ^{F}		0.081
95% CI	14.1 – 15.7	14 – 15.6	14.9 – 16.5		
***P*-value (Changes by time)**	<0.001*	<0.001*	<0.001*		
Effect size (Partial Eta Squared)	0.549	0.710	0.885		

****: Significant at P ≤ 0.05 A,B,C Superscripts in the same row indicate significant differences between groups D,E,F,G Superscripts in the same column indicate significant changes by time***

The mean tragus-Progonion measurements after 7 days showed non-statistically significant difference from pre-operative tragus-Progonion measurement.

As regards the changes by time in Group II, there was a statistically significant change in tragus-Progonion measurement by time (*P*-value <0.001, Effect size = 0.710). Pair-wise comparisons between the time periods revealed that there was a statistically significant increase in tragus-Progonion measurement after 1 day. From 1 day to 3 days as well as 3 to 7 days, there was a statistically significant decrease in mean tragus-Progonion measurements. The mean tragus-Progonion measurements after 7 days showed non-statistically significant difference from pre-operative tragus-Progonion measurement.

While in Group III, there was a statistically significant change in tragus-Progonion measurement by time (*P*-value <0.001, Effect size = 0.885). Pair-wise comparisons between the time periods revealed that there was a statistically significant increase in tragus-Progonion measurement after 1 day. From 1 day to 3 days as well as 3 to 7 days, there was a statistically significant decrease in mean tragus-Progonion measurements. However; the mean tragus-Progonion measurement after 7 days showed statistically significantly higher mean value compared to pre-operative tragus-Progonion measurement.

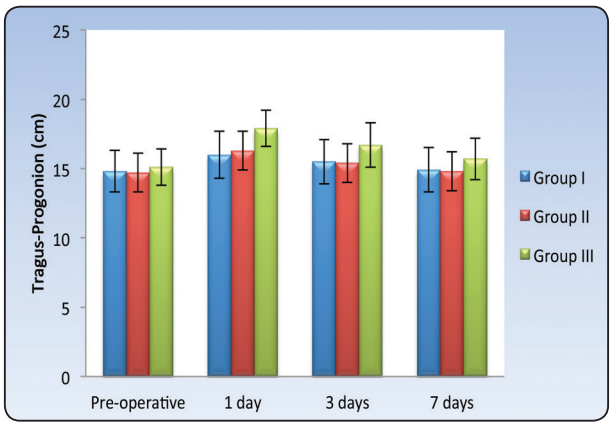

Fig. (10): Bar chart representing mean and standard deviation values for tragus-Progonion measurements in the three groups

DISCUSSION

Surgical removal of the third molar is one of the most common procedures performed by maxillofacial surgeons. post-operative sequelae such as pain, swelling, and trismus. The degree and severity of these depend on many factors such as individual physiologic response to the procedure, duration of surgery, amount of tissue trauma, and manipulation. [94] Post-surgical facial swelling affects the daily life of the patient. Many authors have advocated the use of corticosteroids to limit postoperative edema due to their suppressive action on transudation, but few have made definitive recommendations supported by randomized clinical trials.[95,96]

In most of the studies, the use of corticosteroid drugs has been analyzed.

The most commonly used forms of corticosteroids in dentoalveolar surgery include dexamethasone (oral), dexamethasone sodium phosphate (IV or IM), dexamethasone acetate (IM), methylprednisolone (oral), and methylprednisolone sodium succinate (IV/IM). The corticosteroid selected should have good biological activity and minimal mineralocorticoid effects. Dexamethasone meets these requirements, as it has no mineralocorticoid activity; the half-life is roughly 36 to 72 hours, highly selective, long-acting, synthetic corticosteroid, which has potent anti-inflammatory action. It exerts basic glucocorticoid action and is approximately 25 times more potent than hydrocortisone, 6 times than of prednisolone, 4 times that of methyl prednisolone and triamcinolone, and equipotent to betamethasone.[97]

Grossi et al. [14] compared the two doses of dexamethasone, i.e., 4 and 8 mg and concluded that there is no difference on post-operative sequelae on increasing dexamethasone dose. Based on the following study we choose to use the 8 mg dose of dexamethasone injection.

Intra-Masseteric route is a relatively simple technique of administering corticosteroids to

reduce exacerbated inflammatory responses. The site of injection is close to the already anesthetized region which makes it a painless procedure. Intra-masseteric as well as Sub-mucosal route also ensures immediate local availability; however, their absorption depends on the local blood flow in the area of administration and could also be influenced by the presence of infection, severe inflammation. [98]

A similar treatment strategy had already been proposed in 1975 by ***Messer and Keller***, [99] who administered 4 mg dexamethasone in three different parts of the masseter muscle and reported a significant reduction of pain, swelling, and trismus.

This was in agreement to our study which concluded higher significant reduction in pain and trismus following intra-masseteric dexamethasone injection in group II.

Grossi et al [100] and ***Graziani et al*** [101] in their studies have shown significant decrease in facial edema after sub-mucosal administration of 4 mg of dexamethasone.

This was in agreement to our study that concluded a statistically significant reduction in facial swelling after 1 day. However, from 1 day to 3 days as well as 3 to 7 days, there was a statistically significant increase in its measurement. On the other hand, the mean measurements after 7 days showed non-statistically significant difference from pre-operative measurement.

In our study, intramuscular group showed significant reduction of swelling after 7th day, however, dexamethasone injection intra-masseteric and submucosally showed immediate effect in swelling reduction on the 1st day post-operatively , on the other hand group I and II showed lower mean value at the 7th day than group III.

There are also many studies which compared the administration of submucosal route with intramuscular route. One such study done by ***Majid et al*** [102] found significant reduction in pain and swelling in both sub-mucosal and Intra-muscular dexamethasone but a greater immediate effect on trismus ($p = 0.04$) was seen in sub-mucosal route.

Javier et al [103] reported that preoperative administration of dexamethasone has greater post-operative effects. ***Waraich et al*** [104] in his study demonstrated that sub- mucosally administered dexamethasone is more efficient to manage post-operative discomfort related to swelling and pain compared to control group after the removal of third molar. ***Ehsan et al*** [105] compared the effect of sub-mucosal dexamethasone and found statistically significant reduction of swelling and trismus on 2nd postoperative day when compared with control group.

This was in agreement to our study, the immediate effect on trismus as well as pain reduction following dexamethasone injection submucosally and intra-masseteric on all follow up period post-operatively and swelling reduction on the 1st day.

Effects of corticosteroids on pain control are still debated and not very clear. Studies have not been able to attribute definite analgesic properties to corticosteroids. efficacy of preoperative administration of 1.5 mg/kg methylprednisolone sodium succinate IV versus that of 3 mg/kg followed post-surgery by 2 million IU oral penicillin V, plus acetaminophen 500 mg, was evaluated in patients operated for extraction of lower third molars bilaterally. [34] No significant differences were observed in inflammation, pain and swelling between the two dosage regimens.

Good results were also obtained with 32 mg methylprednisolone and 400 mg ibuprofen administered 12 h before and 12 h after surgery respectively.[35]

Several authors [12,22,37] have reported a reduction in pain but have not found the analgesic effect to be statistically significant. IM route is a relatively simple technique of administering corticosteroids to reduce exacerbated inflammatory responses. The site of injection is close to the already anesthetized

region which makes it a painless procedure. IM as well as SM route also ensures immediate local availability; however, their absorption depends on the local blood flow in the area of administration and could also be influenced by the presence of infection, severe inflammation. [98]

Several authors discussed the effectiveness of antibiotic prophylaxis, and it seems to be highly recommended for patients who present with a high risk of infection or when traumatic surgical procedures have been performed. [53–57].

Our study in treatment of impacted third molars, the use of ice shows a good efficacy in reducing post-surgery swelling and pain was based on several studies done by many authors who demonstrate that ice cold application control pain, swelling and bacterial growth post-operatively.[79,81-83,85,88,90,91]

CONCLUSION

Dexamethasone is an effective pharmacological agent to reduce post-surgical third molar removal sequelae such as pain, swelling, and trismus. Dexamethasone administered through local routes such as the SM route and IM route also provides comparable control of pain and swelling and has the advantage of being injected into previously anesthetized areas and requires less technical skill and better patient compliance/ comfort. Postoperative swelling is a common event after surgery of impacted third molar and may affect, only for a few days, the social and working life of the patient.

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