Research Article

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Comparison of Nimesulide and Ketorolac in Control of Pain, Swelling, and Trismus following Extraction of Impacted Third Molar

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ABSTRACT

Introduction: Dental extraction is the most common procedure in oral surgery. It is a common model for evaluating the effectiveness of analgesics for pain relief.

Objective: To evaluate analgesic effectiveness of Ketorolac (10 mg) and Nimesulide (100 mg) in control of pain, swelling, and trismus after extractions of impacted third molar.

Materials and Method: A non-randomised trial was conducted in the Department of Oral and Maxillofacial Surgery, Kathmandu Medical College from July to September 2020 after obtaining ethical approval. Forty-two patients were divided into two treatment groups (Nimesulide and Ketorolac). The medications were given orally, immediately after extraction followed by twice a day. Pain intensity levels, trismus, and swelling were measured and compared between two groups at six, 12, 24, 48, and 72 hours post-operatively. Data collected were analysed in Statistical Package for Social Sciences v.20 using Mann-Whitney U test, Independent t test and Friedman test.

Result: There was no significant difference in between groups at different time points but identified a significant difference between time points within each group ($P < 0.001$). The difference was significant within each group in mouth opening at different time intervals ($P < 0.001$). Swelling was more pronounced in Nimesulide group than in the Ketorolac group.

Conclusion: Both Ketorolac 10 mg and Nimesulide 100 mg are effective anti-inflammatory and analgesic drugs after surgical extraction. There was no significant difference between two drugs in pain and mouth opening in different time periods. However, Ketorolac was observed to be more effective than Nimesulide as anti-inflammatory drug after extractions.

Keywords: Ketorolac; nimesulide; pain; swelling; third molar; trismus.

INTRODUCTION

The impacted third molar extraction is one of the most common procedures done in the oral surgery department. Some of the expected post-operative sequealae are: pain, trismus, and swelling.[1,2] The incidence and severity of these complaints vary from patient to patient, which directly affects the well-

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being of the people.[3-5] The sequealae mechanism is attributed to the inflammatory response in the surgery site mediated by prostaglandins (PGs), the synthesis of which is initiated by the release of arachidonic acid (AA) from membrane phospholipids. AA to PGs is converted by an enzyme cyclooxygenase (COX) in two isoforms, COX-1 and COX-2.

Nimesulide falls in the group of sulfanilamide derivatives, differing from other non-steroidal anti-inflammatory drugs (NSAIDs), by presenting a sulfonamide radical rather than a carboxylic radical.[6] This drug is a partially selective COX-2 enzymes inhibitor used to treat acute pain. Ketorolac is an NSAID, inhibiting prostaglandin synthesis, and is effective in oral route.[6,7] It also exerts a modulatory effect on opioid receptors and stimulates nitric oxide release contributing to its high potency and efficacy.[8]

This research aims to compare the effectiveness of Nimesulide and Ketorolac in reducing pain, swelling, and trismus following extraction of the impacted third molars.

MATERIALS AND METHOD

The non-randomised trial was conducted in the department of Oral and Maxillofacial Surgery of Kathmandu Medical College (KMCTH), Sinamangal, Kathmandu, from July to September 2020 after obtaining the ethical clearance from the Institutional Review Committee (Ref. 2506202002). All dental patients of KMCTH who gave written informed consent and underwent surgical third molar extractions were included in this research.

A convenience sampling method was used for selecting the participants for this study. The sample size of **42** was calculated using study done by Martins et al.[9] and Pouchain et al.[10] in the following formula:

Sample size = $2\ sd^2\ (Z_\alpha+Z_\beta)^2/(m_1-m_2)^2$

Where, Z_α=1.96 at 95% confidence interval; Z_β=0.84; $sd=sd_1+sd_2/2$;

sd_1=Standard deviation pain intensity of Group 1 (Ketorolac) after six hours (hrs)=9.3;

sd_2=Standard deviation pain intensity of Group 2 (Nimesulide) after six hrs=1.85;

m_1= Mean pain intensity of Group 1 (Ketorolac) after six hrs=8;

m_2= Mean pain intensity of Group 2 (Nimesulide) after six hrs=2.61;

Putting these values in the formula given above, n= $2 \times 31.09 \times 7.84/ (8-2.611)^2 = 16.78$

Adding 20% attrition rate, total sample is = 21 in each group (21X2=42 total).

Patients undergoing surgical extraction of the third molar from age ranging from 18-59 years were included. Medically compromised patients, patients allergic to NSAIDs, patients who had contraindications to receive NSAIDs, and the patients not willing to participate were excluded from the study.

Evaluation of pain was done using the Visual Analogue Scale (VAS) by the sensation of pain. It was evaluated in the periods of six hrs, 12 hrs, 24 hrs, 48 hrs, and 72 hrs post-operatively using a verbal rating scale. From which the patients indicated the intensity of pain according to six descriptive scores (1: no problem, 2: mild pain, 3: moderate pain, 4: severe pain, 5: very severe pain, 6: extreme pain).[11]

Examination of swelling was done by various markings done on the following facial regions before the surgery with a permanent marker. Distances were then used for the evaluation of post-operative swelling: from the angle of the mandible to tragus (Distance I); from the angle of the mandible to the external corner of the eye (Distance II); from the angle of the mandible to the nasal border (Distance III); from the angle of the mandible to the labial commissure (Distance IV) and from the angle of the mandible to the soft pogonion (Distance V).[12] A 2-0 nylon thread (Ethicon, Johnson and Johnson) and a millimeter ruler were used to measure all the distances preoperatively in the interval of six hrs, 12 hrs, 24 hrs, 48 hrs and 72 hrs post-operatively (Figure 1).

The maximum mouth opening was measured to estimate trismus from the upper and lower central incisors' incisal edges using a calibrated vernier caliper in millimeters (mm).[13]

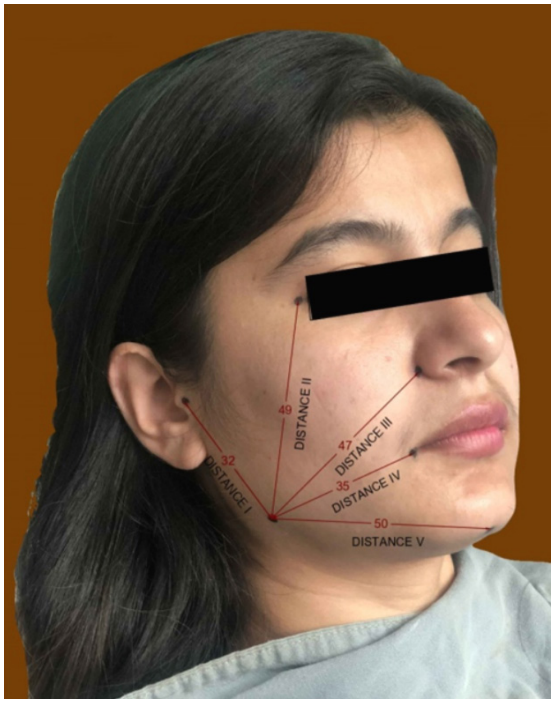

Figure 1: The evaluation of post-operative swelling measured with distances.

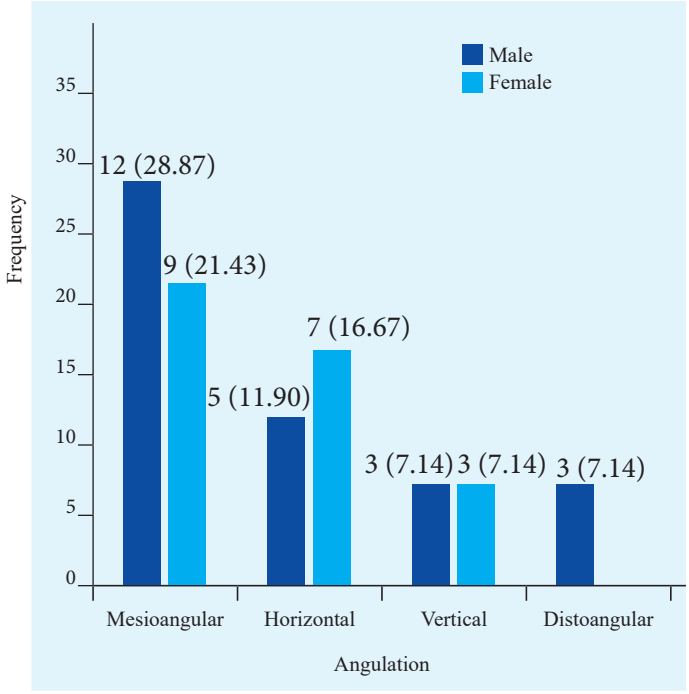

Figure 2: Types of impaction of lower third molar in male and female patients, n (%).

The first 21 patients were enrolled in study group 1, who were prescribed Ketorolac 10 mg orally and the next 21 patients in study group 2 were prescribed Nimesulide 100 mg orally twice a day for five days.

The Microsoft Excel sheet was used for data entry and analysis was done using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA). The frequency and percentage were analysed for categorical data and mean and standard deviation for quantitative data in descriptive statistics. The Mann-Whitney U test was used to analyse the potential differences between the two groups for non-parametric data and independent t-test for normally distributed data for pain, mouth opening, and swelling. The Friedman test was done to assess the differences within each group at different time intervals.

RESULT

All patients were abided with the study protocol, tolerated the surgical procedures well, and completed the follow-up period. No post-operative complications occurred during the study. The study sample comprised of 42 patients. There were 23 (54.76%) males and 19 (45.24%) females, and they ranged in age from 18 to 59 years (mean age = 30.83±9.85). Orthopantomogram was taken to ensure the similarity of the tooth inclinations according to Winter's classification (mesioangular, horizontal, vertical, and distoangular positions, Figure 2).[14]

Comparing pain intensity at each observation time point did not reveal any statistically significant difference between the groups (Table 1). Figure 3 illustrates the mean post-operative pain scores change across the study's different observation time points (six hrs, 12 hrs, 24 hrs, 48 hrs, and 72 hrs). The comparison of pain intensity in different observation periods (six hrs, 12 hrs, 24 hrs, 48 hrs, and 72 hrs) using the Friedman test within each group identified a significant difference between the time points ($P < 0.001$, Table 1).

The mouth openings after removal of third molars were similar in both the groups in different periods of observation. However, there was a significant difference within each group in the mouth opening observed at different times ($P < 0.001$, Table 2).

The measurements for swelling were comparable between two groups before surgery for the distance I ($P=0.276$), distance III ($P=0.12$), distance IV

Table 1: Differences in pain intensity scores for two groups in different study periods.

Period after surgery	Pain score Mean±SD (Median)		P value	Test
	Ketorolac	Nimesulide		
6 hrs	3.43±0.99 (3)	4.05±1.09 (4)	0.055	Mann-Whitney U test
12 hrs	2.86±0.85 (3)	3.38±1.24 (3)	0.201	Mann-Whitney U test
24 hrs	2.33±0.91 (2)	2.76±0.88 (3)	0.077	Mann-Whitney U test
48 hrs	1.90±0.77 (2)	2.05±0.92 (2)	0.669	Mann-Whitney U test
72 hrs	1.52±0.81 (1)	1.52±0.60 (1)	0.677	Mann-Whitney U test
Average	2.408±0.86	2.752±0.94	0.336	Mann-Whitney U test
P value	**<0.001**	**<0.001**		Friedman test

Table 2: Maximum mouth opening (MMO) in different study periods for the ketorolac and nimesulide groups.

Period after surgery	MMO (mm) Mean±SD (Median)		P value	Test
	Ketorolac	Nimesulide		
6 hrs	26.57±6.43 (28)	22.50±7.11 (25)	0.291	Independent t-test
12 hrs	22.76±6.46 (25)	20.48±6.80 (20)	0.271	Independent t-test
24 hrs	23.71±7.37 (24)	19.90±7.54 (18)	0.079	Mann-Whitney U test
48 hrs	25.90±7.58 (25)	22.43±8.46 (19)	0.082	Mann-Whitney U test
72 hrs	27.19±7.13 (25)	25.38±8.39 (24)	0.331	Mann-Whitney U test
Average	25.23±6.99 (63.5)	22.504±7.66 (21.2)	0.21	Mann-Whitney U test
P value	**<0.001**	**<0.001**		Friedman test

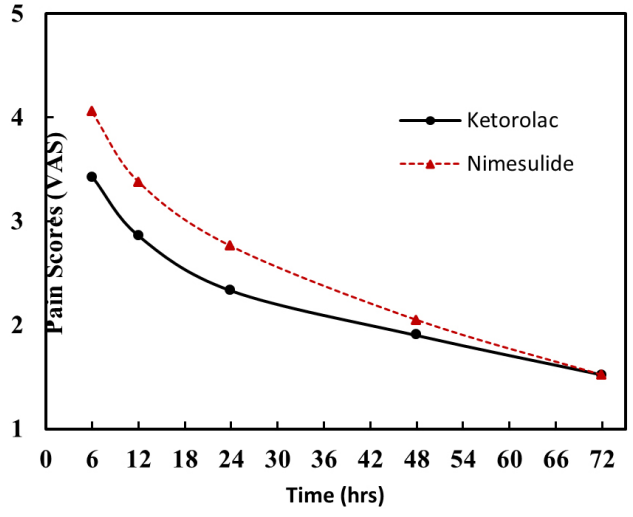

Figure 3: Mean pain intensity scores (VAS) in two groups over the study period.

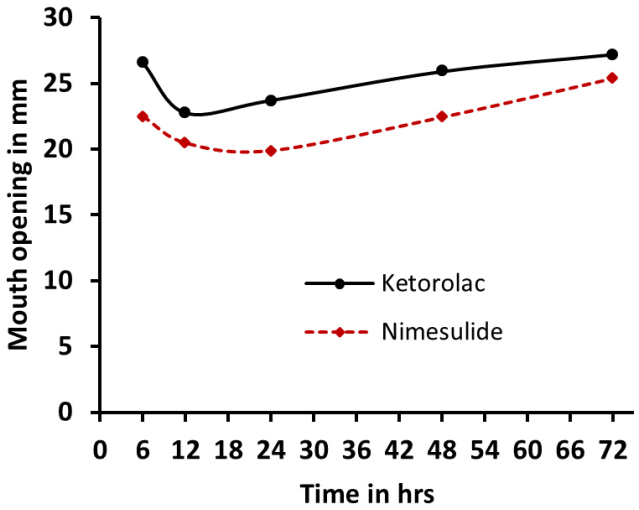

Figure 4: Mean maximum mouth opening over the study period in two groups.

Table 3: Differences between the measurements of the swelling before and after surgery in the ketorolac and nimesulide groups.

	Distance in mm Mean±SD (Median)		P value	Test
	Ketorolac	Nimesulide		
Distance I				
Before surgery	66.19±6.15 (64)	68.38±6.87 (70)	0.276	Mann-Whitney U test
6 hrs	69.10±5.23 (66)	71.19±6.52 (71)	0.331	Mann-Whitney U test
12 hrs	72.95±4.34 (71)	75.86±5.51 (75)	0.095	Mann-Whitney U test
24 hrs	73.19±3.84 (73)	77.00±6.05 (76)	0.033	Mann-Whitney U test
48 hrs	70.29±5.12 (72)	74.95±6.55 (75)	0.014	Mann-Whitney U test
72 hrs	70.10±10.67 (69)	72.52±6.64 (73)	0.064	Mann-Whitney U test
Distance II				
Before surgery	100.33±10.93 (96)	108.43±8.68 (109)	0.014	Mann-Whitney U test
6 hrs	105.00±10.37 (100)	113.29±9.32 (114)	0.010	Mann-Whitney U test
12 hrs	108.43±8.79 (109)	114.52±9.85 (115)	0.049	Mann-Whitney U test
24 hrs	107.62±8.28 (108)	113.62±8.54 (113)	0.026	Independent t-test
48 hrs	105.62±7.18 (103)	112.10±8.44 (112)	0.010	Mann-Whitney U test
72 hrs	104.71±6.85 (100)	110.71±8.35 (111)	0.014	Mann-Whitney U test
Distance III				
Before surgery	108.52±10.45 (102)	117.00±9.26 (119)	0.12	Mann-Whitney U test
6 hrs	108.33±11.25 (100)	115.81±9.19 (116)	0.035	Mann-Whitney U test
12 hrs	109.90±11.72 (103)	120.14±8.44 (120)	0.004	Mann-Whitney U test
24 hrs	110.57±10.88 (104)	118.95±8.92(120)	0.013	Mann-Whitney U test
48 hrs	109.90±10.09 (103)	117.52±8. 83 (120)	0.014	Mann-Whitney U test
72 hrs	108.52±10.35 (102)	115.14±8.46 (115)	0.045	Mann-Whitney U test
Distance IV				
Before surgery	95.86±10.12 (99)	98.15±8.68 (98)	0.439	Independent t-test
6 hrs	100.18±6.85 (99)	101.80±6.81 (99.50)	0.448	Independent t-test
12 hrs	102.41±6.788 (100)	105.95±7.20 (105.50)	0.110	Independent t-test
24 hrs	102.64±8.77 (102.50)	107.25±7.29 (108.50)	0.082	Mann-Whitney U test
48 hrs	100.32±8.84 (100)	100.00±8.84 (105.50)	0.127	Mann-Whitney U test
72 hrs	97.68±6.99 (99)	99.80±7.60 (99.50)	0.426	Mann-Whitney U test
Distance V				
Before surgery	93.76±4.44 (93)	96.05±7.16 (94)	0.291	Mann-Whitney U test
6 hrs	99.33±4.94 (97)	101.24±5.22 (100)	0.146	Mann-Whitney U test
12 hrs	100.24±4.89 (98)	99.24±7.46 (96)	0.205	Mann-Whitney U test
24 hrs	99.76±1.84 (100)	101.57±6.70 (99)	0.351	Mann-Whitney U test
48 hrs	100.14±2.08 (100)	105.14±8.10 (102)	0.049	Mann-Whitney U test
72 hrs	99.62±2.55 (99)	102.38±7.57 (102)	0.116	Mann-Whitney U test

(P=0.439), and distance V (P=0.291). However, a significant difference between groups before surgery was seen in distance II (P=0.014). The difference in various measurements taken for two groups in six hrs, 12 hrs, 24 hrs, 48 hrs, and 72 hrs for swelling are depicted in Table 3.

DISCUSSION

This research's main objective was to conduct a study on two COX inhibitors drugs to compare their analgesic efficacy and analyse their anti-inflammatory effects through a third molar surgery model. The pattern of angulation of impacted third molar in this study was same as study done by Upadhyaya et al.[15] The third molar surgery model was selected because of widely used pharmacological tests since 1976 and is commonly performed in dentistry.[16] Post-operative pain is usually observed in the early stages after the surgical procedure. This model has been considered necessary in clinical investigations to differentiate the analgesic effects of various drugs, as used in this study, and even between different dosages of a single drug.[17]

Pain caused by surgical removal of teeth ranges between moderate and severe during the first 24 hrs after surgery, with the significant pain intensity occurring between six and eight hrs when a conventional local anaesthetic is used.[18] The dentist's primary concern for their patients is to minimise the experience of pain and its consequences after dental extractions. A significant reduction in pain intensity levels after dental extraction will result in rapid post-operative recovery and satisfactory outcomes.

Dental pain is mostly inflammatory and evidence-based medicine has shown that NSAIDs are the best analgesics for dental pain.[19] NSAIDs have been used for more than 25 years to treat rheumatological diseases, to relieve pain after tooth extraction, and to provide post-operative analgesia. When used alone, they are useful in reducing mild to moderate pain, such as maxillofacial surgery, minor orthopaedic, or some ambulatory surgical procedures and postpartum pain. NSAIDs have additional anti-inflammatory activity that is lacking in opioids, which play a vital role in relieving postoperative pain and inflammation.[20]

Ketorolac is a well-known, proven, and prescribed NSAID with analgesic, anti-inflammatory, and antipyretic properties. It is useful in treating a variety of acute and chronic pain and inflammatory conditions.[21] It is commonly used for relieving pain and has analgesic effectiveness after extraction. Ketorolac exerts its action via inhibition of PGs synthesis by inhibiting COX-1 and COX-2 with relative equipotent.[22] Nimesulide (4-nitro-2-phenoxy methane sulfonamide) belongs to the group of sulfanilamide derivatives, differing from other NSAIDs by presenting a sulfonanilide radical rather than a carboxylic radical.[6] This drug is a partially selective COX-2 enzyme inhibitor used to treat acute pain, such as that associated with osteoarthritis.

In the present study, both drugs were administered immediately after the surgical procedure. The pain scores were the same for both drugs at six hrs, but the severity of pain was more in the Nimesulide group. Overall pain reduction in both groups was same at 72 hrs. The pain values decreased significantly after sixth hour post-operatively in the Ketorolac group whereas in the Nimesulide group, the pain was significantly reduced after 24 hrs. Ketorolac showed lower pain scores at six hrs, 24 hrs, 48 hrs, and 72 hrs intervals, in which Ketorolac showed a better analgesic effect than Nimesulide. Preliminary studies have also suggested that oral Ketorolac possesses potent analgesic activity in the post-operative period.[22,23] These data show that although complete pain relief was not observed, the pain level was tolerable to patients of both the groups. A study done by De Menezes and Cury, comparing Nimesulide 100 mg and Meloxicam 75 mg, observed lower pain intensity for the Nimesulide group.[7] However, the present study did not find any statistically significant difference between the drugs studied concerning pain scores.

It has been suggested that trismus results from a protective reflex against inflammatory states of orofacial tissues[24] and avoids maximum mouth opening by the patient due to post-operative pain. The assessment of trismus was done by measuring the maximum mouth opening. Decreased mouth opening was observed in the Nimesulide group at six hrs. On the other hand, it decreased in the Ketorolac group at 12 hrs. A gradual increase in mouth opening occurred at 24 hrs in the Ketorolac group, whereas it happened at 48 hrs in the Nimesulide group. There was no statistically

significant difference in the comparison between the Nimesulide and Ketorolac groups.

Regarding swelling, a significant increase was observed in the first 12 and 24 hrs after the surgical procedure for both Keterolac and Nimesulide groups. These results differ from the data reported by Troullos et al.[25] and De Menezes and Cury,[7] where the maximum swelling occurred at 48 hrs and 72 hrs, respectively, after the extraction of the third molars. There was no statistically significant difference when the groups in this study were compared with each other, which is in contrast to the results from the study of Bjornsson et al.[26] where they found a statistically significant reduction in swelling on the third and sixth post-operative days for the Ketoprofen group. In that study, the reduction in swelling with Ketoprofen use was 27.8% on the third day, increasing to 70.8% on the sixth day of observation. In this study, the distance between the angle of the mandible and the labial commissure (Distance IV) was most affected by the swelling, which is in agreement with a previous study by Bastos et al.[27] Post-operative swelling was more pronounced in the Nimesulide group than in the Ketorolac group. Ketorolac has been shown to be superior to other NSAIDs for the control of post-operative swelling. The distances where swelling were more prominent in the interval of time in our study were at a distance I at 24 hrs post-operatively, Distance II at 12 hrs post-operatively, Distances III at 12 hrs post-operatively, Distance IV at 24 hrs, Distance V at 48 hrs post-operatively.

Different pharmacological studies are aimed to investigate the tolerability of different drugs. In a review of hepatic adverse effects, a more significant number and severity of hepatotoxic events were demonstrated for patients who used Nimesulide with other NSAIDs.[28] Macio et al. found that the patients with a higher risk of hepatotoxicity with Nimesulide use were older, female and had a median of 62 days.[28] However, De Menezes and Cury described no adverse effects in patients with younger ages who used Nimesulide for a very short time.[7] Adverse effects such as stomachaches or other gastrointestinal discomforts, drowsiness, and migraine, although observed, were mild in intensity and well tolerated on oral Ketorolac.[29]

In the present study, patients who were given Ketorolac had lower pain intensity and a long time of analgesia anti-inflammation compared to patients administered with Nimesulide after lower third molar extraction. From the results of this study, it is evident that patients who received Ketorolac had less dental pain when compared to the Nimesulide group. This will help clinicians in prescribing analgesics after dental extractions. Ketorolac showed better overall results as compared to Nimesulide.

However, this study has some limitations. The methods used in this study to measure facial swelling may not be as accurate as computed tomography scans or magnetic resonance imaging, but it was a non-invasive, simple, cost-effective, and time-saving method of obtaining numeric values for the determination of soft tissue contour changes.[30] Likewise, significant difference between groups before surgery was seen in distance II (P=0.014), which showed that they were not comparable. Therefore, the results obtained may not depict the clear difference.

CONCLUSION

The findings of the study conclude that both Ketorolac 10 mg and Nimesulide 100 mg are effective anti-inflammatory and analgesic drugs after surgical extraction. There was no significant difference between two drugs in pain and mouth opening in different time periods. However, Ketorolac was more effective than Nimesulide as an anti-inflammatory drug after extractions.

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Conflict of Interest: None.

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