RESEARCH ARTICLE

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Effects of Preemptive Single Dose Sustained Release Non-Steroidal Anti-Inflammatory Drugs on Postoperative Complications Following Third Molar Surgery

ABSTRACT

Objective: The aim of this study was to compare the effectiveness of two preemptive sustained-release non-steroidal anti-inflammatory drugs in terms of pain, edema and trismus following third molar surgery.

Methods: Overall, 30 patients with double-sided vertically positioned impacted third molars were included in this study. The study was randomized and double-blinded. 30 minutes before the surgery, patients were given sustained-release (SR) dexketoprofen trometamol 75 mg and following the surgery the drug administration continued postoperatively for 1 week, once a day. 2 weeks later, the same procedure was applied for the counterside impacted third molar with 75 mg. sustained-release (SR) diclofenac sodium. The pain was assessed postoperatively by VAS (Visual Analogue Scale) levels at the 6th, 8th, 12th, 24th and 48th hours and on the 3rd, 5th, and 7th days. Edema and trismus measurements were evaluated on the postoperative 2nd and 7th days.

Results: There was a statistically significant difference between the groups in VAS levels at 6th, 8th, 12th, 24th, and 48th hours, and on the 3rd and 5th days ($P < 0.01$). Dexketoprofen trometamol SR group had lower VAS levels than diclofenac sodium SR group. There was no statistically significant difference between the groups in terms of mean trismus and edema measurement on the 2nd and 7th days ($P < 0.05$).

Conclusions: Dexketoprofen trometamol SR and diclofenac sodium SR are similarly effective for the reduction of edema and trismus following impacted third molar surgery; however, dexketoprofen trometamol SR is found to be more efficient in reducing pain.

Keywords: Third Molar, Postoperative Complications, Sustained-Release Preparations, Nonsteroidal Anti-Inflammatory Agents

Preemptif Tek Doz Sürekli Salınımlı Non-steroid Antienflamatuar İlaçların Üçüncü Molar Cerrahisi Sonrası Postoperatif Komplikasyonlar Üzerine Etkileri

ÖZET

Amaç: Bu çalışmanın amacı, üçüncü molar cerrahisini takiben iki preemptif sürekli salınımlı nonsteroidal antienflamatuar ajanın ağrı, ödem ve trismus açısından etkinliğini karşılaştırmaktır.

Gereç ve Yöntem: Çift taraflı vertical pozisyonda gömülü üçüncü azı dişleri olan 30 hasta çalışmaya dahil edildi. Çalışma randomize ve çift kör olarak planlandı. Ameliyattan 30 dakika önce hastalara 75 mg sürekli salınımlı (SR) deksketoprofen trometamol verildi ve ameliyat sonrası ilaç uygulaması günde bir kez olmak üzere 1 hafta boyunca devam etti. 2 hafta sonra, 75 mg sürekli salınımlı (SR) diklofenak sodyum ile diğer gömülü üçüncü molar için aynı prosedür uygulandı. Ağrı postoperatif 6., 8., 12., 24. ve 48. saatlerde ve 3., 5. ve 7. günlerde VAS (Görsel Analog Skala) ile değerlendirildi. Ödem ve trismus ölçümleri postoperatif 2. ve 7. günlerde gerçekleştirildi.

Bulgular: 6., 8., 12., 24. ve 48. saatlerde ve 3. ve 5. günlerde VAS düzeylerinde gruplar arasında istatistiksel olarak anlamlı bir fark bulundu ($p < 0.01$). Deksketoprofen trometamol SR grubunun VAS düzeyleri, diklofenak sodyum SR grubundan daha düşüktü. Gruplar arasında 2. ve 7. günlerde trismus ve ödem ölçüm ortalamaları açısından istatistiksel olarak anlamlı fark yoktu ($p < 0.05$).

Sonuç: Deksketoprofen trometamol SR ve diklofenak sodyum SR, gömülü üçüncü molar cerrahisini takiben ödem ve trismusun azaltılması için benzer şekilde etkilidir; bununla birlikte, deksketoprofen trometamol SR'nin ağrıyı azaltmada daha etkili olduğu bulunmuştur.

Anahtar Kelimeler: Üçüncü Azı Dişi, Postoperatif Komplikasyonlar, Sürekli-Salınımlı Preparatlar, Steroid Olmayan Antienflamatuar Ajanlar

INTRODUCTION

Due to several reasons such as adjacent teeth position, mucosal thichkness or high bone density, third molars can remain impacted in the mandibula (1). According to studies the prevalence of third molar impaction is 20%–30% of the population and this makes mandibular third molar surgeries one of the most frequent procedure in oral and maxillofacial surgery (2).

Despite the atraumatic techniques, third molar removal surgeries can generate an inflammatory reaction which may cause trismus, pain and edema in the maxillofacial region (3). Postoperative complication reduction increases the quality of life, especially in the first three days following surgery (4). A great number of articles and methods are introduced for managing instant inflammatory response associated with the surgery. They involve using drain for edema elemination, the use of medications such as corticosteroids, analgesics, antihistaminics and antibiotics or nerve stimulation for pain reduction (5,6).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed to patients in order to avoid postoperative inflammatory symptoms such as edema, pain, trismus and infection. They are mostly used for their capacity of anti-inflammation, antipyretic and analgesic effets in routine practice (7). Dexketoprofen trometamol is a NSAIDs and inhibits COX-1 and COX-2 for its well known anti inflammatory and analgesic effects. By means of its lipophilic properties, it is rapidly absorbed and its activity starts in a very short time (8). Diclofenac is a derivative of benzene acetic acid and prescribed for pain and edema since 1974 (9). It is available in two different salt formulations; diclofenac sodium and diclofenac potassium. Diclofenac sodium is a well-known NSAID with anti-inflammatory, analgesic and antipyretic activities. Many studies showed efficacy of diclofenac as compared to other NSAIDs in management of inflammatory findings following dental surgical procedures (10,11).

Long lasting anti-inflammatory effects needs continuous medication, independent of the strategy selected. Besides, patients' cooperation might decrease considerably when a drug needs to be administrated more than once a day, which is a risk for postoperative complications. Sustained release (SR) of the medications; meaning release of the medications in small quantites over a prolonged period of time, is an effective approache for managing post surgical complications (12).

Recent developments in postoperative pain management have revealed the concept about preemptive medication. The essential prediction of this concept is that, if NSAIDs are adminestered to patient before the onset of surgery, postoperative comorbidities might be prevented or reduced (13).

The objective of this study is to compare the preemptive administration of diclofenac sodium SR and dexketoprofen Trometamol SR on postoperative management of trismus, pain and edema following surgical removal of mandibular third molars.

MATERIAL AND METHODS

This study received approval from Ethics Commitee (Date: 25.01.2017 Decision Number:1/8) and was conducted in accordance with the guidelines on the Helsinki Decleration on Human Rights. The experimental part was performed at Dentistry Faculty, Oral and Maxillofacial Surgery Department. 30 patients with double sided vertically positioned fully impacted third molars without any sign of infection, with absence of smoking and alcohol consumption and absence of hypersensitivity reaction to NSAIDs and aspirin were included. The exclusion criteria of this study were the absence in show up controls on postoperative days, incomplete filling of VAS (Visual Analogue Scale), prolonged surgery time for more than 25 minutes, pregnancy, lactation, NSAIDs or antibiotic intake within the last 3 weeks before surgery and alveolitis development. Detailed information was provided to all patients and patients gave consent for inclusion in the study via a consent form.

In present study, all the surgeries were performed by the same surgeon. 60 mandibular impacted third molars which matched the inclusion criterias were surgically extracted from 30 patients. Following n. alveolaris inferior and n. buccalis blocks, buccal mucoperiosteal flap was elevated through a sulcular and a horizontal incision. The bone tissue was osteotomized with steel rond and fissure burs under physiological saline irrigation (0.9 %) and the third molar was extracted by means of bein elevators and forceps. All the surgeries were performed under 2 cartridges of 40 mg/ml Articaine hydrochloride with 0.0012 mg/ml epinephrine hyrochloride (Ultracain DS forte-Aventis İlaç Sanayi Tic., Türkiye). Following the extraction, the mucoperiosteal flap was repositioned primarily and sutured with 3-0 silk sutures. During all operations, both bone osteotomy time and total surgery time were recorded. Sutures were removed at the end of the 7th postoperative day. After the soft tissue healing was observed, an appointment was made for the other mandibular impacted third molar operation 15 days later.

The patients were randomly divided into two groups (according to the medications given) by the assistant physician and the surgical nurse. Patients were given dexketoprofen trometamol 75 mg sustained-release (Dexfull SR 75 mg tablet, Neutec Drugs, Turkey) in tablet form in order to start 30 minutes before the first operation and continue postoperatively for 7 days, once a day and at the same time every day. Before the second operation, patients were given diclofenac sodium 75 mg sustained-release (Voltaren SR 75 mg tablet, Novartis Health, Food and Agricultural Products,

Turkey) in tablet form for starting 30 minutes before the second operation and continue postoperatively for 7 days, once a day and at the same time every day. Antibiotics (625 mg amoxicillin + clavulanic acid, Augmentin, Glaxo Smith Kline Drug, Turkey) and 0.2% chlorhexidine gluconate (Klorhex Mouthwash, 200 mL, Drogsan Drug Industries, Turkey) were also given to all patients following the surgery.

Measurement of Pain Intensity: For every patient the VAS score of 100 mm was recorded by a questionnaire at the 6th,8th,12th,24th and 48th hours and on the 3rd, 5th and 7 days following the operation. The first pain assessment for establishing the effectiveness of the preemptive analgesics was evaluated at the 6th hour as the alleviation of local anesthesics effects and the maximum levels of postoperative pain observed between 6-8 hours.

Measurement of Trismus – Mouth Openning Capacity: Digital calipers were used for measuring (in mm) the mouth opening capacity pre and postoperatively on 2nd and 7th days. The incisal edges of maxillary and mandibullary 1 st incisal teeth were used as reference points before and after the surgery. The measurements were done 3 times repeatedly and mean values were recorded.

Measurements of Edema: Soft tissue measurements were obained in order to evaluate swelling preoperatively and on the postoperative 2nd and 7th days using the method of Üstün et al. (14). Points on the face were used for measurement of swelling: eye cantus – angulus mandibula, tragus – corner of mouth, and tragus – pogonion. The distances between these points were marked, measured, and recorded.

Statistical Analysis: For the statistical analyses, Minitab 17 (Minitab Inc., State College, PA, USA) was used for the findings obtained in the study were evaluated. Shapiro Wilks test was run in order to test the normality distribution of the parameters. Student's t-test was used for between-group comparison of normally distributed parameters and the Mann-Whitney U test was used for between-group comparison of non-normally distributed parameters. Variance analysis was carried out for repeated measures in within-group comparisons. Significance value level was accepted as $p<0.05$ and $p<0.001$.

RESULTS

The study was conducted on 30 patients, 19 (63.3%) female and 11 (36.7%) male, aged between 18-33. The mean age of the patients was 23.73 ± 3.85. There was no statistically significant difference between the groups in terms of total operation time and bone osteotomy time ($P > 0.05$) (Table 1).

Table 1. Evaluation of total surgery times and bone osteotomy times

	Dexketoprofen Trometamol SR Group	Diclofenac Sodium SR Group	p
	Mean±SS	Mean±SS	
Total surgery time (min)	15.44±2.39	15.07±2.00	0,596
Bone osteotomy time (min)	2.05±0.81	2.18±0.82	0,667

Mann Whitney U test

A statistically significant difference was found between the groups in terms of VAS levels at the 6th, 8th, 12th, 24th and 48th hours and on the 3rd and 5th days ($P < 0.05$, $P < 0.01$). Pain levels of Dexketoprofen Trometamol SR group were statistically significantly lower than the Diclofenac Sodium SR group (Table 2).

In the evaluations of the VAS levels within the group, statistical differences were detected on the 6th, 8th, 12th, 24th, and 48th hours, and on the 3rd, 5th, and 7th days ($P < 0.01$). In both groups, the maximum pain level was determined at the 6th hour postoperatively (Table 2).

Table 2. Postoperative pain intensity values measured by VAS (Visual analogue scale)

VAS (mm)	Dexketoprofen Trometamol SR Group	Diclofenac Sodium SR Group	p
	Mean±SS	Mean±SS	
6th hour	43.33±16.88	50.67±16.39	0.001
8th hour	43.33±16.26	49.00±17.29	0.03
12th hour	35.67±15.47	43.67±14.50	0.001
24th hour	25.33±14.08	36.67±14.93	0.000*
48th hour	15.67±12.51	26.33±13.51	0.000*
3rd day	11.00±9.95	18.67±11.37	0.002
5th day	6.67±8.02	12.67±11.12	0.008
7th day	1.33±3.45	2,00±4.06	0.489
p	0.000*	0.000*	

Student t test *p<0.001

There was no statistically significant difference between the groups in terms of mean trismus values on the 2nd and 7th days (P > 0.05) (Table 3).

There was a statistically significant difference between the mean trismus values in the preoperative, 2nd, and 7th days within the group (P= 0.000; P < 0.01). The decreases seen in the 2nd and 7th-day measurements compared to the mean trismus values in the preoperative period are statistically significant (P < 0.01). The increase in trismus values on the 7th day compared to the 2nd day is statistically significant (P < 0.01) (Table 3).

Table 3. Evaluation of the groups in terms of trismus measurements

Trismus	Dexketoprofen Trometamol SR Group	Diclofenac Sodium SR Group	[1]p
	Mean±SS	Mean±SS	
Preop	42.36±4.23	42.36±4.23	-
2nd day	33.50±4.79	33.16±4.41	0.430
7th day	40.93±4.11	40.30±4.15	0.487
[2]p			
Preop-2nd day [2]p	0.000*	0.000*	
Preop-7th day [2]p	0.000*	0.000*	
2nd day-7th day [2]p	0.000*	0.000*	

[1]*Student t test* [2]*Analysis of variance in repetitive measurements* *p<0.01

There was no statistically significant difference between the groups mean edema values between the eye cantus-angulus mandible, tragus-pogonion and tragus-corner of mouth anatomical points on the 2nd and 7th days (P > 0.05) (Table 4). In the intra-group evaluations, the increases observed on the 2nd day compared to the preoperative period of the eye cantus-angulus mandible, tragus-pogonion and tragus-corner of mouth measurement average in both groups were statistically significant (P < 0.01). A decrease observed in the edema values between the eye cantus-angulus mandible, tragus-pogonion and tragus-corner of mouth anatomical points on the 7th day compared to 2nd day was statistically significant (P < 0.01; P < 0.05). There was no significant difference between the preoperative and 7th day edema measurements in both groups (P < 0.05) (Table 4).

Table 4: Postoperative swelling measurements in milimetres (eye cantus-angulus mandibula, tragus pogonion, tragus-corner of mouth) preoperatively, on the 2nd and 7th days

Eye cantus/angulus mandible	Dexketoprofen Trometamol SR Group	Diclofenac Sodium SR Group	p
	Mean±SS	Mean±SS	
Preop	101.50±4.79	101.50±4.79	-
2nd day	105.33±5.16	106.20±5.09	0.572
7th day	102.00±4.70	102.43±4.86	0.759
[1]p			
Preop-2nd day [1]p	0.0009*	0.0001*	
Preop-7th day [1]p	0.566	0.340	
2nd day-7th day [1]p	0.0025*	0.0014*	
Tragus/pogonion			
Preop	144.46±7.76	144.46±7.76	-
2nd day	149.20±7.99	149.63±8.62	0.634
7th day	145.16±7.86	145.36±8.11	0.940
p			
Preop-2nd day [1]p	0.002*	0.0014*	
Preop-7th day [1]p	0.583	0.577	
2nd day-7th day [1]p	0.0084*	0.0048*	
Tragus/corner of mouth			
Preop	111.80±5.10	111.80±5.10	-
2nd day	115.60±5.83	116.53±5.96	0.573
7th day	112.13±5.30	112.60±5.46	0.694
[1]p			
Preop-2nd day [1]p	0.0088*	0.002*	
Preop-7th day [1]p	0.812	0.552	
2nd day-7th day [1]p	0.016	0.0103	

Mann Whitney U test **p<0.01*

DISCUSSION

Impacted third molar surgeries and management of postoperative complications are crucial for the patient's quality of life. These complications such as edema, pain, trismus can be resolved with NSAIDs and these medications are usually prescribed inorder to compete with these symptoms (15). In the present study, the efficacies of sustained- release forms of dexketoprofen trometamol and diclofenac sodium on edema, pain and trismus following third molar surgery were evaluated. Third molar surgery is accepted as a convenient and highly presumable procedure for investigating the preemptive effects of different drugs, especially NSAIDs (14).

Despite the existence of numerous reports in the literature about the use of drugs in the prevention of postoperative edema, trismus and pain following impacted third molar surgery (14,15), to the best of our knowledge; this is a preliminary study comparing the preemptive effects of two very commonly used drugs in their sustained-release forms, diclofenac sodium, and dexketoprofen trometamol. Although this surgery is very common, a consensus hasn't been created about the optimal type, method of administration, timing, and the dose of the drugs in order to us for the prevention of postoperative complications.

Postoperative complication occurence have been found to be related to extended surgical time (16). In the pesent study, there was no significant difference between the operation and bone osteotomy times in all groups. All the surgeries are performed under 20 minutes.

Following a third molar surgery, patients' inflammatory symptoms are usually the greatest during the first 2 days, accompanying the most intense pain experience on the surgery day (17). In the present study, the evaluation of pain was performed on the 6th,8th,12th,24th and 48th hours following the operation. 3rd, 5th and 7th days were chosen for evaluating the late findings of pain perception following the operation. The results show that in all groups patients indicated their highest VAS scores at 6 hours postoperatively. Since the effect of local anesthesia would pass approximately at 4 hours following administration, this finding was considered as normal.

Trismus and edema are commonly reported complication following third molar surgery. In the literature, measurements of interincisal distance pre and postoperatively are frequently preferred for the evaluation of trismus, as in this study (18). When evaluating trismus, no statistically significant difference was found among the 2 groups. In both groups the trismus on the 7th day was found to be lesser than the 2 nd day as expected.

According to the literature, some investigators preferred preemptive analgesics administration for ameliorating anesthesia effects for a tardy postoperative pain development (19). Preemptive analgesia also provides analgesia before the onset of painful stimulus, leading to a complete or partial block of nociception. The most frequently used method to prevent pain is "preemptive analgesia" that prevents the mechanisms caused by pain before they appear. In the present study, preemptive sustained-release NSAIDs are preferred. The authors of this study believe that the preemptive application of analgesics has a positive outcome on the perception of pain.

The oral and parenteral route is preferred for preemptive use in different surgical branches such as oral and maxillofacial surgery, orthopedic surgery, gynecological surgery, thoracic surgery for postoperative analgesia (20). In the present study, Diclofenac sodium SR and Dexketoprofen trometamol SR were used as oral tablets for preemtive pain control.

The effects of diclofenac sodium were found to be better than tramadol and ketorolac in managing postoperative pain, however less efective than piroxicam, nimesulide and tenoxicam (21). Akbulut et al. (22) examined the efficacy of NSAIDs on pain, trismus and edema on 42 patients. The study concluded that edema on postoperative 2nd day was significantly lowest with diclofenac as compared to others. In the present study, the analgesic efficacy of dexketoprofen trometamol has been shown to be superior to diclofenac sodium. However, in terms of trismus and edema evaluation, there was no difference in efficacy between dexketoprofen trometamol and diclofenac sodium.

Eroğlu et al. (23) evaluated the effectiveness of preoperative dexketoprofen and paracetamol administration in impacted third molar surgery and found that dexketoprofen provides better analgesia. Kesimci et al. (24) evaluated the efficacy of preoperative dexketoprofen, paracetamol, and placebo in lumbar surgery patients. The authors reported that dexketoprofen reduced the use of additional analgesics compared to paracetamol and placebo. In the present study, the effects of dexketoprofen trometamol and diclofenac sodium, which were started preemptively for pain control in impacted third molar surgery, and continued postoperatively, were evaluated. It has been reported that dexketoprofen trometamol is more effective on pain than diclofenac sodium, but complications such as edema and trismus are equally effective.

Nunamaker et al. (25) stated that analgesics, which are sustained-released and used as a single dose, provide sufficient analgesia, increase drug use compliance, and facilitate the postoperative period. In the present study, single dose sustained-release NSAIDs were preferred in order to facilitate the postoperative period, to prevent using too much medication to protect the gastrointestinal system,

and to ensure patient-drug use compliance optimally.

Seymour et al. (26) created an incisional acute minor pain model on laboratory animals. They compared the normal analgesic usage protocol with the sustained-release analgesic usage protocol. As a result of the study, SR formulation has a longer duration of action, causes less stress in animals, and has single-dose ease of use. In the present study, the effectiveness of SR forms of dexketoprofen trometamol and diclofenac sodium were evaluated in postoperative complication management. It has been determined that SR form is effective in the management of postoperative complications in two drugs and it can be used instead of routine 2x1 or 3x1 analgesic regimen due to its ease of use.

Decreasing the number of analgesics consumed after surgical operations reduce the incidence of side effects and increase patient comfort (27). For this reason, in the study, SR forms of diclofenac sodium and dexketoprofen trometamol used as a single dose and sustaining long-term activation throughout the day were used.

CONCLUSION

Despite the widespread literature search, no head-to-head comparative studies were found between SR forms of dexketoprofen trometamol and diclofenac sodium. The present study is one of the rare studies on the effectiveness of SR form NSAIDs in the prevention of postoperative complications after surgical procedure. Therefore, it is difficult to compare the present results with published studies. In conclusion, dexketoprofen trometamol SR found to be more effective in pain relief than diclofenac sodium SR however, equally effective on edema and trismus.

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