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ORIGINAL ARTICLE

Ketorolac and Dexamethasone Injection Comparison on Postoperative-Pain in Impacted Mandibular Third Molars Surgery in Pterygomandibular Space: A Randomized Clinical Trial

Elham Farokh-Gisour[1,2], Saeed Hajmohamadi[1,3], Mahboobeh Shokrizadeh[2], Sina Yousefnia Shahrbabaki[2], Homa Kamyabi[4]

[1]Kerman Social Determinants on Oral Health Research Center, Kerman University of Medical Sciences, Kerman, Iran.
[2]Department of Pediatric Dentistry, School of Dentistry, Oral and Dental Research Center, Kerman University of Medical Science, Kerman, Iran.
[3]Department of Oral and Maxillofacial Surgery, School of Dentistry, Kerman University of Medical Sciences, Kerman, Iran.
[4]School of Public Health, Health Sciences Center, Louisiana State University, New Orleans, LA, United States.

Corresponding author: Homa Kamyabi **E-mail:** h.kamyabi1244@gmail.com

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ABSTRACT

Objective: To compare the effects of ketorolac and dexamethasone on postoperative pain in patients who underwent impacted mandibular third molars surgery. **Material and Methods:** A double-anonymized clinical trial study involving 60 patients with impacted third molars. The samples were randomly divided into two groups by block randomization method: DG: Dexamethasone (8 mg) and KG: Ketorolac (30 mg). The severity of pain was assessed using the visual analog scale and Wong-Baker Faces Pain Rating Scale immediately and during the first to seventh days after the surgery. **Results:** Among the participants, 65% were female, and the mean age was 40.8 years. The study groups did not show a significant difference in the frequency of the two sexes or mean age (p=0.529 and p=0.214). The average pain scores were significantly greater in the DG compared to the KG during the first week (p<0.001). **Conclusion:** Injection of dexamethasone into the pterygomandibular space can help to decrease the postoperative pain following lower third molar surgery.

Keywords: Steroids; Indomethacin; Mandible; Molar, Third.

Introduction

The impacted third molar is a disorder where the third molars (i.e., wisdom teeth) are prevented from erupting into the mouth, and surgical removal is introduced as the most common procedure for treating this disorder [1]. It is common to experience pain and swelling following impacted third molar surgery in the lower jaw [1,2].

The factors such as patient age, gender, anxiety, and surgical difficulty, affect postoperative pain [2-5]. Moderate and severe pain is experienced during the first 24 hours after removing mandibular third molars [6-8]. Postoperative pain and discomfort associated with trismus due to impacted mandibular third molars surgery can be prevented with the administration of different drugs.

The literature suggests using nonsteroidal anti-inflammatory drugs (NSAID) after the removal of the impacted third molar to reduce pain [9,10]. Ketorolac's effectiveness in oral and parenteral administration has been verified in previous studies, as it acts as an NSAID by blocking cyclooxygenase-1 and 2, which decreases prostaglandin production [11]. Among NSIAD drugs, ketorolac has been shown to have better results in pain control after third molar surgery [12]. It is the only NSAID that has an intravenous injectable form in Iran.

Corticosteroids have been a standard component in pain management over the last decades. Dexamethasone is a potent glucocorticoid. The impact of dexamethasone on the body is diverse. Its mechanism involves blocking neutrophil migration and slowing down lymphocyte colony proliferation [13]. Corticosteroids, such as dexamethasone, are used in submucosal, intra-alveolar, intravenous, intramuscular, and oral forms [14]. Corticosteroids, such as dexamethasone, are used in submucosal, intra-alveolar, intravenous, intramuscular, and oral forms [14]. Corticosteroids effectively reduced inflammatory complications following third molar surgery and did not result in any serious adverse effects [15]. Among the corticosteroids, dexamethasone 8 mg was the best preoperative option to control inflammatory complications after third molar surgery [15].

The pterygomandibular space lies between the internal and external pterygoid muscles and the inner surface of the ramus. Inflammation of the pterygomandibular space often results in trismus and reduced mouth opening, causing a decline in quality of life for several weeks [16]. Therefore, managing pain and inflammation following impacted third molar surgery in this region is crucial. Only a few studies assess the injection of dexamethasone and ketorolac into the pterygomandibular space. Given the importance of preventing complications due to lower third molar extraction, this study was carried out to compare the effects of ketorolac and dexamethasone injection into the ptrygomandibular space on pain relief following the removal of the third mandibular molar.

Material and Methods

Study Design and Ethical Clearance

This study was a randomized, double-blind clinical trial on all patients referred to the Dentistry School of Kerman University of Medical Sciences in Kerman, Iran, for bone-impacted third molars surgery in 2020. The research was approved by the Ethics Committee of Kerman University of Medical Sciences (IRCT20180910040981N1). Inform consent was obtained from all the participants.

Inclusion and Exclusion Criteria

The inclusion criteria were the need for impacted mandibular unilateral third molars surgery, age higher than 18 years, weight lower than 100 kg, and being in the American Society of Anesthesiologists 1-2

categorization [17]. The patients who used sedatives or tranquilizers 24 hours before the treatment and those with a history of allergy to dexamethasone or ketorolac or who received more than three local anesthetic vials were excluded. The same occurred with those participants who did not respond to the questionnaire.

Sampling

The parameters adopted were: $\alpha = 0.05$; Power = 0.9; Mean VAS control =1.17; Mean VAS Tramadol = 0.63; SD VAS control = 0.79; SD VAS Tramadol = 0.67. The sample size was estimated at 30 subjects in each group using STATA Software (StataCorp LLC, College Station, TX, USA).

Clinical Procedures

Patients were divided into two groups (DG: Dexamethasone 8 mg and KG: Ketorvalek 30 mg), using the block randomization method. In this method, 10 blocks with a length of 6 were produced by a statistician, and they were put in a container. The sheets were randomly removed from the container without replacement and continued until all the blocks were removed. After the injection of an anesthetic agent, dexamethasone or ketorolac was injected into the pterygomandibular space while the surgeon and the patient were blind. The severity of pain was assessed immediately after the surgery and during the first to seventh days (i.e., every day) and then recorded in a checklist by the researchers. The severity of pain was measured based on the visual analog scale and Wong-Baker Faces Pain Rating Scale.

Wong-Baker (FACEs): The FACEs scale utilizes six ordinal, color-coded faces with globally recognized facial expressions. These expressions correspond to scores that are multiples of two. The FACEs were scored as 0, 2, 4, 6, 8, and 10 for our analysis. The reliability and validity of NPS and FACEs have been shown over many patient populations [18].

Visual Analogue Scale (VAS): A simulated eye scale considered a self-report scale—a simple scale consisting of a 10 cm horizontal line graded from 0 to 10. Zero indicates no pain, 1 – 3 indicates mild pain, 4 – 7 indicates moderate pain, and 8 – 10 indicates severe pain. The visual tool is the most straightforward tool for checking the pain level of the patients, which the patient himself can easily understand. The patient himself completes this tool. Many studies have confirmed the VAS reliability and validity [19,20].

Statistical Analysis

The data analysis was carried out using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). The descriptive information was evaluated in terms of frequency and mean. Shapiro measured the normality of the data using the Wilk test. The independent t-test was utilized to analyze the variables. A p-value less than 0.05 was considered statistically significant.

Results

Out of the 60 participants in the study, 65% were women. The mean age of the study's participants was 40.8 (SE=3.5) years. There was no significant difference in the frequency of the two sexes in the study groups ($p=0.529$). Furthermore, the mean age did not differ significantly between the two groups ($p=0.214$). Every participant who enrolled also completed the study (Figure 1).

According to data, the mean scores of pain were between 6.5±2.76 to 2.03±1.15 and 3±2.19 to 0.5±0.6 during the first and seventh days after the surgery in the Dexamethasone and Ketorolac groups, respectively ($p<0.001$). Table 1 presents the mean scores of pain between the two groups. In the DG, a significant decrease

was observed in pain scores after surgery compared to every day except for the second day. In the KG, a considerable decrease was observed in pain score after surgery in comparison to after surgery every day except for the second day and fifth day compared to the fourth day (p<0.001) (Figure 1).

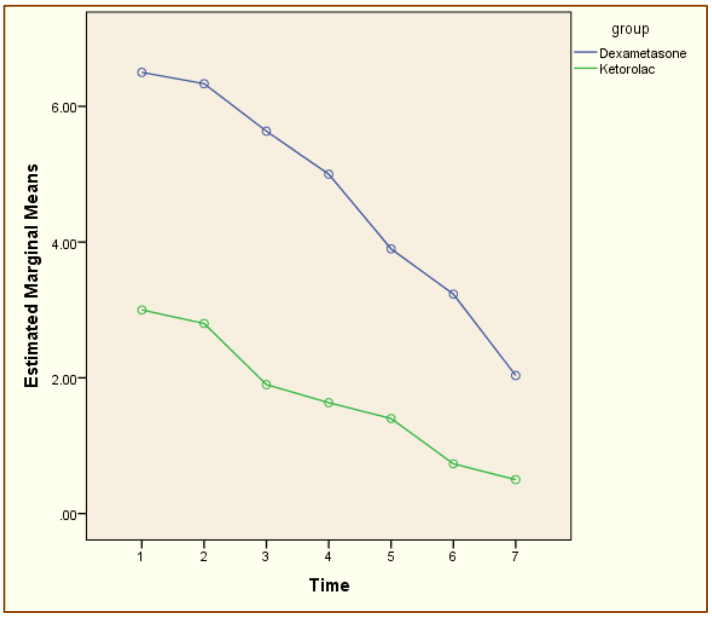

Figure 1. The trend of pain in both groups over time.

Table 1. The severity of pain between dexamethasone and ketorolac groups.

Day	Dexamethasone		Ketorolac		p-value
	Mean	SD	Mean	SD	
First Day	6.5	2.76	3.0	2.19	<0.005
Second Day	6.3	2.23	2.8	1.95	<0.005
Third Day	5.6	2.14	1.9	1.90	<0.005
Fourth Day	5.0	1.90	1.6	1.75	<0.005
Fifth Day	3.9	1.56	1.4	1.52	<0.005
Sixth Day	3.2	1.59	0.7	1.15	<0.005
Seventh Day	2.03	1.15	0.5	0.68	<0.005

The mean difference in the pain scores within the Dexamethasone and Ketorolac groups is shown in Table 2. It was demonstrated that on the first day after the surgery, the rate of severe pain was higher in the DG; however, the subjects in the KG were reported to have higher rates of mild and moderate pain (p<0.001). On the second and third days, mild pain was more frequently observed in the KG; nevertheless, moderate to severe pain levels were more commonly reported in the DG (p<0.001).

Table 2. The mean difference in pain score between dexamethasone and ketorolac groups.

Day	Dexamethasone			Ketorolac		
	Mean	SD	p-value	Mean	SD	p-value
First-Second	0.16	1.20	0.45	0.20	0.76	0.16
Second-Third	0.70	1.20	0.004	0.90	0.54	<0.005
Third-Fourth	0.63	1.69	0.04	0.26	0.69	0.04
Fourth-Fifth	1.10	1.44	<0.005	0.23	0.85	0.14
Fifth-Sixth	0.66	0.60	<0.005	0.66	0.84	<0.005
Sixth-Seventh	1.20	1.34	<0.005	0.23	0.67	0.07

The same results were obtained on the fourth and fifth days. In addition, some people in the KG reported no pain ($p<0.001$). On the sixth and seventh days, none of the patients in the KG had moderate or severe pain, and only minor pain was observed; nonetheless, some participants still had pain in the DG. According to Table 3, the rate (3.3%) of severe pain was higher in the patients who received dexamethasone, which persisted until the sixth day. However, the subjects in the KG had a lower rate (6.7%) of severe pain until the third day.

Table 3. Frequency of pain severity between dexamethasone and ketorolac groups on different days.

Day	Dexamethasone				Ketorolac				p-value
	No Pain N (%)	Mild N (%)	Moderate N (%)	Severe N (%)	No Pain N (%)	Mild N (%)	Moderate N (%)	Severe N (%)	
First	0 (0.0)	7 (23.3)	3 (10.0)	20 (66.7)	3 (10.0)	17 (56.7)	7 (23.3)	3 (10.0)	<0.005
Second	0 (0.0)	4 (13.3)	8 (26.7)	18 (60.0)	0 (0.0)	22 (73.3)	5 (16.7)	3 (10.0)	<0.005
Third	0 (0.0)	4 (13.3)	10 (33.3)	16 (53.3)	8 (26.7)	18 (60.0)	2 (6.7)	2 (6.7)	<0.005
Fourth	0 (0.0)	5 (16.7)	20 (66.7)	5 (16.7)	10 (33.3)	17 (56.7)	3 (5.0)	0 (0.0)	<0.005
Fifth	0 (0.0)	8 (26.7)	19 (63.3)	3 (10.0)	7 (23.3)	20 (66.7)	3 (10.0)	0 (0.0)	<0.005
Sixth	1 (3.3)	18 (60.0)	10 (33.3)	1 (3.3)	17 (56.7)	13 (43.3)	0 (0.0)	0 (0.0)	<0.005
Seventh	1 (3.3)	27 (90.0)	2 (6.7)	0 (0.0)	17 (56.7)	12 (40.0)	0 (0.0)	0 (0.0)	<0.005

Discussion

This study aimed to compare the effects of two injectable medications, ketorolac and dexamethasone, on pain relief in patients who underwent impacted mandibular third molars surgery. Results of the present study showed that on the first day after the surgery, severe pain was more frequently observed in the DG. However, the subjects in the KG were reported to have higher rates of mild and moderate pain. On the second to fifth days, mild pain was higher in the KG; moderate to severe pain was more frequent in the DG.

This study's strength is in measuring pain after impacted mandibular third molars surgery for seven days. In this way, the severity of pain reduction days after surgery has been compared in two groups. Moreover, no postoperative limitations were included in this study, apart from the typical medical guidelines following impacted mandibular third molars surgery. Therefore, the findings of this research align more closely with real-world scenarios.

On the sixth and seventh days, none of the patients in the KG had moderate or severe pain, and only minor pain was reported; nonetheless, in the DG, some participants still had moderate to severe pain. Comparing pain severity in the two groups indicated that the patients in the KG had significantly less pain and discomfort than those in the DG.

Increasing postoperative pain resulted in acute inflammation induced by tissue damage. The effectiveness of preoperative use of corticosteroids in decreasing swelling, trismus, and pain following impacted third molar surgery is confirmed in previous studies [14,21,22]. Similarly, the analgesic effects of ketorolac as an NSAID have been demonstrated. According to the literature, ketorolac tromethamine has more antinociceptive effects than other NSAIDs and even opioids [23]. However, a small number of studies compared the analgesic effects of ketorolac with those of dexamethasone.

Similar to the results of the present study, Claseman et al. [24] indicated that postoperative analgesia was more significant in the ketorolac tromethamine group than in the dexamethasone group after the surgery. In a study by Paiva-Oliveira et al. [25], antinociceptive treatment by dexamethasone and ketorolac was used one hour before the third molar extraction and every eight hours after the surgery for two days. According to the authors, ketorolac and dexamethasone showed similar analgesic effects. However, the amount of analgesic consumption after the end of the anesthesia was lower in the ketorolac group in comparison to that in the

dexamethasone group [25]. On the other hand, some discomfort was more frequently reported in the individuals who used ketorolac [26]. It was shown that administering ketorolac and single-dose dexamethasone is helpful in controlling edema. The aforementioned results regarding the similar analgesic effects of ketorolac and dexamethasone were confirmed in a study by Sotto-Maior et al. [27].

Dionne et al. [28] compared dexamethasone alone with dexamethasone plus ketorolac. A higher reduction in pain, as well as prostaglandin and thromboxane levels, was observed after using dexamethasone in combination with ketorolac. However, the inflammation levels decreased at the surgical site only in the DG [28].

NSAIDs, such as ibuprofen and ketorolac, are among the recommended methods for the reduction of pain and swelling in patients who undergo third-molar surgery. According to the literature, due to the contradictory results on the analgesic effects of ketorolac in comparison to those of dexamethasone, the efficacy of these drugs is still under investigation [29].

Esen et al. [30] recommended dexamethasone injection only for cases with technical difficulty. In the present study, bone removal and tooth sectioning were necessary for all the patients; therefore, all the subjects were relatively cases of technical difficulty. The pterygomandibular space was chosen for the injection of dexamethasone and ketorolac because the absorption rate of this agent depends on the blood flow in the administrated region, and the pterygomandibular space is adjacent to the lower third molar [14]. Moreover, loose areolar tissue with a rich vascular helps with the faster absorption of dexamethasone.

The effects of submucosal and intramuscular injection of dexamethasone on the postoperative complications of lower third molar surgery were assessed in another study. Injection of submucosal dexamethasone was recommended as an effective alternative to the systemic use of dexamethasone [31,32]. In a previous study [33], both submucosal and systemic dexamethasone (8 mg) administration had similar effects on decreasing postoperative pain, inflammation, and limited mouth opening after the third molar surgery.

Limitation of mouth opening and edema, as the main complications of the third molar extraction, were not investigated in the present study. However, these variables were assessed in previous studies showing that less limitation of the mouth opening (i.e., trismus) and reduced facial edema were reported in patients using corticosteroids compared to those using NSAIDs [34-36].

Acute inflammation can be controlled by glucocorticoids, which suppress multiple signaling pathways involved in the inflammatory response [28]. Administration of both dexamethasone and ketorolac has anti-inflammatory effects. Sotto-Maior et al. [27] obtained similar results in terms of edema in both dexamethasone and ketorolac groups. Nevertheless, there was a problem with the limitation of mouth opening in the dexamethasone group within the postoperative period of 1-7 days [27].

Similarly, Markiewicz et al. [35] observed a smaller opening limitation in patients who underwent corticosteroid therapy for 1-3 days compared to another anti-inflammatory. It was shown that dexamethasone decreased the edema during the first to the third postoperative days. In addition, López-Carriches et al. [37] demonstrated a remarkable reduction in mouth opening between dexamethasone and ketorolac groups 7 days after the operation. Accordingly, the ketorolac group had a more significant limitation of mouth opening [37].

Since preemptive methods with a conventional single dose are not applicable to achieve postoperative analgesia, the analgesic treatment should also be performed after the third molar extraction, the time of which is related to the type of surgery. Isiordia-Espinoza et al. [12] compared the preemptive analgesic effects of oral ketorolac plus submucous local placebo with oral ketorolac plus submucous local tramadol on the pain following mandibular third molar surgery. The results showed that the severity of pain was lower in patients who reported the preemptive use of oral ketorolac plus submucous local tramadol.

The use of corticosteroids, such as dexamethasone, before and after the third molar surgery is common for reducing postoperative symptoms, primarily pain and inflammation; however, it is limited due to possible complications [38,39]. In general, NSAIDs are highly variable in terms of the onset and duration of the analgesic effect during the half-life of the drug. Increasing the doses of NSAIDs accelerates the effects and prolongs the shelf life. The NSAIDs are usually prescribed several times a day and typically are more effective at higher doses [23]. Dionne et al. showed that 8 mg dexamethasone produced similar analgesia equal to 10 mg ketorolac [28].

Dexamethasone administration leads to decreased pain with the consideration of its potential anti-inflammatory effects. The drug seems safe for periods shorter than 2 weeks [40]. The effectiveness of dexamethasone in decreasing pain and other consequences of the third molar extraction depends on the received dose [28]. Different dosage of dexamethasone for controlling pain was examined by Alexander and Throndson [22], and a dosage between 8-12 mg was recommended for the best results. In the present study, 8 mg dexamethasone was used to reduce the pain after the third molar extraction. The half-life of dexamethasone is estimated to be between 36-54 h, which helps with the durability of its effects [41]. There is an agreement that the pain reaches its maximum severity in the first six hours after the third molar surgery [28,42], which aligns with the enhanced production of chemical mediators of pain at the surgical site. Usually, analgesics and NSAIDs are administered for 2 or 3 days after the surgical procedure [43]. The present study injected ketorolac tromethamine and dexamethasone every eight hours for two days.

In different studies, ketorolac tromethamine was usually administered every eight hours for 2 days [44], and its analgesic effect is proven [26,45]. The required time for the treatment with dexamethasone is approximately four times lower than that for the treatment with ketorolac tromethamine. On the other hand, lower mouth opening limitation at 24 h and 7 days was observed in patients using dexamethasone compared to that in subjects using ketorolac after the surgery. Therefore, single-dose dexamethasone is also a selective treatment for the surgical extraction of the third molars.

There have been no reports of side effects due to using ketorolac or dexamethasone. However, the possibility of gastrointestinal complications should be considered for ketorolac tromethamine. Nevertheless, the likelihood of gastrointestinal bleeding is very rare. In addition, the risk of the incidence of postoperative complications is higher in older individuals [25]. However, due to contradictory results in the literature, the choice of one of the pharmacological treatments should be carefully assessed, and other factors, such as the related cost and treatment duration, should be considered in this regard.

Although the present study's findings indicated that ketorolac's analgesic effects were more potent than those of dexamethasone, previous study did not support this findings [46]. However, the results of some studies are in line with the similar analgesic effects of ketorolac as much as dexamethasone in patients undergoing dental surgery [47,48]. Similar to NSAIDs, the potential for corticosteroid side effects depends on the amount and duration of therapeutic use.

One of the significant limitations of the present study was the small sample size. Another limitation was the failure to investigate other complications of the third molar surgery, including edema and mouth-opening limitation. Moreover, it was impossible to generalize the findings, as no similar study examined the different dosages of ketorolac and dexamethasone on different days. Considering the importance of analgesics for controlling pain in patients undergoing the third molar surgery, it is recommended to perform further studies with larger sample sizes and focus on other complications of this surgery. In addition, since the results of the present study are inconsistent with the findings of most studies, it is suggested that further studies be conducted to compare corticosteroids and NSAIDs.

Conclusion

Injection of dexamethasone into the pterygomandibular space can help to decrease the postoperative pain following lower third molar surgery in the first week.

Authors' Contributions

EFG	https://orcid.org/0000-0002-5907-2119	Investigation and Supervision.
SH	https://orcid.org/0000-0002-8361-4918	Validation and Visualization.
MS	https://orcid.org/0000-0003-0840-2736	Methodology and Formal Analysis.
SYS	https://orcid.org/0009-0005-6717-1909	Investigation and Funding Acquisition.
HK	https://orcid.org/0000-0001-7199-9489	Writing - Original Draft and Writing - Review and Editing.

All authors declare that they contributed to a critical review of intellectual content and approval of the final version to be published.

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None.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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