Effect of submucosal or oral administration of prednisolone on postoperative sequelae following surgical extraction of impacted mandibular third molar: A randomized controlled study

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ABSTRACT

Background: The aim of the study was to evaluate the effect of preoperatively administered submucosal and oral prednisolone on postoperative pain, facial swelling, and trismus following third molar surgery. Patients and Methods: This was a randomized controlled trial in which subjects were randomly distributed into three groups. Group A consisted of subjects who received 40 mg oral prednisolone; Group B consisted of subjects who received 40 mg submucosal injection of prednisolone while Group C consisted of subjects who did not receive prednisolone. Each group had 62 subjects. Measurements for facial width/facial swelling, pain, and mouth opening were recorded preoperatively and postoperatively. The postoperative evaluation points were postoperative days 1, 3, and 7. These measurements were compared with the preoperative values both within and among the groups. Results: Most of the subjects were in their third decade of life. A considerable increase in the mean postoperative values for pain, facial width and trismus was observed. Notably, subjects who did not receive prednisolone showed comparatively higher values for the measured parameters throughout the postoperative evaluation period. Subjects who received submucosal injection of prednisolone showed overall lower values compared to those who received oral prednisolone. Conclusion: The results of this study indicate that the administration of prednisolone has a significantly beneficial effect in ameliorating the postoperative sequelae of the third molar surgery. In addition, the effect of submucosally injected prednisolone is comparable to the orally administered prednisolone; indeed it shows superiority to the latter in a number of dimensions. Submucosal injection of prednisolone offers a simple, effective, easy, safe, and minimally invasive option to existing therapeutic methods of reducing these postoperative sequelae.

Key words: Sequelae, submucosal, third molar

INTRODUCTION

The extraction of impacted third molars, which may be prophylactic or therapeutic, is one of the most frequently performed operative procedures in oral and maxillofacial surgery.\(^1,2\) Surgical extraction of impacted third molars inevitably results in trauma to soft and hard tissues; consequently, significant pain, swelling, and trismus may be experienced by patients who undergo such extractions.\(^3,4\) Frequently, they experience significant postoperative distress and a decline in quality of life (QoL).\(^5-7\)

The undesirable consequences of impacted mandibular third molar surgery on the patients' postoperative QoL...
have been reported to show a 3-fold increase in patients who experience pain, swelling, or trismus alone or in combinations, compared to those who had none of these symptoms.\textsuperscript{7} Various techniques intended to mitigate the detrimental effects of third molar surgery have been proposed, including the use of mouth washes, drains, specific suture techniques, steroids, ice packs, laser, analgesics, and drains, among others.\textsuperscript{4,9,11} The administration of corticosteroids such as dexamethasone and prednisolone considerably reduces the manifestations of inflammation such as swelling, redness, warmth, and tenderness that are frequently observed at the operative site.\textsuperscript{7} Steroids may be administered along with nonsteroidal anti-inflammatory drugs and this combination has been found to have a distinct effect in reducing the severity of postoperative pain, swelling, and trismus.\textsuperscript{1,4,9,11}

Prednisolone, which is a synthetic analog of cortisol, has a half-life of 2.1–3.5 h. It is about 4 times as potent as hydrocortisone, has duration of action of 18–36 h and quite importantly, a low mineralocorticoid activity.\textsuperscript{12,13} Prednisolone has a long record of efficacy and safety.\textsuperscript{12,14} The various routes of administration have been described, which include oral, intramuscular, intravenous, and submucosal routes.\textsuperscript{13,15}

Majid and Mahmood,\textsuperscript{16} in a randomized controlled clinical trial where dexamethasone was administered intramuscularly and submucosally to two groups of subjects, reported comparable results between both groups with evidence of reduction in the postoperative measurements of pain, trismus, and edema. Subjects in the control group were found to have experienced a greater severity of postoperative sequelae in comparison to subjects in the test groups.\textsuperscript{16}

Oral administration of prednisolone may have associated gastrointestinal side effects. In addition, systemic availability in oral administration may be unpredictable, and compliance may be a problem in extended usage.\textsuperscript{4,13,17,18} Intramuscular administration of prednisolone on the other hand may predispose to the higher frequency of systemic adverse effects.\textsuperscript{19,20} Submucosal administration on the other hand is quicker to take effect than when given orally and there is no possibility of associated gastrointestinal disturbances.\textsuperscript{9,21} Furthermore, submucosal administration exhibits less systemic effects and has effects confined largely to the operative site since the drug is concentrated at the operative site.\textsuperscript{16,21}

The objective of this study was to compare the effect of submucosally injected methylprednisolone (adjacent to the surgical site) with that administered orally, on the postoperative sequelae of surgically extracted impacted mandibular third molars in the immediate postoperative period.

**PATIENTS AND METHODS**

This was a prospective, randomized controlled clinical study to evaluate the effect of submucosal and oral administration of prednisolone on postoperative sequelae after third molar surgery. Ethical approval was obtained from the Health Research and Ethics Committee of the Lagos University Teaching Hospital. All subjects were at least 18 years old. All potential subjects with known contraindications to the use of steroids such as hypertension, gastrointestinal tract ulcer, diabetes, glaucoma, active bacterial/fungal/viral infections, history of thromboembolic/cardiovascular events, glaucoma, psychosis, were excluded from the study. In addition, pregnant or lactating females and patients determined to be on anti-inflammatory drugs were also excluded from the study.

Subjects were allocated into three groups (Groups A, B, and C) using a computer-generated table of random numbers. Subjects in Group A received 40 mg prednisolone per oral, which was administered 30 min preoperatively; Group B consisted of subjects who had submucosal administration of 40 mg prednisolone, which was administered preoperatively 5 min after local anesthesia had been achieved [Figure 1]. The surgical incision was made 2 min after submucosal injection of prednisolone. Subjects in Group C did not receive any prednisolone, and they were the control. All subjects received amoxicillin 500 mg orally 8 hourly for 5 days and metronidazole 200 mg perorally 8 hourly for 5 days after surgery; and ibuprofen 200 mg perorally immediately after the surgery and then 8 hourly for 3 days, regardless of their group.

All subjects were informed about the procedures and objectives of this study, and a written consent was also obtained from each participant. Preoperative data were obtained from the subjects: Demographics (age, sex), indications for extraction, location of the third molar (left or right), type of impaction, and the degree of impaction.

Preoperative and postoperative assessment for facial width/swelling, trismus, and pain was done for all subjects using the same methods and by the same operator. All the impacted mandibular third molars were classified according to Winter’s classification and Pelle and Gregory classifications using a standard periapical radiograph. The reasons for extraction and location of impacted tooth were also recorded. Preoperative measurements formed the baseline values for pain, mouth opening, and facial width.

The preoperative pain was assessed using the linear 100 mm visual analog scale (VAS). The subjects were asked to mark on the line with a pen; the point they felt was most representative of their pain perception, with the “worst imaginable pain” and “no pain” represented by either extreme ends of the scale. Subsequently, the VAS score
for each subject was decided by measuring in millimeters from the left extreme of the line to the point marked by the subject.

Facial width was determined preoperatively using the tape measuring method described by Gabka and Matsumura. Three measurements were made as follows: The tip of the tragus to the soft tissue pogonion ipsilaterally (line A), tip of the tragus to the ipsilateral oral commissure (line B), and lateral canthus of the eye to the angle of the mandible ipsilaterally (line C) [Figure 2]. The measurements were taken thrice, and the average was recorded in centimeters. All measurements were done by a single operator for all subjects and recorded.

Preoperative mouth opening measurement was done with the aid of the mono-block basic Vernier caliper as the maximum inter-incisal distance [Figure 3]. Where the incisors were absent, the occlusal part of the edentulous ridges using the labial frenum as a guide for centrality was used. This measurement was taken with the subject seated upright and the Frankfurt plane parallel to the floor. These measurements were done thrice, and the average was recorded in millimeters.

**Operative procedures**

All operations were carried out under local anesthesia with 2% lignocaine hydrochloride with 1:80,000 adrenaline. The inferior alveolar nerve and lingual nerve anesthesia were achieved using the conventional technique, whereas the standard buccal nerve block technique was used to achieve long buccal nerve anesthesia. A three-sided mucoperiosteal flap was raised for access. The buccal guttering technique was used to expose and undermine the tooth under copious irrigation with normal saline. Where necessary, sectioning of the tooth was done, and delivery was done with coupland elevator. Following tooth delivery, copious irrigation of the surgical site with sterile water was done. The flap was repositioned and secured with 3/0 black silk interrupted sutures.

**Postoperative assessment**

Postoperatively, all subjects were assessed for pain, facial swelling, and maximal inter-incisal distance using an identical method to that used preoperatively. For pain measurement, each subject was given a postoperative pain assessment form/diary (VAS) to be filled each day for 7 consecutive days. Subjects were instructed to fill it at 8:30 pm daily. Postoperative facial width was measured exactly as described previously for the preoperative baseline measurement. The measurements were done and recorded on the postoperative days (PODs) 1, 3, and 7. Postoperative mouth-opening ability was obtained using maximum inter-incisal distance as described for the preoperative measurement using Vernier calipers.

The measurements were done and recorded on the PODs 1, 3, and 7.
Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). The Student’s t-test was used in the analysis of measures of pain, inter-incisal mouth opening, and facial swelling. The comparison of scores among the three groups was done using the analysis of variance. The critical level of significance was set at \( P < 0.05 \).

RESULTS

One hundred and ninety-eight subjects who satisfied the inclusion criteria and consented to participate were recruited for the study. However, 186 subjects out of the 198 participated in all stages of this study and were then included in the final analysis. Statistically, 69 were males, and 117 were females, giving a male to female ratio of 1:1.7. Overall, the mean age (±standard deviation [SD]) and sex distribution for all the subjects were 28.1 (7.4) years (range, 18–51 years) [Table 1]. The mean age (±SD) of subjects was 28.5 (7.9) years, 27 (6.6) years, and 28.8 (7.5) years for Groups A, B, and C, respectively (\( P > 0.05 \)).

The most frequent type of impaction seen, using Winter’s classification, was mesioangular which constituted 40.9% of cases, followed by distoangular (25.8%), vertical (16.1%), horizontal (13.4%), and others (3.8%). Recurrent pericoronitis (52.7%) was the most frequent reason for surgical extraction, followed by caries and its sequelae (26.3%), periodontal disease (11.3%), and orthodontics (5.4%). Other indications for surgical extraction accounted for the remaining 4.3%. There was no statistically significant difference between Groups A, B, and C regarding mean preoperative inter-incisal distance, pain, and facial width (\( > 0.05 \)) [Table 2].

The highest mean pain score was recorded on POD1 and it gradually decreased over the 7 days postoperative period in all three groups [Table 3]. The severity was observed to be lower among subjects in Groups A and B when compared with those in Group C throughout the immediate postoperative period [Table 3]. Both prednisolone groups showed a statistically significant lower pain magnitude in comparison with the control group at all intervals (\( P < 0.05 \)) [Table 3]. There was no statistically significant difference in pain perception between subjects in Groups A and B at all the postoperative evaluation points [Table 4].

There was a decrease in the mean postoperative inter-incisal mouth opening distance for all groups in the immediate postoperative period in comparison with the preoperative measurements [Table 5]. Furthermore, there was a significant reduction in the mean inter-incisal distance
on POD1, POD3, and POD7 in Group C when compared with Groups A and B \( (P < 0.05) \). Subjects in Group C also exhibited higher mean postoperative swelling on POD1, POD3, and POD7 when compared with Group A and B \( (P < 0.05) \) [Table 5]. A comparison of mean inter-incisal distance between Groups A and B revealed a statistically significant difference on POD1 and POD3 [Table 6].

**Postoperative facial swelling**

There was an increase in the mean postoperative facial swelling for all groups on POD1, POD3, and POD7 [Table 7] in comparison with the preoperative facial width measurement. In all groups, the swelling was most severe on POD1 followed by the POD3, to approximately reach the preoperative measures by the 7th day. Subjects in Group C exhibited the highest mean postoperative swelling as measured on POD1, POD3, and POD7 [Table 7]. There was a statistically significant difference in the mean postoperative facial swelling between prednisolone groups (Groups A and B) and control (Group C) at POD1 and POD3 [Table 7]. However, a comparison of the postoperative facial swelling between subjects in prednisolone groups (Groups A and B) showed no statistically significant difference (POD1, \( P = 0.8 \); POD3, \( P = 0.9 \); POD7, \( P = 0.6 \)).

**DISCUSSION**

The mean age of subjects observed in this study is similar to the reports by Majid and Mahmood as well as Bamgbose *et al*., who reported mean ages of 26.9 years and 27.9 years, respectively.\(^1,16\) Most of the subjects were in their third or fourth decades of life; this is in agreement with reports in the literature.\(^{23,24}\) Some authors have hypothesized that this observation may be due to the fact that most mandibular third molars erupt between ages 17 and 25 years.\(^{25,26}\)

A slightly higher female prevalence was observed in this study. This finding is similar to reports by Morales-Trejo *et al*., Bamgbose *et al*., and Obiechina *et al*.\(^{1,2,23,27}\) This is in contrast to the report by Bui *et al*., who reported a male to female ratio of 1.3:1.\(^{28}\) Quek *et al*., reported no sex prevalence in a study of a Singaporean Chinese population while a study of a Chinese population by McGrath *et al*. reported a clear female preponderance with a male to female ratio of 1:2.9.\(^{6,29}\)

The most common type of impaction in this study was mesioangular impaction. This is in agreement with studies by Akinbami and Ofomala, and Adeyemo *et al*.\(^{30,31}\) However, Bui *et al*. reported the most common Winter’s classifications as vertical and mesioangular 63.9% and 25.7%, respectively.\(^{28}\) Ladeinde *et al*. reported distoangular impaction (46%) as the most common.\(^32\)

There is no consensus on the reason for higher prevalence of mesioangular impaction in the literature; however, some authors have postulated that the primordial tooth germ of mandibular third molar develop high up in the mandibular ramus with its occlusal surface slanting mesially or sometimes horizontally.\(^33,34\)

In the present study, recurrent pericoronitis was the most common indication for the removal of impacted mandibular third molar. This is supported by many other studies including those by Laureano Filho *et al*., Adeyemo *et al*., and Ladeinde *et al*.\(^{31,32,33,36}\) Unrestorable caries and its sequelae on impacted mandibular third molar and the adjacent tooth was the second most common indication for extraction (26.3%). This is in consonance with the studies by Laureano Filho *et al*. and Adeyemo *et al*.\(^{31,33}\) Periodontal disease accounted for 11.3% of indications for surgical extractions in this study. This is similar to the report by Adeyemo *et al*., who reported periodontal disease as an indication in 9.2% of cases.\(^36\) Obiechina *et al*. reported pericoronitis and periodontal disease as accounting for 42.92% of cases seen in their study.\(^27\) Orthodontic reasons for surgical extraction accounted for 5.4% extractions done while other reasons for extraction such as facial neuralgia and prosthodontic reasons accounted for the remaining 4.3%.

Surgical extractions of third molars for prophylactic reasons are not common in our environment. In a study by Adeyemo *et al*., it accounted for 0.6% of cases.\(^37\) This is in contrast with European studies where it is reported that between 18% and 50.7% undergo surgical extraction of third molars for prophylactic reasons.\(^38\)

Postoperatively, an interwoven cascade of functional and structural changes, which are often expressed as pain,
swelling, and trismus, occur. These expected sequelae have been reported to be detrimental to the patients’ QoL in the immediate postoperative period.

Pain is often experienced by patients after surgical extraction of impacted mandibular third molars. It characteristically increases in intensity in the early postoperative period until it peaks within the first 24–48 h postextraction. In addition, Snyder et al. reported that patients who experience pain sufficient to prompt taking pain medications experienced a comparative significant interference with recovery for lifestyle and oral function after third molar surgery. In this study, the VAS was used to evaluate pain perception by the subjects. It has been used in the evaluation of postoperative pain after mandibular third molar surgery by several. The highest pain intensity in this study was recorded on POD1, but it gradually decreased in value in all groups during the immediate postoperative period. The lowest pain scores were observed on POD7.

Higher mean pain scores were observed in the control group throughout the immediate postoperative period than in the oral and submucosal prednisolone groups. These differences in pain scores among the groups were statistically significant all through the immediate postoperative period. The mean pain scores observed in the immediate postoperative period were slightly higher in Group A than Group B except on POD2. This is in agreement with the findings of Twana et al., who found lower pain values in the corticosteroid group in the postoperative period compared with the control. In a systematic review by Markiewicz et al., the authors observed that subjects in the corticosteroid group reported less VAS points for pain than the control group, 1–3 days after surgery. This decrease in pain may be credited to corticosteroid effects which may have decreased patients’ inflammatory response and reaction to pain by repressing tissue bradykinin and β-endorphin intensity.

In the present study, there was a significant reduction in postoperative swelling in prednisolone groups (Groups A and B) in comparison with the control group on POD1 and POD3. The prednisolone groups also had lower values for facial swelling measurement on POD7; however, the difference in values obtained was not statistically significant when compared with the control group. A comparison of the difference in facial swelling measurement values on POD1, POD3, and POD7 for the Groups A and B was not statistically significant. This is in agreement with the study by Majid, who evaluated the effect of submucosal dexamethasone in subjects undergoing surgical extraction of the lower third molar. Shah et al. and Hassan also reported similar findings.

Milles and Desjardins performed a crossover study on 11 patients using 16 mg methylprednisolone orally, the evening before surgery. They reported that the low dose of methylprednisolone reduced swelling by 34% at 48 h postoperatively. Warraich et al., using a single dose (4 mg) of submucosal dexamethasone preoperatively, reported significantly less swelling in the subjects receiving corticosteroids than the subjects in the control by the 2nd postoperative day. Similar observations were made by Grossi et al. and Majid. In addition, Grossi et al. also observed that there was no statistically significant difference in postoperative edema measurements between the corticosteroid and control groups. Furthermore, Neupert et al. reported no statistically significant reduction in postoperative swelling on the 2nd and 7th postoperative days between the corticosteroids and control groups. However, it was noted that the dosage of the steroid used was subtherapeutic.

Mouth-opening ability was evaluated by measuring the maximum inter-incisal distance between the corresponding central incisors with the Vernier caliper; this method has been used in numerous researches. The mean postoperative inter-incisal distance decreased in comparison with the mean preoperative inter-incisal distance in the immediate postoperative period. This difference was statistically significant on POD1, POD3, and POD7.

The severity of the trismus seen is a direct effect of the degree of inflammatory response. Subjects in Group A and B had a less severe limitation in mouth opening in the immediate postoperative period compared to those in Group C. This is likely due to the anti-inflammatory effects of prednisolone administered. Subjects in Group B had a slightly higher mean inter-incisal distance compared with those in Group A. This finding is in consonance with reports by Tiigimae-Saar et al. and Kang et al., who administered 30 mg and 20 mg of prednisolone, respectively in subjects undergoing third molar extraction. This is possibly because of the local administration of prednisolone in Group B subjects which is close to and concentrated at the operative site. In addition, it bypasses the gastrointestinal tract and the liver, thereby increasing the bioavailable fraction of the drug.

However, Grossi et al. in their study noted no statistically significant difference between the study and control groups. This may have been because of the relatively small sample size of 61 subjects which they randomly divided into three groups.

**CONCLUSION**

This study has shown that the administration of prednisolone has a significant impact in reducing postoperative pain, edema, and trismus following third molar surgery. The submucosal route of prednisolone administration is a viable alternative to the other routes.
Indeed, it exhibited significant comparative advantages over the oral route of administration. In addition, it offers a safe, simple, cost-effective, and painless method, which produces a high concentration of prednisolone at the operative site, thereby lessening the systemic effects.

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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