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Article

Effect of a Single Dose of Deflazacort on Postoperative Pain, Swelling and Trismus after Impacted Lower Third Molar Surgery: Randomised Clinical Trial

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Abstract: *Background and Objectives:* The complications seen after lower impacted third molar surgery affect the quality of life of the patients. The aim of the study was to investigate the efficacy of a single preoperative dose of deflazacort on pain, swelling and trismus following impacted lower third molar surgery. *Materials and Methods:* This randomised, prospective, double-blind, split-mouth clinical study included 30 healthy individuals with bilaterally impacted lower third molars that was removed for orthodontic purposes between September 2017 and September 2018. Group 1 was given a placebo (single dose vitamin C tablet) and group 2 was given a single 30 mg dose of deflazacort 1 hour prior to the surgery. Pain was evaluated using the visual analog scale for 1 week postoperatively. Edema (in mm) and trismus (in mm) were evaluated preoperatively and on postoperative days 2 and 7. The Mann-Whitney U test was applied for group analysis. p values < 0.05 were considered statistically significant. *Results:* When postoperative pain scores were evaluated, a significant difference was found between the groups only at the 6th and 12th hours (p<0.05). The lower swelling values in the first 12 hours may be a factor in measuring less postoperative pain scores in the second group. Pain scores were similar until the 5th day (p>0.05). Even high trismus values were recorded on the 2nd day, it was observed that the trismus resolved on the 7th day. There were no significant differences in trismus between the groups at any time point (p>0.05). Evaluation of swelling showed that there was no statistically significant difference between the study and control groups at any time point (p>0.05). No side effect was detected in both the study and the control groups. *Conclusions:* This was the first split-mouth study evaluating the anti-inflammatory effect of deflazacort after lower impacted third molar surgery. A single dose of 30 mg deflazacort was shown to be effective in reducing pain at 6 and 12 hours postoperatively.

Keywords: deflazacort; corticosteroid; pain; swelling; trismus; impacted third molar surgery

1. Introduction

Impacted lower third molars are the most common impacted teeth in the jaws and their treatment usually requires surgical removal. Surgical extraction of these teeth take an important part of the routine workflow of oral and maxillofacial surgery clinics [1,2]. This procedure is associated with several postoperative sequela that have both social and biological effects. In addition to serious complications such as paresthesia, infection, jaw fractures and alveolitis; patients generally complain of pain, edema, and trismus due to post-operative inflammatory response [3,4]. The peak intensity of these complications occurs in the first 48 hours after surgery, gradually decreasing in severity and resolving within 7 days. Inflammation resulting from surgical trauma is a major contributor to these complications. The overall aim of post-operative interventions is to prevent or reduce complications

that affect the patient's quality of life. There are several treatments and methods for controlling and assessing the extent of postoperative complications [5,6].

When the treatment methods used to prevent complications of impacted wisdom teeth are examined; a number of analgesics have been used to manage postoperative pain and swelling. Among these, paracetamol and NSAIDs stand out as commonly used options and are often considered basic by many practitioners. In addition, they may be supplemented with opioids or corticosteroids to increase their effectiveness [7,8]. Topical gels containing antimicrobial agents enable direct application of the drug to postoperative surgical sites. Their efficacy surpasses that of mouthwashes due to the gel's ability to prolong drug release, provide targeted alveolar action and enhance bioavailability. Unlike mouthwashes, which carry a risk of clot dissolution within the first 24 hours, gels can be applied immediately after tooth extraction. While mouthwashes provide localised action and mechanical debridement, gels are cost-effective and have fewer side effects. In addition, they do not require a prescription and eliminate the need for clinic visits, reducing costs for both patients and clinicians [6,9]. Cryotherapy, which involves applying ice to the area outside the surgical site, is a straightforward method that many clinicians prefer. The principle behind cryotherapy is that lower temperatures induce vasoconstriction, reducing post-operative swelling. In addition, it can reduce nerve fibre conduction velocity, resulting in an analgesic effect [10]. The surgical principles utilized to access impacted teeth has been subject to investigation for managing healing complications after lower impacted third molar extraction. An envelope flap may result in reduced postoperative pain and swelling when compared to a triangular flap [11]. Suture material is known to influence postoperative complications. The positive effects of polybutester sutures on pain control in lower impacted third molar surgery have been demonstrated [12]. In surgical practice, irrigation involves the delivery of a fluid stream for purposes such as washing or debridement. In the context of third molar surgery, irrigation is employed during the postoperative phase to manage alveolar osteitis. The removal of necrotic debris or food particles via irrigation is hypothesized to eliminate potential sources of inflammation and pain [6,13]. Moreover, when extraction sockets are irrigated with rifamycin, there is an evidence suggesting reduction in the incidence of alveolitis, prevention of infection, and the induction of analgesia following surgical removal of impacted third molars [13,14].

For more than 50 years, corticosteroids have been used to prevent post-operative complications after impacted lower wisdom tooth surgery, and there are several studies published in the literature on this issue [15,16]. The anti-inflammatory effects of corticosteroids are attributed to the inhibition of Phospholipase A2, which reduces the release of arachidonic acid derivatives. This process leads to a decrease in the synthesis of leukotrienes and prostaglandins, thus preventing the accumulation of neutrophils in the inflamed area [17]. Corticosteroids have two main forms: the glucocorticoids and the mineralocorticoids. Glucocorticoids, such as endogenous cortisol, primarily demonstrate anti-inflammatory and immunosuppressive effects. These actions entail inhibition of the production and function of various inflammatory cells and provoke redistribution of immune cells to different body compartments, resulting in a reduced number of circulating immune cells overall. On the other hand mineralocorticoids, including endogenous aldosterone, play a role in regulating the balance of salt and water in the body. Specifically, mineralocorticoids act on the renal tubules, promoting the reabsorption of sodium and the excretion of potassium [18]. Glucocorticoids; such as dexamethasone, methylprednisolone and triamcinolone are commonly used in oral surgery, because of their anti-inflammatory activities with minimal effects on fluid and electrolyte balance [19].

Deflazacort belongs to the group of synthetic corticosteroids and is quickly and totally absorbed in the intestinal tract when taken orally [20]. Deflazacort is an oxazoline derivative of prednisolone. It is used for a wide number of different clinical conditions regarding its anti-inflammatory and immunosuppressive effects [21,22]. Studies have shown that deflazacort is as effective as prednisone or methylprednisolone in the treatment of rheumatoid arthritis, severe asthma, nephrotic syndrome, Duchenne muscular dystrophy and systemic lupus erythematosus [23,24]. Compared with other glucocorticoids, deflazacort appears to have limited adverse effects on bone and carbohydrate

metabolism at doses with equivalent clinical efficacy [25]. The incidence of gastrointestinal disorders is also lower in patients treated with deflazacort [22,23].

The hypothesis of this study was that a single preoperative dose of deflazacort would be effective in preventing postoperative complications in subjects undergoing impacted lower third molar surgery. The purpose of the study was to investigate the efficacy of a single preoperative dose of deflazacort on pain, swelling and trismus following impacted lower third molar surgery.

2. Materials and Methods

2.1. Study sample

This randomised, prospective, double-blind, split-mouth clinical trial was conducted at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Van Yuzuncu Yil University between September 2017 and September 2018. The study included 30 healthy individuals (any congenital or acquired systemic disorders according to patients' anamnesis) owning impacted lower third molars with an indication of surgical extraction due to orthodontic purposes. Patients were included if they were aged from 18 to 40 years, had bilateral impacted mandibular third molars with bone retention at similar angulations and with similar degrees of impaction. Patients who were smokers, substance abusers and alcoholics, pregnant or breastfeeding mothers, taking medication within one week before the surgery and those who had facial asymmetry were excluded from the study. Ethical approval was confirmed by Van Yuzuncu Yil University, Faculty of Medicine, Clinical Investigations Ethics Committee (decision number: 19.07.2017-06). The researchers adhered to the Declaration of Helsinki throughout the study. The clinical trial was recorded on ClinicalTrials.gov (registration number: NCT04365088). Written informed consent was obtained from all volunteers after they were informed about the study.

2.2. Surgical procedure

In the trial, patients received placebo or deflazacort 1 hour prior to the surgery. Group 1 was given a placebo (single dose vitamin C tablet) and group 2 was given a single 30 mg dose of deflazacort. A permutation method was used in the MedCalc 11.5.1 software package to randomise which drug would be used on which side and which side would be used for the first operation. The surgical team was blinded to group allocation during surgery and at post-operative follow-up period. The operations were performed by the same surgeons on Monday, Tuesday and Wednesday mornings according to a standard protocol. The time interval between surgical extractions of bilaterally impacted lower third molars were at least 3 weeks. Patients were given local anaesthesia of 2 ml of articaine hydrochloride with epinephrine solution (40 mg/ml; 0.01 mg/ml; Maxicaine Fort; Vem Pharmaceuticals Ltd, Istanbul, Turkey). A full-thickness flap was elevated using a horizontal incision. All procedures included removal of bone and/or segmentation of tooth under sterile saline irrigation. After extraction, any granulation tissue was removed and the extraction socket was irrigated. Once haemostasis was achieved, the flap closure was performed with 3/0 silk sutures. Antibiotic (amoxicillin 875 mg + clavulanic acid 125 mg, twice a day; Augmentin-BID 1000 mg; GlaxoSmithKline Pharmaceuticals Ltd, Istanbul, Turkey), analgesic (600 mg Ibuprofen, twice daily; Brufen 600 mg; Abbott Laboratories Ltd, Istanbul, Turkey) and oral antiseptic (% 0.3 benzydamine hydrochloride, 3 times a day; Tanflex Fort 15 ml spray; Abdi İbrahim Pharmaceuticals Industry and Trade Inc., Istanbul, Turkey) were prescribed as postoperative medication. Antibiotics and analgesics were given immediately after surgery, and mouthwash was started one day after surgery and continued for one week postoperatively. For the first 24 hours after surgery, patients were advised to eat only soft foods and not to use dental floss, toothbrushes or mouthwash.

2.3. Data collection

The study involved groups that used preoperative corticosteroid (30 mg deflazacort) or placebo medication. Self-reported pain scores during the first postoperative week, mouth opening and facial swelling measurements (in mm) at postoperative days 2 and 7 were used as outcome variables.

Surgical interventions and post-operative patient assessments were performed by different researchers.

Maximum mouth opening (MMO) was measured in millimetres from the incisal edge of the right upper and lower incisors using a caliper to evaluate trismus. The preoperative MMO values were subtracted from the MMO values on postoperative days 2 and 7, and the proportional changes in measurements compared to the preoperative MMO were calculated.

Swelling was assessed by measuring the distance between several facial landmarks using a millimeter ruler. Measurement I (from the mandibular angulus to the labial commissure); Measurement II (from the labial commissure to the gonion); and Measurement III (from the gonion to the lateral canthus) (Figure 1). To evaluate swelling, the preoperative measurements were subtracted from the measurements on postoperative days 2 and 7, and the proportional changes compared to the preoperative measurements were calculated. For each evaluation interval, a single swelling value was obtained by averaging the 3 measurements and evaluations were performed according to this single value.

Patients were given a visual analogue scale (VAS) to rate their postoperative pain at postoperative hours 6, 12, 24 and daily from 2nd to 7th postoperative days. Patients were asked to rate their pain on a 100-point VAS, with 0 being no pain at all and 100 being the worst pain they have experienced until now. On postoperative days 2 and 7, patients were assessed for swelling and trismus. Any complications such as alveolitis and infection were also recorded.

2.6. Statistical analysis

The power analysis was carried out using the PASS programme according to previous studies [26,27] which showed that the standard deviation (SD) for pain scores varied from 4.87 to 5.39. The SD was therefore set at 5. The effect size was assumed by the researcher to be 2 for the 95% confidence level and based on the approximate power of 80%, and Z value of 1.96 was used for the type I error rate of 0.05. Based on the calculation of the sample size, the sample size was determined to be 24. Taking into account possible losses, it was decided to include 30 people, which was 25% more than this number. Descriptive statistics (minimum and maximum, standard deviation, mean, frequency) were calculated for every parameter. The Mann-Whitney U test was applied for group analysis. All analyses were performed using SPSS 21.0. p values < 0.05 were considered statistically significant.

3. Results

In total, 30 patients met the inclusion criteria, but 4 patients were excluded from the study because they failed to attend 1 or more follow-up visits during the study. Finally, data from 26 patients were analysed. The patients included in the study were 14 females (53.8%) and 12 males (46.2%), and their mean age was 23.31 ± 5.01 , ranging from 18 to 35 years (Table 1).

Table 1. Demographic characteristics distribution.

Gender	Male (%)	12 (46.2)
	Female (%)	14 (53.8)
Age (year)	Min-Max (Medyan)	18-35 (22.5)
	Mean±SD	23.31±5.01

SD: standard deviation.

When postoperative pain scores were evaluated, a significant difference was found between the groups only at the 6th and 12th hours ($p < 0.05$). Post-operative pain scores was significantly low in deflazacort group (Group 2) at postoperative hours 6 and 12 ($p < 0.05$). However, although there was no statistically significant difference in post-operative swelling between the groups on post-operative day 2, post-operative swelling was less in the second group. In conclusion; the lower swelling values in the first 12 hours may be a factor in measuring less postoperative pain scores in the second group. In further measurements, pain scores were similar until the 5th day ($p > 0.05$) (Table 2).

Table 2. Intergroup comparison of VAS scores.

	6th hour		12th hour		24th hour		2nd day		3rd day		4th day		5th day		6th day		7th day	
	Mean ±SD	Medi an	Mean ±SD	Medi an	Mean ±SD	Medi an	Mean ±SD	Medi an	Mean ±SD	Medi an	Mean ±SD	Medi an	Mean ±SD	Medi an	Mean ±SD	Medi an	Mean ±SD	Medi an
Group 1	5.8±2.1	6.00	4.81±2.19	5.0	4.35±3.02	5.0	3.92±2.64	3.0	3.04±2.72	2.5	1.96±2.22	1.5	1.46±1.90	0.5	1.04±1.28	0.0	0.85±1.54	0.0
Group 2	3.1±1.6	3.00	3.27±2.49	3.0	4.27±2.71	5.0	4.04±2.68	4.0	2.73±2.41	2.0	1.77±2.10	1.5	0.85±1.26	0.0	0.65±1.02	0.0	0.50±0.81	0.0
p	10.000*		10.025*		10.912		10.861		10.773		10.832		10.276		10.290		10.520	

¹Mann-Whitney U test; SD: standard deviation

Group 1: Control Group 2: Deflazacort.

Even high trismus values were recorded on the 2nd day, it was observed that the trismus resolved on the 7th day. There were no significant differences in trismus between the groups at any time point ($p>0.05$) (Table 3).

Table 3. Intra-group comparison of the MMO values on postoperative days 2 and 7.

		n	Mean	SD	Median	Minimum	Maximum	p
MAXIM UM	Day 2	Group 1	26	-31.93	15.25	-30.59	-60	-4.08
		Group 2	26	-32.91	14.28	-34.52	-55.56	0.00
MOUTH OPENIN G (%)	Day 7	Group 1	26	-13.17	11.75	-9.05	-43.75	0.00
		Group 2	26	-17.22	11.99	-15.65	-41.67	-2.04
		n	Mean	SD	Median	Minimum	Maximum	p
MAXIM UM	Pre-op	Group 1, and Group 2	26	44.5	5.13	45	31	55
		Group 1	26	30.15	7.17	30.00	16	47
MOUTH OPENIN G (mm)	Day 2	Group 2	26	29.35	4.33	29.00	20	36
		Group 1	26	38.54	6.56	38.00	25	55
	Day 7	Group 1	26	36.58	5.36	38.00	28	48
		Group 2	26	36.58	5.36	38.00	28	48

¹Mann-Whitney U test; SD: standard deviation; Group 1: Control group; Group 2: Deflazacort group.

Evaluation of swelling showed that there was no statistically significant difference between the study and control groups at any time point ($p>0.05$). Although there was no statistically significant difference, there was less swelling in group 2 on both post-operative day 2 and 7 ($p>0.05$) (Table 4).

Table 4. Intra-group comparison of facial measurements on post-operative days 2 and 7.

	Group 1		Group 2		p
	Mean±SD	Median	Mean±SD	Median	
Day 2 Distance	4.12±2.13	3.67	3.07±2.37	3.05	10.089
Day 7 Distance	1.74±1.80	1.12	1.44±1.71	0.91	10.349

¹Mann-Whitney U test; SD: standard deviation; Group 1: Control group; Group 2: Deflazacort group.

No side effects were observed in either the study or control groups.

4. Discussion

The anti-inflammatory activity of deflazacort and the other synthetic corticosteroids is the first reason for their therapeutic use. The synthesis of novel compounds with greater anti-inflammatory activity and reduced incidence of side effects compared to cortisone was the focus of early corticosteroid research. Prednisolone and prednisone, which were synthesized for this purpose, have greater anti-inflammatory activity compared with natural steroids, while mineralocorticoid activity

was attenuated by about half [28]. There are other corticosteroids, including fluorinated glucocorticoids such as dexamethasone, which have no mineralocorticoid activity and some typical adverse events due to their long-term use have been reported. The reality is that the side effects of corticosteroids often affect patients' quality of life, and concerns about safety of these drugs are particularly important in certain groups of patients treated with steroids [29,30]. The primary goal of deflazacort synthesis was to create novel agents that would be more tolerable in all age groups. The unique pharmacological properties of deflazacort are mainly due to its structural design. These properties include a significant reduction in sodium retention, potent immunosuppressive and anti-inflammatory effects, and reduced interference with metabolism of phosphorus and carbohydrates compared with previous corticosteroids. There are numerous and significant risks of adverse effects and toxicities associated with chronic treatment with systemic corticosteroids [31,32]. These drugs affect every organ system and metabolic process in the human body. The risk of adverse effects associated with corticosteroid therapy depends on the dose and duration of the therapy, as well as the specific corticosteroid prepartate used [28]. Additionally, in cases of steroid use for less than three weeks, the dose can be stopped suddenly. Therefore, there is no harm in discontinuing the single dose of deflazacort administered to patients. [33]. In this study, authors chose to use a single dose of deflazacort, a corticosteroid whose efficacy has not been evaluated in a split-mouth study in systemically healthy subjects for lower impacted third molar surgery, to protect them from the potential side effects of long-term steroid use described in the literature.

One of the main advantages of deflazacort is that it has fewer side effects on bone metabolism than other corticosteroids. In rheumatoid arthritis, deflazacort may protect against bone destruction and joint damage [34]. Deflazacort has been shown to inhibit synovial cell invasiveness and proliferation in a dose-dependent manner by differentially modulating individual components of the fibrinolytic system. It has been shown in the pre-pubertal population that deflazacort prevents excessive bone loss in comparison with methylprednisone maintenance. In one study, the use of deflazacort in kidney transplant patients was associated with less loss of bone mineral density at the lumbar spine compared to prednisone [20]. The development of osteoporosis has been linked to the negative calcium balance caused by chronic administration of glucocorticoids higher than physiological doses. Therefore, the less severe adverse effects on calcium balance observed with deflazacort treatment may indicate that it has a reduced adverse effect on bone mineral metabolism compared with prednisone. Several authors have supported this theory by using a variety of methods, that deflazacort causes less loss of bone mass or density than prednisone. It has been shown that deflazacort, although comparable to prednisone in context of its anti-inflammatory activity, is significantly less harmful to cancellous bone than prednisone. Studies evaluating the ability of glucocorticoids to induce glycogen deposition have demonstrated that deflazacort is a potent enhancer of gluconeogenesis and hepatic glycogen synthesis, approximately 10 times more effective when compared to prednisolone at equivalent doses. Deflazacort's anti-inflammatory efficacy is 10-20 times higher than that of prednisolone and 40 times higher than that of cortisol. In addition, its duration of anti-inflammatory action is longer than that of other glucocorticoids given at equivalent doses. It has been shown in the literature that deflazacort has fewer side effects than other corticosteroids, is more effective at similar doses and lasts longer. In the studies in which deflazacort has been used in oral procedures, Anitua et al. used deflazacort prophylactically in dental implant surgery in individuals with oral lichen planus at a daily dose of 20 mg for 2 days preoperatively, 15 mg for 3 days postoperatively, and 7.5 mg for the next 3 days [35]. Konagala et al. used deflazacort 30 mg as a single dose prior to root canal treatment to control post-endodontic pain [36]. de Vicente et al. used deflazacort 60 mg on the day of surgery and 60 mg the following day in patients undergoing open maxillary sinus augmentation via the lateral approach [37]. A few number of studies in the literature show that the preferred dose and duration of deflazacort in dental procedures vary. Therefore, a single dose of 30 mg deflazacort was preferred to use in this study.

Only one study was found in the literature that evaluated the effects of deflazacort on lower impacted third molar surgery (the study was in Spanish, and we found it in our detailed literature search) and in this study Flores et al compared the anti-inflammatory effects of deflazacort (given 30

mg daily for 7 days) with betamethasone. They found that betamethasone was more effective on inflammation in the first postoperative day and the effect of betamethasone and deflazacort on the duration of inflammation was similar [38]. Konagala et al compared the analgesic effect of a single dose of 30 mg deflazacort, administered 1 hour before root canal treatment, with proxicam, dexamethasone and placebo after endodontic treatment. They reported that pain levels were lower in the deflazacort group compared with placebo and similar to the proxicam and dexamethasone groups at 6, 12 and 24 hours after surgery [36]. In this study, as in the study by Konagala et al, the pain scores were lower in the deflazacort group than in the control group at 6 and 12 hours postoperatively. There was no difference in swelling and trismus compared to the control group. These results suggest that the anti-inflammatory effect of a single dose of deflazacort is effective in the first 12 hours postoperatively, depending on the half-life of the drug. The reason why there was no difference between the deflazacort group and the control group on postoperative day 2, the first day of trismus and swelling assessment, is thought to be due to the time-dependent decrease in the anti-inflammatory effect of deflazacort. The fact that the pain, swelling, and trismus scores were similar in the control group on postoperative days 2 and 7 supports this idea. As there is no recommended dose of deflazacort in the literature for sub-embedded wisdom surgery, we used the study by Konagala et al as a reference and preferred the single dose 30 mg tablet form of the drug. If we had preferred a higher single dose or long-term use of the current dose, this could have changed the results. In this clinical trial the split-mouth study design was preferred to eliminate personal differences between individuals related to pain perception and the severity of inflammatory response. The limitation of this study was that the postoperative administration of Ibuprofen in both groups may have affected the assessment of the anti-inflammatory efficacy of deflazacort because NSAIDs may provide an additional benefit to reduce inflammation when given in conjunction with corticosteroids.

5. Conclusions

In conclusion, this was the first split-mouth study evaluating the clinical efficacy of deflazacort after lower impacted third molar surgery. Although its anti-inflammatory activity is limited in terms of analgesia; a single preoperative dose of 30 mg deflazacort was shown to be effective in reducing pain at postoperative hours 6 and 12. Further comparative clinical trials with other corticosteroids including larger sample size should be conducted to evaluate the anti-inflammatory effects of deflazacort on postoperative complications after lower impacted third molar surgery and other oral surgical procedures.

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Institutional Review Board Statement: This research was conducted in accordance with the Declaration of Helsinki, and the Ethics Committee of Van YuzuncuYil University Non-Interventional Clinical Research Ethics Committee approved the study (decision number: 19.07.2017-06).

Informed Consent Statement: All subjects included in the study signed an informed consent form. Patients provided written informed consent for the publication of this article.

Data Availability Statement: Access to the dataset used in this study is available upon request. It is not publicly available as it contains information that could compromise the participants' privacy.

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