Original Article - Comparative Study

Submucosal Infiltration versus Intravenous Administration of Dexamethasone in Decreasing Post-operative Inflammatory Sequelae after Third Molar Surgery - A Comparative Study

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Abstract

Introduction: Surgical removal of lower third molar is one of the most common surgical procedures and is quite stressful for many patients. In this study, two different routes of administration of dexamethasone 8 mg (intravenous [IV] vs. submucosally infiltrated) were used to evaluate the role of dexamethasone in reducing the post-operative inflammatory sequelae following lower third molar removal. **Materials and Methods:** Sixty patients who had to undergo surgical removal of mandibular third molars were randomly divided into two groups, each group consisting of 30 patients. One group of patients was administered 8 mg dexamethasone submucosally five min before the surgery. Another group of patients received 8 mg dexamethasone intravenously five min before the surgery. Facial swelling and pain were measured on the 2nd, 4th and 7th post-operative days. **Results:** The results of this study revealed that both the routes were effective in controlling post-operative pain and swelling. IV route of dexamethasone showed higher efficacy compared to submucosal (SM) route of dexamethasone in reducing the post-operative inflammatory sequelae in the surgical removal of impacted lower third molar teeth. **Discussion:** It was seen that IV dexamethasone (8 mg) and submucosal dexamethasone (8 mg) had equivalent ratings in terms of reduction of swelling and pain. Although the results of this study showed both the routes are effective in controlling post-operative swelling and pain after third molar surgery, the study concluded that certain benefits of submucosal route make the sm route to be a valuable alternative to iv dexamethasone.

Keywords: Dexamethasone, intravenous, submucosal, swelling, third molar surgery

Introduction

Surgical removal of impacted mandibular third molars is one of the most important and most frequently performed oral surgical procedures.[1] It involves trauma to soft tissue and bone, resulting in post-operative inflammation, significant pain, swelling, trismus, dry socket and dysfunction as direct and immediate consequences of the surgical procedure.[2] The quality of life after lower third molar surgery is affected three times more in patients with pain, swelling and trismus alone or in combinations compared to those who were asymptomatic.[3] Pain is often of short duration and is usually accompanied by buccal swelling and trismus. Although after third molar removal, the overall complication rate is low and most complications are minor, third molar removal is so common that even those minor complications may be significant.[4] The factors contributing to post-operative pain, oedema and dysfunction are complex, but many of the contributing factors are related to the inflammatory process. However, the inflammatory reaction often seems more pronounced than seen in case of normal healing process.[4,5] This is not desirable as it adversely affects and delays the process of healing.[6,7]

Pain and oedema of varying degrees follow all operative procedures, and many pharmacological and physical methods

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have been employed in an attempt to reduce them.[2] In oral surgery, the principal effective physical method for relieving oedema is the use of drains, while of all the pharmacological agents tried, the anti-inflammatory steroids appear to be the most successful and remain in common usage.[5,8,9] Although steroids appear to be the most successful, immunosuppressive effects of cortisol and its synthetic analogues are well recognised in medicine.[10,11] Increasing knowledge of the mechanism of pain and inflammation has resulted in effective new measures of controlling post operative pain, swelling and trismus.[12,13] The effectiveness of glucocorticoids as anti inflammatory agents was first reported by Dr. Philip S. Hench and Edward C. Kendall in 1948. Since this initial discovery of anti inflammatory actions of steroids, these agents have been used in more than 50 clinical conditions with inflammatory and allergic manifestations.[12-14] In 1957, Arth and co workers synthesised a new family of steroid compounds containing in common a cyclopentonoperhydrophenanthrine ring with methyl grouping at the 16th carbon position of steroid nucleus, one of these compounds was dexamethasone.[15] This new synthetic adrenocortical steroid, dexamethasone, was used to reduce facial swelling, control oedema and decrease trismus and pain after oral surgical procedures.[3,16,17] Even though there have been various natural, semisynthetic and synthetic adrenocortical steroids, these synthetic corticosteroids exhibit a profound effect in reducing the post-operative inflammatory sequelae. Among these newer synthetic corticosteroids, dexamethasone has been proved highly effective in mandibular third molar surgical procedures.[6,17-19] Dexamethasone exerts basic glucocorticoid action and is apparently 25 times more potent than hydrocortisone.[1] At equipotent anti inflammatory dose, it essentially lacks the sodium retaining properties. If the usual undesirable effects do occur, they are reversible and disappear when steroid is discontinued.[1] In literature even though multiple routes of administration of dexamethasone has been explained there is a dearth of studies in comparing different submucosal route with intravenous route.[1,2,20] Thus, the objective of the study is to compare the submucosal infiltrations of dexamethasone and IV injection of dexamethasone for reducing the post operative inflammatory sequelae after mandibular third molar surgery.

Methodology

This prospective comparative study was reviewed and approved by Bapuji Dental College and Hospital, Davanagere, Institutional Review Board (IRB No. BDC/Exam/467/2012-13). This study was conducted using the CARE checklist guidelines. All the methods used in this study were performed in accordance with the Declaration of Helsinki 2013 principles. The authors confirmed that written informed consent was obtained from all subjects and/or their legal guardian (s) for information/image publication, and the patients agreed to reveal their facial photos for academic purposes.

Patients reporting to the Department of Oral and Maxillofacial Surgery, Bapuji Dental College and Hospital, Davanagere, for the removal of impacted mandibular third molar were selected for this study, and a total of 60 patients were selected. The selected patients consisted of 28 females and 32 males, age ranging from 18 to 40 years. Patients were subjected to a thorough evaluation of their history, clinical, blood investigations and radiographs. Patients were categorised into two groups: submucosal (SM) dexamethasone group and intravenous (IV) dexamethasone group. Selected patients were allocated to each group equally by randomisation procedure, irrespective of age and sex.

The inclusion criteria for the study were patients aged between 18 and 40 years, healthy patients who were categorized as ASA Class I, patients requiring the removal of impacted lower third molars through mucoperiosteal flap elevation, buccal bone guttering with or without sectioning of the tooth (based on radiographic evidence), patients who were not having inflammation, infection and pain in the area of operation seven days before the surgery.

The exclusion criteria were patients with systemic diseases, patients with hypersensitivity to dexamethasone, pregnant patients, breast-feeding patients, patients on any other medicinal therapy, patients with swelling, inflammation or infection in the area of operation 7 days before the surgery and any procedure that extended beyond 90 min.

Standard general medical history of patients was recorded in each case as per proforma and was followed by routine clinical examination. Pain scores and facial swelling measurements were recorded as follows: to measure the extent of swelling preoperatively and postoperatively measurements were taken by marking six fixed points and five surgical baselines to cover all possible directions of extension of swelling.[21] Post-operative measurements were done on the 2nd, 4th and 7th days. The pre-operative and post-operative measurements were made in closed mouth position. The following were the reference points: Point 1 – from the tragus of the ear to the angle of the mandible, Point 2 – from the lateral canthus of the eye to the angle of the mandible, Point 3 – from ala of the nose to the angle of the mandible, Point 4 – from the corner of the mouth to the angle of the mandible and Point 5 – from the menton to the angle of the mandible. Using a measuring tape to follow the contour of the face, linear distances were noted. The sum of all measurements was taken as the facial swelling. The pain was recorded objectively using the Visual Analogue Scale (VAS) and was graded depending on the pain experienced by the patient on the 2nd, 4th and 7th post-operative days.[22,23] The data thus obtained were tabulated and subjected to appropriate statistical analysis. Results were expressed as mean ± standard deviation and percentages. Post-surgical changes compared to baseline were analysed by Student's unpaired *t*-test and Chi-square test.

Results

The study included a total of 60 patients (with 32 males and 28 females) in which 15 males and 15 females were in the

dexamethasone submucosal group in which 43.3% were in 18–24 age group, 23.3% were in 24–29 age group, 26.7% were in 30–34 age group and 6.7% were in 35–39 age group with a mean age of 26.43 ± 6.10 between 18 and 40 years. In the dexamethasone Intravenous group, there were 13 males and 17 females in which 50.0% were in 18–24 age group, 20.0% were in 24–29 age group, 13.3 % were in 30–34 age group and 16.7% were in 35–39 age group with a mean age of 26.50 ± 6.28 between 18 and 40 years. The duration of surgery was recorded for both the groups. In the SM dexamethasone group, the mean duration of the surgery was 33.83 ± 10.17 min. In the IV dexamethasone SM group, the mean duration of surgery was 32.53 ± 10.23. Hence, the difference in both the groups was not significant ($P > 0.05$) [Table 1]. In the SM dexamethasone group, the mean difference in facial measurement on the 2nd, 4th and 7th post-operative days was taken. There was an increase in size by 3.93 ± 0.86 cm (8.8%) difference in the 2nd post-operative day ($P < 0.001$). There was 2.90 ± 0.83 cm (6.5%) difference from the post-operative measurement on the 4th post-operative day ($P < 0.001$). There was 1.39 ± 0.57 cm (3.1%) difference in swelling on the 7th post-operative day from the pre-operative measurements ($P < 0.001$). There was a statistically significant difference in size of swelling between the pre-operative and 7th post-operative days. In the IV dexamethasone group, the mean difference in facial measurement was measured on the 2nd, 4th and 7th post-operative days. There was 1.32 ± 0.39 cm (2.9%) difference in facial swelling on the 2nd post-operative day ($P < 0.001$). There was 0.86 ± 0.39 cm (1.9%) difference from the pre-operative measurement on the 4th post-operative day ($P < 0.001$). There was 0.24 ± 0.17 cm (0.5%) difference in swelling on the 7th post-operative day from the pre-operative measurements ($P < 0.001$). There was less statistical difference in size of swelling on the 7th post-operative day [Table 2]. The mean individual and comparative efficacies of IV dexamethasone and SM dexamethasone in reduction of pain on the 2nd, 4th and 7th post-operative days were compared, and it was found that on the 2nd post-operative day in the SM dexamethasone group, the patients with pain score 2 were 67% (2 patients) while in the IV dexamethasone group were 36.7% (11 patients). Patients with pain score 4 in the SM dexamethasone group were 76.7% (23 patients) while in the IV dexamethasone group were 63.3% (19 patients). Similarly, patients with a pain score of 6 in the SM dexamethasone group were 16.7% (5). Thus there was a statistically significant difference between the two groups which showed less pain experienced by patients in the IV dexamethasone group on the 2nd post-operative day ($P = 0.003$S) [Table 3]. On the 4th post-operative day in the SM dexamethasone group, the patients with pain score 2 were 33.3% (10 patients) while in the IV dexamethasone group were 66.7% (20 patients). Patients with pain score 4 in the SM dexamethasone group were 66.7% (20 patients) while in the IV dexamethasone group were 33.3% (10 patients). Thus, there was a statistically significant difference between the two groups which showed less pain experienced by patients in the IV dexamethasone group as compared to the SM dexamethasone group on the 4th post-operative day ($P = 0.01$, significant). On the 7th post-operative day in the SM dexamethasone group, the patients with pain score 0 were 16.7% (5 patients) while in the IV dexamethasone group were 26.7% (8 patients). In the SM dexamethasone group, patients with pain score 2 were 46.7% (14 patients) while in the IV dexamethasone group were 73.3% (22 patients). Patients with pain score 4 in the dexamethasone group were 3.3% (1 patient), while in the IV dexamethasone group, no patient had pain score of 4. Thus, there was no statistically significant difference between the two groups with regards to pain on the 7th post-operative day ($P = 0.41$, non-significant) [Table 3].

Table 1: Duration of surgery amongst the two groups

Groups	Number of cases	Duration (min), mean±SD	*P*
SM dexamethasone	30	33.83±10.17	>0.05 NS
IV dexamethasone	30	32.53±10.23	

NS: Non-significant, SM: Submucosal, IV: Intravenous, SD: Standard deviation

Discussion

Post-operative inflammation is characterised by increased vascular permeability, migration of leucocytes into the inflamed area, the release of chemical mediators of inflammation from leucocytes and interaction of these mediators with other mediators, such as kinin and complement.[24] By pharmacologically controlling the extent of the inflammatory process, post-operative sequelae, such as pain and swelling, may be reduced in intensity or severity.[10] In an attempt to overcome these problems, steroids, non-steroidal anti-inflammatory drugs, antihistaminics, long-acting local anaesthetics and antibiotics have been tried with varying degrees of success.[24-27]

Glucocorticoids are a group of steroids that possess anti-inflammatory properties. It is a subdivision of adrenocorticoids secreted by the adrenal cortex. The primary glucocorticoid secreted by the zona fasciculata of the adrenal cortex is cortisol (hydrocortisone).[28-30] Under normal

Table 2: Comparison of changes in the facial swelling between submucosal and intravenous dexamethasone groups

Facial swelling (mm)	Dexamethasone SM, mean±SD	Dexamethasone IV, mean±SD	Mean difference	*P* value*, significant
2nd day	3.93±0.86	1.32±0.39	2.61	*P*<0.001 HS
4th day	2.90±0.83	0.86±0.39	2.04	*P*<0.001 HS
7th day	1.39±0.57	0.24±0.17	1.15	*P*<0.001 HS

*Student's unpaired *t*-test. SM: Submucosal, IV: Intravenous, SD: Standard deviation, HS: Highly significant

Table 3: Comparison of changes in the pain between submucosal and intravenous dexamethasone groups

Pain score	SM dexamethasone, *n* (%)	IV dexamethasone, *n* (%)	*P*
2nd day			
2	2 (6.7)	11 (36.7)	0.003 significant
4	23 (76.7)	19 (63.3)	
6	5 (16.7)	0	
4th day			
2	10 (33.3)	20 (66.7)	0.05 significant
4	20 (66.7)	10 (33.3)	
7th day			
0	5 (16.7)	8 (26.7)	0.41 NS
2	14 (46.7)	22 (73.3)	
4	1 (3.3)	0	

NS: Non-significant, SM: Submucosal, IV: Intravenous

non-stressful conditions, the body produces approximately 15–30 mg of hydrocortisone per day.[31] Perhaps, one of the most important actions of corticosteroids is the suppression or prevention of inflammation by interfering with capillary dilatation, oedema formation, fibrin deposition, leucocyte migration and phagocytosis.[32] The exact mechanism by which the glucocorticosteroids inhibit inflammation is not fully understood.[32-34]

Dexamethasone has been the commonly used corticosteroid in dentoalveolar surgery, and various forms include dexamethasone (oral), dexamethasone sodium phosphate (IV or intramuscular [IM]) and dexamethasone acetate (IM); many authors recommend a minimum pre-operative loading dose of 8–12 mg dexamethasone as some studies showed little to no oedema reduction with only 4 mg.[26,34,35]

Dexamethasone, a glucocorticoid receptor,[36] decreases the release of bradykinin, tumour necrosis factor, interleukin-1, interleukin-2 and interleukin-6 and decreases the production of prostaglandins.[34,37-39] The biological half-life of dexamethasone is about 3 h and half life (t1/2) is 36–50 h, although the duration of action may be much longer. Dexamethasone is bound to plasma proteins in much lower levels than other glucocorticoids.[40] In an effort to gauge and compare scientifically the efficacy of SM dexamethasone and IV dexamethasone in controlling swelling and pain following mandibular third molar surgery, we conducted a randomised study by administering dexamethasone IV and dexamethasone through local infiltration submucosally in the operative region. Pain assessment is not a one-time phenomenon. The most widely used scales are visual, verbal and numerical or some combinations of all three forms. In our study, the amount of pain experienced by the patient was recorded using the Faces Pain Scale-Revised which is a form of VAS.[24,25]

The results of this study were promising. Although the criteria that were evaluated were just facial swelling [Table 2] and pain [Table 3], in the IV dexamethasone group, there was a statistically higher significant result found in post operative swelling on the 2nd, 4th and 7th post operative days as compared to the SM dexamethasone group. It also showed that maximum facial swelling is expected 48 h after the surgical procedure. The swelling seen in the SM dexamethasone group was statistically much higher as compared to that seen in the IV dexamethasone group on the 2nd post-operative day. The difference in the swelling seen in patients of the IV dexamethasone group and the SM dexamethasone group went on decreasing on the subsequent 4th and 7th post-operative days. There was a statistically significant difference in swelling reduction between the two groups; however, clinical reduction in swelling between the two groups was almost similar, indicating that both IV and SM routes of dexamethasone was effective in decreasing swelling postoperatively. It is reported that swelling may increase on the 3rd day after surgery in patients treated with corticosteroids and there is a need to continue corticosteroid therapy for a minimum of 3 days to maintain the blood level of the drug.[1,40]

It is pertinent to note that reduction of facial swelling in the IV dexamethasone group during the 2nd, 4th and 7th post-operative days was statistically highly significant compared to the SM dexamethasone group, indicating that IV dexamethasone is an effective route for reducing swelling after third molar surgery. Patients who were more apprehensive for needle injection were more comfortable with SM injections. Pain scores were significantly less in the IV dexamethasone group compared to the SM dexamethasone group on the 2nd post-operative day. However, there was no significant difference in the IV and SM dexamethasone-treated groups. The study aimed to achieve an optimum reduction in inflammatory reaction and reduce side effects, using a single dose of 8 mg dexamethasone IV and 8 mg dexamethasone SM. This regimen significantly reduced the inflammatory reaction in the post-operative period. An effort should be made to standardise the procedure. Application of a constant dose of dexamethasone can result in different plasma concentrations of the drug related to individual variations in the body mass.[15,34,40]

Some studies have shown that there is a significant benefit of a high single IV dose of dexamethasone over the lower dose in preventing pain, swelling and trismus after third molar surgery.[24,26] Considering the minimal potential side effects associated with the application of dexamethasone at a higher dose, it was concluded that there is no contraindication for higher doses in third molar surgery.[3-5] However, this divergence may be related to the relatively low dose of dexamethasone (4 mg) used in a study as compared with the relatively high dose that was used in the other studies.[16] This is supported by a randomised clinical trial that compared the administration of placebo, dexamethasone (10 mg) and other corticosteroids. Consistent with this study, both the groups had equivalent pain ratings on the VAS irrespective of the route of administration.[3-5]

IV route of dexamethasone has one significant adverse effect compared to submucosal route. Genital irritation is being

reported in many studies done on IV dexamethasone. This effect has been reported since 1988 when Taleb published his studies. In subsequent years, more reports describe the same adverse event appearing after IV administration of dexamethasone. The symptoms were described as itching, burning, tingling, irritation or pain in the genital or perineal area. It appears immediately during or shortly after IV administration of dexamethasone. The symptoms resolve within several minutes.[41] More females than males are reported to be affected. In our study, 15 out of 17 females and 1 out of 13 males reported genital irritation in the IV group whereas none in the SM group reported any irritation. It is thought that perineal symptoms are caused by the corticosteroid phosphate ester of dexamethasone sodium phosphate. The same reaction is also described with hydrocortisone-21-phosphate sodium and prednisolone phosphate, but not with other non-corticosteroid phosphate drugs.[8] Furthermore, the incidence and severity of the symptoms seem to increase as the organic phosphate content of the injection increases.[6] The short duration of the symptoms might represent the time required to hydrolyse the ester bond to dexamethasone and phosphate ions.[41,42]

Furthermore, in some studies, an interesting finding was that plasma glucose excursions during the oral glucose tolerance test (OGTT) were only increased at 24 h following the intake of either 2 or 4 mg dexamethasone, while plasma insulin and C peptide levels were significantly increased. This suggests that the well known effects of dexamethasone increasing insulin resistance in peripheral tissues, including skeletal muscle and liver, and stimulating gluconeogenesis were accompanied by an increase in insulin secretion resulting in near normal plasma glucose levels during the OGTT. In contrast, the administration of 8mg of dexamethasone was followed (at 24 h) by a significant increase in fasting plasma glucose levels.[36,37,42] The authors concluded that a single oral dose of 8 mg dexamethasone increases blood glucose, insulin and C-peptide levels maximally at 24 h, 1 h following 75-g OGTT and suggested that a dexamethasone stress test might identify persons at increased risk for type 2 diabetes.[42] Hence, when using 8 mg dexamethasone IV or SM for surgical removal of III molars in diabetic individuals, a dexamethasone stress test might be helpful.

Although we have standardised this study, there is a necessity to undertake more randomised control trials to compare the anti-inflammatory properties of both the routes of corticosteroids. The smaller sample size is one of the limitations of the study, and in further studies, a higher cohort can be selected. Furthermore, in our study, we have not emphasised the potential effects of the difficulty of impaction and the amount of bone removal and the complexity of the technique used in the removal of the tooth on the overall swelling and pain and how dexamethasone IV or SM route plays a role in affecting these parameters. These, however, are in the domain of further research that can be conducted. The results of this study, however, do show that dexamethasone in SM route is equally effective in controlling post-operative swelling and pain after third molar surgery as compared to dexamethasone in IV route. Dexamethasone does play an important role in the reduction of post-operative inflammatory sequelae without the possibility of any side effects. Both SM and standard IV routes provide promising results, and a note of worth is that needle phobic patients tolerated submucosal injection better than IV injection.

Conclusion

Within the limitations of the study, it can be concluded that IV route of dexamethasone showed higher efficacy compared to SM route of dexamethasone in reducing the post-operative inflammatory sequelae in the surgical removal of impacted lower third molar teeth. It was also seen that IV dexamethasone (8 mg) and submucosal dexamethasone (8 mg) had equivalent ratings in terms of reduction of swelling & pain and there were no signs of any systemic toxicity clinically between both the routes. Although the results of this study showed both the routes are effective in controlling post-operative swelling and pain after third molar surgery, certain benefits of submucosal route make the sm route to be a valuable alternative to iv dexamethasone.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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