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ORIGINAL ARTICLE

Role of Dexamethasone in reducing Postoperative Sequelae following Impacted Mandibular Third Molar Surgery: A Comparative Clinical Study

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ABSTRACT

Aims and objectives: To understand the benefits of dexamethasone and compare the effects of submucosal *vs* intramuscular (IM) administration of dexamethasone in reducing postoperative sequelae following impacted mandibular third molar surgery.

Materials and methods: The study was conducted on 90 patients, who were divided into three groups of 30 each. The two experimental groups were given dexamethasone 4 mg submucosally or intramuscularly (preoperatively), and the control group did not receive any form of corticosteroid. Measurements of facial swelling and maximal interincisal distance were made preoperatively and on the 1st, 3rd, and 7th postoperative days. Pain was evaluated from patients' response to visual analog scale and recording the number of rescue analgesic tablets taken at the end of the 7th postoperative day.

Results: Both dexamethasone groups showed a significant reduction in pain, swelling, and trismus as compared with the control group at all intervals. There was a statistically significant reduction in magnitude of swelling in the submucosal dexamethasone group as compared with the IM dexamethasone group on the 1st postoperative day, but there was no significant difference among two experimental groups at other times and their effects were comparable for all variables.

Conclusion: Dexamethasone 4 mg is an effective therapeutic strategy for reducing postoperative sequelae following surgical removal of impacted third molars and submucosal dexamethasone is an effective alternative to dexamethasone given systemically.

Keywords: Corticosteroids, Submucosal dexamethasone, Third molar surgery.

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INTRODUCTION

The surgical removal of lower third molars is still the most common procedure performed by oral and maxillofacial surgeons.[1] The removal of impacted third molars by surgical means involves trauma to soft and hard tissues and can result in significant postoperative sequelae.[2]

Third molars show a high incidence of impaction and are often associated with diverse conditions, such as pericoronitis, periodontal pocket in the distal aspect of the second molar, caries formation in third molar or second molar, pressure resorption of second molar, and different types of cysts and odontogenic tumors. The removal of impacted tooth usually involves incision, flap reflection, and bone removal, which results in considerable postoperative pain, swelling, and trismus.[3]

To reduce these postoperative complications, therefore seems to be a logical goal. Many clinical studies have investigated the treatments to reduce postoperative sequeale by using antiseptic mouthwashes, use of drains, flap design, antibiotics, enzymes, corticosteroid treatment, muscle relaxants, and physiotherapy. Among them, the use of corticosteroids has gained wide acceptance.

Corticosteroids that have extensively been used in dentoalveolar surgery are dexamethasone and methylprednisolone, owing to their nearly pure glucocorticoid effects, virtually no mineralocorticoid effects, and the least adverse effects on leukocyte chemotaxis.[2]

Dexamethasone is a white odorless compound, which is slightly soluble in water. It has a melting point of 240 to 260°C. It is a synthetic analog of prednisolone in which a methyl group has been added at the carbon 16 position and

a fluorine atom at carbon 9 position. It has been known that the addition of fluorine at the carbon 9 position enhances the anti-inflammatory activity of dexamethasone.[4]

Dexamethasone has a longer duration of action than methylprednisolone and is found to be more potent of the two.[2] It has no mineralocorticoid activity and the half-life is roughly 36 to 72 hours. The potency of dexamethasone is about 20 to 30 times that of natural corticosteroid.[5] It is also considered to have the least depressing effect on leukocyte chemotaxis. Dexamethasone has been extensively used in oral and maxillofacial surgeries because of its very potent nature and long half-life.

Various routes have been used; orally administered glucocorticoids are rapidly and almost completely absorbed. However, in order to maintain adequate blood concentration throughout the immediate postoperative period, repeated dose is required. Intravenous (IV) route results in instantaneous blood levels, but requires expertise and additional armamentarium.[6]

Intramuscular route has been the most commonly prescribed route in outpatient settings and gives good plasma concentration of the drug and prolonged anti-inflammatory action. The submucosal route is well suited for third molar surgery, as the injection is given in close proximity to the operative field and local infiltration of dexamethasone injected submucosally around the site of surgery is expected to provide slow absorption and prolonged duration of action.

This study was designed to compare the effect of preoperative administration of inj. dexamethasone given via the submucosal and IM routes, on the postoperative sequelae after removal of impacted lower third molars.

AIMS AND OBJECTIVES

Objectives of the study:

- To evaluate the efficacy of dexamethasone in reducing postoperative sequelae following surgical extraction of impacted mandibular third molars.
- To compare the effect of preoperative administration of inj. dexamethasone given via submucosal and IM routes, on the postoperative sequelae after removal of impacted lower third molars, which include
  - Pain
  - Facial swelling and
  - Trismus

Pharmacology of Dexamethasone

Dexamethasone is a member of the glucocorticoid class of corticosteroids. It is a synthetic corticosteroid, highly potent, and has anti-inflammatory and immunosuppressant effects. Its potency is 25 times that of cortisol in terms of its glucocorticoid effect, while it has minimal mineralocorticoid activity.

It is included in the World Health Organization's List of Essential Medicines, which enlists the most important medications needed in a basic health system.

Chemical formula (Dexamethasone sodium phosphate): $C_{22}H_{28}FNa_2O_8P$

Molecular weight: 516.

DESCRIPTION

Dexamethasone phosphate (as sodium) is a white or slightly yellow, very hygroscopic, crystalline powder. It is an odorless compound or has a slight odor of alcohol. Dexamethasone phosphate (as sodium) is Soluble in water(ratio 1:2), slightly soluble in alcohol, insoluble in chloroform and ether, and very slightly soluble in dioxan.[4]

Dexamethasone sodium phosphate in an injectable form is a clear and colorless solution, free from visible particulate matter. Each milliliter of solution contains dexamethasone sodium phosphate equivalent to 4 mg of dexamethasone phosphate. The 8 mg/2 mL vial formulation contains sodium citrate, disodium edetate, and sodium sulfite anhydrous. No preservatives are present.

The pH of the solutions is adjusted using sodium hydroxide and/or hydrochloric acid.

PHARMACOLOGY

Dexamethasone is a long-acting synthetic adrenocorticosteroid with glucocorticoid activity. It has no mineralocorticoid activity, the half-life is around 36 to 72 hours, and the drug is 25 times more potent than hydrocortisone. It is also considered to have the least adverse effect on leukocyte chemotaxis.[1]

Dexamethasone is known to have anti-inflammatory and immunosuppressive actions. Glucocorticoids prevent the development of the inflammatory response. They also inhibit capillary dilation and phagocytosis and appear to prevent the hypersensitivity response.

The principal metabolic actions of dexamethasone are on carbohydrate, protein, and calcium metabolism. Dexamethasone also influences the mobilization, oxidation, synthesis, and storage of fats. Dexamethasone causes inhibition of endogenous corticotropin secretion by suppressing the release of adrenocorticotropic hormone from the pituitary.

Pharmacokinetics

Dexamethasone phosphate (as sodium) is rapidly absorbed following administration by oral, IM, or IV routes.

Metabolism

Dexamethasone being a synthetic derivative is less extensively protein bound and more slowly metabolized

than hydrocortisone, and, hence, has a longer duration of action. Dexamethasone penetrates into tissue fluids and cerebrospinal fluids. The corticosteroids are metabolized mainly by hepatic microsomal enzymes. These metabolites are further conjugated with glucuronic acid and sulfate and are excreted in urine. Small amounts of unchanged drug are also excreted in the urine.

MATERIALS AND METHODS

The present study was undertaken in the Department of Oral and Maxillofacial Surgery, The Oxford Dental College & Hospital, Bengaluru, India, after obtaining ethical clearance. This study included both male and female patients, who were referred to the Department of Oral and Maxillofacial Surgery for removal of impacted mandibular third molars.

Inclusion Criteria

- Patients aged 18 to 50 years
- Patients with impacted mandibular third molars indicated for surgical extraction

Exclusion Criteria

- Patients with systemic disorders
- Pregnant and lactating females

Study sample included 90 patients who underwent surgical extraction of impacted mandibular third molars. The patients were divided into three groups of 30 each:

- *Group I (submucosal dexamethasone group)*: Patients received 4 mg (1 mL) dexamethasone via submucosal route (around the tooth to be extracted) half an hour prior to the procedure.
- *Group II (IM dexamethasone group)*: Patients received 4 mg (1 mL) dexamethasone via IM route (dorsogluteal site) half an hour prior to the procedure.
- *Group III (control group)*: Patients in this group did not receive any form of corticosteroid.
- Preoperatively, facial measurements and interincisal opening were recorded, and this was taken as baseline. The evaluations were made subsequently on 1st, 3rd, and 7th postoperative days and compared with baseline.

Evaluation of Pain

Pain was evaluated using standard visual analog scale (VAS) on 1st, 3rd, and 7th postoperative days and also taking into account the number of rescue analgesic tablets taken at the end of 7th postoperative day.

Evaluation of Facial Swelling

Facial swelling on the operated side was evaluated by two facial measurements (Figs 1 and 2):

- Tragus–midline (Tr-Md) and
- Gonion–lateral canthus (Go-Lc)

This was done using a flexible measuring tape. The preoperative sum of two values was taken as the baseline for that side.

Facial measurements were made subsequently on 1st, 3rd, and 7th postoperative days and compared with the baseline.

Evaluation of Trismus

Maximal mouth opening was recorded preoperatively, which was taken as baseline.

Mouth opening values were recorded subsequently on 1st, 3rd, and 7th postoperative days and compared with the baseline for evaluation of trismus.

Postoperative Instructions

Regular postextraction instructions were given. All patients were given amoxicillin 500 mg thrice daily for

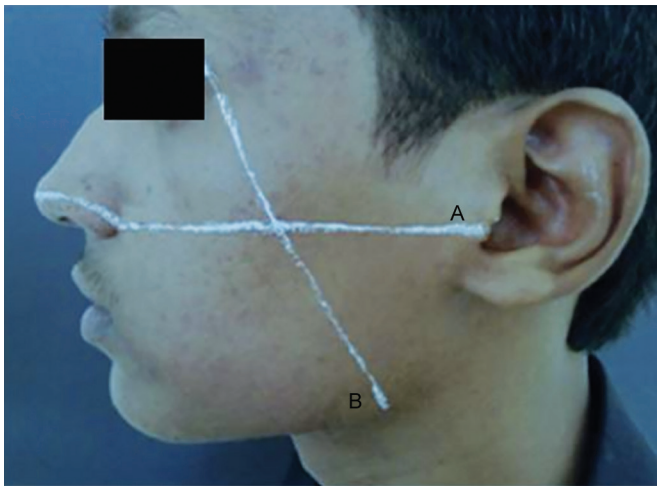


Fig. 1: Evaluation of facial swelling. (A) Tragus–midline; and (B) gonion–lateral canthus

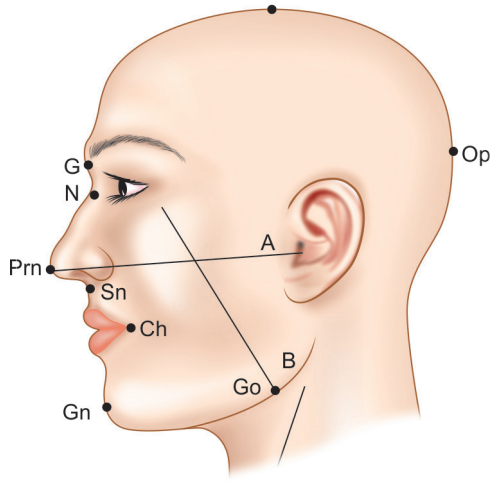


Fig. 2: Evaluation of facial swelling. (A) Tragus–midline; and (B) gonion–lateral canthus

5 days, and tramadol 50 mg orally as required as rescue analgesia. Chlorhexidine mouth wash was to be used twice daily starting 1 day after operation for 5 days.

RESULTS

There were 54 men and 36 women in the age range of 19 to 45 years. Following completion of clinical study on the patients, the measurements and data taken from all patients were tabulated for statistical studies. The results of our study are described in brief as follows:

Pain

In all groups, the mean postoperative pain score was highest at postoperative day 1 and gradually reduced over the following 7 days (Tables 1 to 4 and Graphs 1 and 2). The mean postoperative pain was lower in the submucosal dexamethasone group at all time points when compared with the control group. The IM dexamethasone group showed significant difference in mean postoperative pain values on 1st and 3rd postoperative day as compared with the control group; however, there was no significant difference between the two groups on the 7th postoperative day. The accumulated number of rescue analgesic tablets also differed significantly between the dexamethasone groups and control group. However, there was no significant difference in mean postoperative pain score and the total number of rescue analgesic tablets in either dexamethasone group at any interval.

Table 1: Mean and standard deviation of pain on 1st postoperative day treatment-wise

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	28.33	6.989
Intramuscular dexamethasone	30	30.00	5.872
Control group	30	39.67	8.087
Total	90	32.67	8.585

F: 22.658; Degrees of freedom: 2.87; $p < 0.001$

Table 2: Mean and standard deviation of pain on 3rd postoperative day treatment-wise

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	14.67	8.604
Intramuscular dexamethasone	30	17.33	6.915
Control group	30	22.33	7.279
Total	90	18.11	8.196

F: 7.798; Degrees of freedom: 2.87; $p < 0.001$

Table 3: Mean and standard deviation of pain on 7th postoperative day treatment-wise

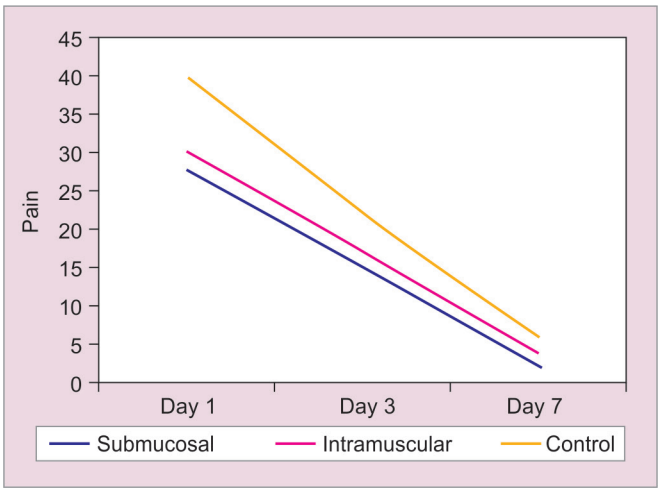
Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	2.33	4.302
Intramuscular dexamethasone	30	4.00	4.983
Control group	30	5.67	5.040
Total	90	4.00	4.926

F: 3.637; Degrees of freedom: 2.87; $p < 0.05$

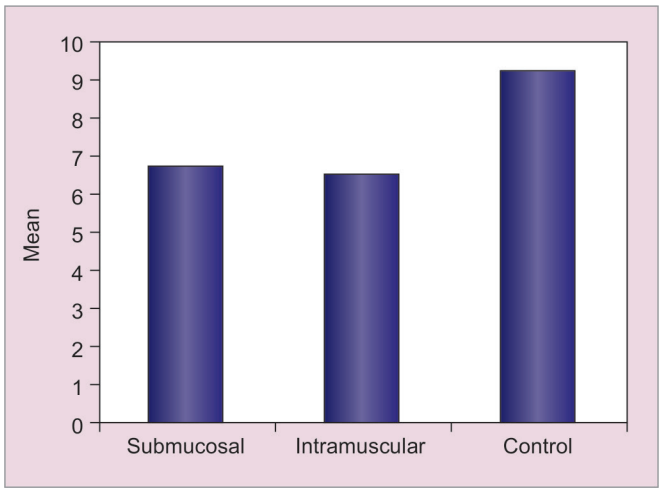
Table 4: Mean of number of rescue tablets taken treatment-wise

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	6.70	1.442
Intramuscular dexamethasone	30	6.50	1.456
Control group	30	9.23	1.278
Total	90	7.48	1.862

F: 35.817; Degrees of freedom: 2.87; $p < 0.001$



Graph 1: Mean pain on day 1, day 3 and day 7 treatment-wise



Graph 2: Mean number of rescue analgesics taken treatment-wise

Table 5: Mean and standard deviation of facial swelling (Tr-Md + Go-Lc) at baseline

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	25.8333	1.12444
Intramuscular dexamethasone	30	25.5000	1.13715
Control group	30	25.3833	1.33703
Total	90	25.5722	1.20523

F: 1.130; Degrees of freedom: 2.87; $p > 0.05$

Table 6: Mean and standard deviation of increase in facial swelling (Tr-Md + Go-Lc) on 1st postoperative day

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	0.0833	0.18952
Intramuscular dexamethasone	30	0.2167	0.25200
Control group	30	0.5833	0.26533
Total	90	0.2944	0.31707

F: 35.526; Degrees of freedom: 2.87; $p < 0.001$

Table 7: Mean and standard deviation of increase in facial swelling (Tr-Md + Go-Lc) on 3rd postoperative day

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	0.0667	0.17287
Intramuscular dexamethasone	30	0.2500	0.36554
Control group	30	0.8500	0.52768
Total	90	0.3889	0.50713

F: 34.185; Degrees of freedom: 2.87; $p < 0.001$

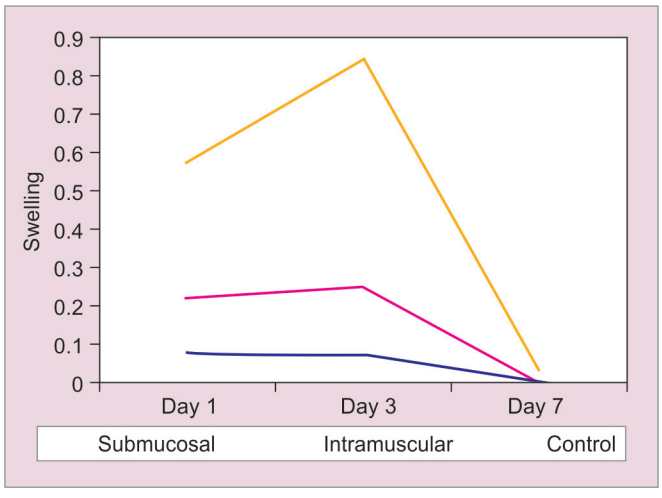
Table 8: Mean and standard deviation of increase in facial swelling (Tr-Md + Go-Lc) on 7th postoperative day

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	0.0000	0.00000
Intramuscular dexamethasone	30	0.0000	0.00000
Control group	30	0.0333	0.18257
Total	90	0.0111	0.10541

F: 1.000; Degrees of freedom: 2.87; $p > 0.05$

Swelling

The postoperative facial swelling was highest on the 1st and 3rd postoperative days compared with the baseline in the control group (Tables 5 to 8 and Graph 3). Both dexamethasone groups showed a significant difference in magnitude of swelling on 1st and 3rd postoperative days as compared with the control group. There was also a statistically significant reduction in magnitude of swelling in submucosal dexamethasone group as compared with the IM dexamethasone group on the 1st postoperative day. In all groups, the values reached baseline by the 7th postoperative day.



Graph 3: Mean increase in swelling on day 1, day 3 and day 7 treatment-wise

Mouth Opening

Patients in the control group consistently had lower maximal interincisal opening on the 1st and 3rd postoperative days as compared with the dexamethasone-treated groups (Tables 9 to 12 and Graph 4). However, there was no significant difference among the dexamethasone-treated groups for the above parameter. The interincisal mouth opening values reached baseline in all the three groups by the 7th postoperative day.

Analysis of variance technique was used to test the mean difference between three treatment groups, namely,

Table 9: Mean and standard deviation of mouth opening at baseline treatment-wise

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	47.80	2.631
Intramuscular dexamethasone	30	47.67	3.642
Control group	30	48.53	3.431
Total	90	48.00	3.250

F: 0.613; Degrees of freedom: 2.87; $p > 0.05$

Table 10: Mean and standard deviation of mouth opening on 1st postoperative day treatment-wise

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	32.00	3.063
Intramuscular dexamethasone	30	30.23	3.884
Control group	30	25.73	3.667
Total	90	29.32	4.403

F: 24.789; Degrees of freedom: 2.87; $p < 0.001$

Table 11: Mean and standard deviation of mouth opening on 3rd postoperative day treatment-wise

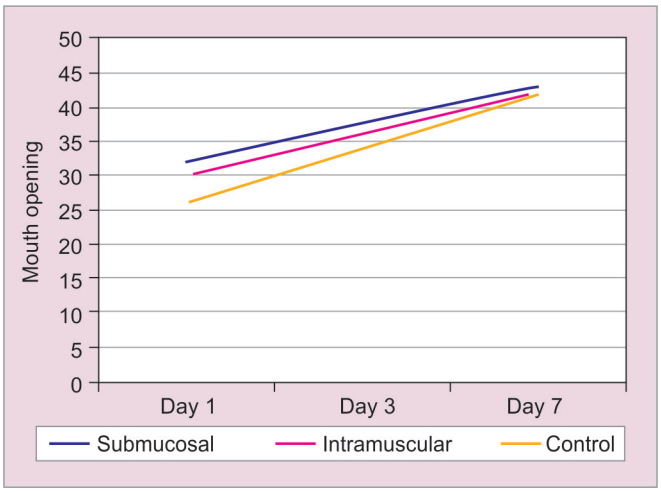
Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	36.93	3.373
Intramuscular dexamethasone	30	36.17	3.582
Control group	30	32.77	4.174
Total	90	35.29	4.109

F: 10.631; Degrees of freedom: 2.87; p < 0.001

Table 12: Mean and standard deviation of mouth opening on 7th postoperative day treatment-wise

Descriptives	*n*	*Mean*	*Standard deviation*
Submucosal dexamethasone	30	43.40	2.920
Intramuscular dexamethasone	30	42.10	3.689
Control group	30	41.73	3.352
Total	90	42.41	3.375

F: 2.069; Degrees of freedom: 2.87; p > 0.05



Graph 4: Mean mouth opening on day 1, day 3 and day 7 treatment-wise

submucosal dexamethasone, IM dexamethasone, and control group.

To see which of the treatment groups are significantly different, the least significant difference technique was used by taking two treatments at a time.

DISCUSSION

The removal of impacted third molar by surgical modality can result in considerable pain, swelling, and dysfunction. The factors that contribute to postoperative pain and edema are complex, but many of the these factors correlate to the process of inflammation. Careful attention to surgical techniques will minimize the sequelae of inflammation, but will not prevent them.[7] Postoperative inflammation is a biological response characterized by increased vascular permeability, increased movement of leukocytes into the inflamed area, and the release of chemical mediators of inflammation. By controlling the extent of the inflammatory process, using pharmacologic measures, postoperative complications, such as pain, swelling, and trismus, can be minimized.[7,8]

For more than 30 years, glucocorticoids have been used in an attempt to reduce the severity or intensity of postoperative sequelae after surgical removal of impacted third molars.[6] The use of corticosteroids has gained wide acceptance in the field of oral and maxillofacial surgery, and numerous reports are now available supporting the use of systemic corticosteroids in the setting of third molar surgery.[9] Markiewicz et al,[10] in a meta-analysis, concluded that giving corticosteroids perioperatively produces mild-to-moderate reduction in edema and improvement in range of motion after third molar removal. More recently, Herrera-Briones et al,[11] in a systematic review on the use of corticosteroids after third molar surgery, concluded that administration of corticosteroids improves the postoperative experience of patients and has a significant impact on trismus and inflammation. The results achieved appeared to be even better when using parenteral route and by administering corticosteroids before the surgery.

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).[7] 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, and its potency is 25 times that of hydrocortisone. It is also considered to have the least adverse effect on leukocyte chemotaxis.[1] Dexamethasone also has a longer duration of action than methylprednisolone, thereby considered more potent.[2,3]

Dexamethasone is available in oral, parenteral, and topical formulations, and is largely used in oral surgery due to its high efficacy and long half-life. In our study, we aimed to evaluate the effectiveness of dexamethasone given via two different routes (submucosal and IM) on postoperative sequelae after impacted third molar surgery.

Consistent with published data, third molar surgery in the control group was associated with significant postoperative sequelae.[1,9] The postoperative sequelae including pain and trismus reached its peak on 1st daypost operatively and facial swelling was the highest on 3rd day postoperatively. They gradually reduced to reach near baseline (preoperative) values by the 7th postoperative day.

Submucosal Dexamethasone

Postoperative edema can be controlled with dexamethasone administered in the submucosa. Grossi et al[2] compared dexamethasone given in two different doses (4 or 8 mg) as a submucosal injection. It was reported that both dosages improved swelling *vs* untreated groups, but no difference was observed between the dosage regimens. In striking contrast with this observation, Laureano Filho et al[12] reported that in patients undergoing surgery for impacted third molars, administration of 8 mg dexamethasone 1 hour before surgery produced a better control of swelling compared with treatment with 4 mg dexamethasone.

In the present study, submucosal dexamethasone 4 mg given half an hour preoperatively, showed a significant reduction of swelling on all postoperative intervals as compared with the controls, which is in agreement with the previous studies.[2,13] These results add more strength to the concept that locally applied dexamethasone near surgical site in a subtherapeutic dose (4 mg) is a valuable tool to reduce edema after third molar surgery.

Unlike previous studies that reported only a limited effect on trismus and pain, our patients showed significantly less trismus and pain at all times of evaluation in the submucosal group as compared with controls, which may have been the result of higher concentration of drug at the site of injury.

Although there is an agreement about their effects on swelling, the role of corticosteroids in the prevention of postoperative pain is controversial. Recently, Waldron et al[14] in a meta-analysis reported that patients treated with dexamethasone experienced comparatively lesser postoperative pain, required less opioids in postoperative period, had longer time to first analgesic dose, and needed less rescue analgesia. They concluded that perioperative single-dose dexamethasone was associated with small, but statistically significant analgesic benefits.

Intramuscular Dexamethasone

Intramuscular route is one of the most commonly used one when a steroid injection is prescribed in outpatient settings. Intramuscular dosing studies have suggested that this route can be effective if a single dose is given either preoperatively or postoperatively.[1]

In our study, IM dexamethasone 4 mg given half an hour preoperatively showed a significant reduction of swelling and pain on 1st and 3rd postoperative days as compared with the controls, which comes in agreement with the previous studies.[1,5,9,15,16]

An important finding was the significant reduction of trismus on all postoperative visits, which is in contrast with the previous studies. Further research is, however, needed to confirm these results.

In the present study, a comparison was drawn between two different routes of administration of dexamethasone. Both dexamethasone groups were associated with a significant reduction in pain, swelling, and trismus; submucosal dexamethasone had a significant effect on facial swelling on 1st postoperative day as compared with IM dexamethasone, but the effect in two groups were comparable overall for all variables.

Overall, the comparable results obtained show that submucosal dexamethasone is an effective alternative to systemically administered dexamethasone. The expertise of the surgeon and the discomfort caused to the patient are factors that may limit the use of IM route. Submucosal dexamethasone, on the contrary, is simple, less invasive, and painless. It is well suited for third molar surgery and provides a low-cost solution for the typical discomfort associated with extraction of impacted third molars.

CONCLUSION

In this study, inj. dexamethasone sodium phosphate was used as an adjunct to reduce postoperative sequelae following surgical removal of impacted third molars.

It indicates a definite reduction in pain, swelling, and trismus after third molar surgery in patients treated with dexamethasone as compared with the control group. These findings signify and highlight the use of dexamethasone certainly as a valid method in reducing postoperative sequelae in patients undergoing third molar surgery.

This study provides a basis for preoperative administration of dexamethasone in a subtherapeutic dose of 4 mg to reduce the intensity of postsurgical sequelae, such as pain, swelling, and trismus.

This study also compares two routes of administration of dexamethasone; the comparable results obtained show that submucosal dexamethasone is an effective alternative to dexamethasone given systemically. It offers a simple, painless, less invasive, and cost-effective solution for typical discomfort associated with surgical extraction of third molars.

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