Original Research Paper

University J Dent Scie 2026; Vol. 12, Issue 2

Effects of Co-Administered Nimesulide and Dexamethasone Following Surgical Extraction of Third Molars- A Split Mouth Study

Abstract:
This study aimed to determine the effect of the co-administration of dexamethasone 8 mg and nimesulide 100 mg given 1 h before mandibular third molar surgery. A prospective, randomized, double-blind, split-mouth clinical trial was conducted in Department of Oral and Maxillofacial Surgery at SudhaRustagi College of Dental Sciences and Research Faridabad. A pilot study was first performed (95% confidence interval, 80% test power, and 5% error), and a sample of 20 patients aged between 18 and 40 years was selected. The patients were randomized and divided into two groups: nimesulide + placebo and dexamethasone + nimesulide. The following parameters were evaluated: pain (numerical rating scale), oedema, trismus, and patient satisfaction. The paired t-test and the Wilcoxon test were used to compare means. Statistically significant differences were found between the groups in pain values at 2, 4, and 12 h postoperatively. Oedema and trismus were similar in the two treatment groups and decreased over time postoperatively. The coadministration of dexamethasone and nimesulide reduces pain intensity and the need for rescue medication after third molar surgery.

Key-words: Third molar, pain, oedema, trismus, anti-inflammatory agents

Introduction:

The surgical extraction of third molars, a routine procedure for oral and maxillofacial surgeons, commonly results in postoperative pain, swelling, and trismus due to inflammatory and bacterial responses [1]. These complications can greatly impact patient quality of life and lead to additional financial burdens. Postoperative pain is triggered by changes in the central and peripheral nervous systems caused by surgical trauma, which activates cyclooxygenase-2 (COX-2) and prostaglandin activity. This, in turn, sensitizes nociceptors and promotes inflammation [2].

Nimesulide, a selective COX-2 inhibitor with analgesic, antipyretic, and anti-inflammatory properties, is commonly used to manage acute pain, including that associated with osteoarthritis. It is generally better tolerated than traditional NSAIDs and is associated with fewer gastrointestinal side effects. Its rapid analgesic effect is apparent 15 minutes post-administration, making it valuable for rapid pain relief [3].

Access this article online

Website:
www.ujds.in

DOI:
https://doi.org/10.21276/ujds.2026.12.2.1

Corticosteroids are commonly administered preoperatively to manage postoperative complications such as pain, swelling, and trismus [4]. They effectively control acute inflammation by disrupting signaling pathways and enhancing the synthesis of lipocortin, which inhibits phospholipase A2. This, in turn, reduces the formation of arachidonic acid from cell membrane phospholipids, leading to a decreased production of inflammatory mediators like leukotrienes, prostacyclins, prostaglandins, and thromboxane A2 [5].

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Received : 10 Oct., 2024, **Published :** 30 June, 2026

How to cite this article: Vishal Aneja. (2026). Effects of Co-Administered Nimesulide and Dexamethasone Following Surgical Extraction of Third Molars- A Split Mouth Study. UNIVERSITY JOURNAL OF DENTAL SCIENCES, 12(2).

Dexamethasone, a corticosteroid known for its potent anti-inflammatory effects and extended half-life, is used in various protocols for third molar surgery [6]. When combined with etodolac, dexamethasone has been shown to provide superior pain relief compared to the use of either medication alone [7].

In oral and maxillofacial surgery, the pre-emptive co-administration of NSAIDs and corticosteroids is intended to prevent and reduce postoperative complications. The combination of a long-acting corticosteroid like dexamethasone with a fast-acting anti-inflammatory analgesic like nimesulide is considered ideal for minimizing these issues [8]. However, studies evaluating the effectiveness of pre-emptive oral administration of 8 mg dexamethasone with 100 mg nimesulide are currently lacking.

This study aimed to compare the effects of preoperative nimesulide in managing postoperative pain, swelling, trismus, and associated complications, both alone and in combination with oral dexamethasone after the surgical removal of impacted third molars.

Materials and methods Study design and sample:

A randomized, split-mouth design-controlled trial was performed in the Oral and Maxillofacial Surgery Department of SRCDSR, Faridabad. Patients selected for the study underwent the surgical removal of bilaterally symmetrical impacted mandibular third molars.Uniform procedure was done by using conventional rotary instruments and other armamentarium as shown in fig 1. Orthopantomogram and periapical radiographs were taken for each patient. Fig 2 showing pre-operative opg of a study patient having bilaterally symmetrical impacted mandibular third molars.

The two surgeries were performed in two separate clinical sessions with a minimum 1– week interval as the patient would get enough time to recover from the previous surgery. The drugs were administered orally 1 hour before surgery, nimesulide + placebo (group A), or dexamethasone + nimesulide (group B). Tablet Ketorolac Tromethamine 10 mg (orally) was given as a rescue analgesic to the patients who felt discomfort corresponding to the level of 3 in the numerical rating scale (NRS) of pain.

The following inclusion criteria were applied: 1.ASA 1 status (American Society of Anesthesiology classification; a healthy patient with no systemic disease and not on continuous medication); 2. Similar root formation characteristics, position, and degree of impaction for both mandibular third molars; 3. No signs of inflammation at the time of surgery.

Exclusion criteria encompassed patients who were allergic to any of the drugs used in the study, Chronic smokers, Pregnant or breast-feeding women, Patients who were diabetic, patients on medication like aspirin and certain anti- cancer drugs such as dasatinib and lapatinib as they could interact with the drugs in the study, Patients who refused to participate after reading the informed consent form, Patients who were suffering from liver diseases like hepatitis, jaundice etc.

Randomization:

Patients eligible to participate in the study were invited into a room, where envelopes containing details of the treatment allocation were opened. These envelopes were sealed, opaque, sequentially numbered, and contained the combination of drugs to be administered and the side to be operated on. Based on this, patients were allocated to the respective groups.

Overview of Surgery

Once the surgical field was prepared, a conventional ward incision was given and third molar was extracted after the bone guttering and sectioning/elevation as per requirement and the surgical wound was cleaned by irrigation with 8% saline. The flap was repositioned and sutured.

Outcome measures:

The variable 'pain' was measured using NRS, consisting of a vertical or horizontal line, with a total of 11 numbers, ranging from 0 to 10, denoting no pain to the worst possible pain, respectively. The patients were asked to indicate the intensity of their pain on this scale. Patients were instructed to record their pain score at 30 min after surgery and then at 2, 4, 6, 8, 12, 16, 24, 48, and 72 h postoperative.

To quantify oedema, three measurements were performed using reference points: Point A. Corner of the eye/angle of the jaw; Point B. Tragus/pogonion; Point C. Tragus/corner of the mouth

The measurements were performed in the preoperative period (baseline) and at 24, 48, 72 hours and 7 days after surgery. The evolution of edema was determined by subtracting the total value at each postoperative time point (average of three values) from the average measured at baseline (preoperative period) [9].

Trismus was also measured using the standardized method by digital a Vernier caliper between the maxillary central and lower left incisors. The measurements were performed at 24, 48, 72 h and 7 days postoperatively. The reduction in mouth opening was calculated as the difference between the preoperative value and the postoperative value at each time point.

Frequency of postoperative complications like infections, dry sockets and fever were also recorded. Duration of surgery was noted each time the procedure was performed from the incision to suturing in minutes. Patient satisfaction was also being recorded using the posse (postoperative symptom severity scale) on 1st,3rd,5th and 7th days [4].

Statistical analysis:

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 21 (IBM Corp., Armonk, NY). Descriptive data was reported for each variable. Summarized data was presented using Tables and Graphs. Shapiro wilk test was used for assessing the normality of data. If p value more than 0.05: Parametric test: paired t test was used. If p value less than 0.05, non-parametric test was used: Wilcoxon signed rank test was used. Chi square test was used for categorical variables. Level of statistical significance was set at p-value less than 0.05.

Results:

A total of 130 patients were screened for study eligibility. 110 patients were excluded because they did not meet the study criteria. 20 patients were divided into two groups. The gender wise comparison of patients is shown in Table 1. The mean duration of surgery was 23.65 + 2.368 min for the nimesulide + placebo group and 23.90 + 2.049 min for the dexamethasone + nimesulide group; the difference was not statistically significant (P = 0.455). No accidents or complications were observed. Table 2 shows the comparison of pain levels between the two pharmacological protocols administered, at the different postoperative time points. Statistically significant differences were observed at 2 h (P = 0.033), 4 h (P = 0.048),6h (P= 0. 022), 8h (P= 0. 002) and 12 h (P = 0.003) postoperatively.

Table 3 shows the comparison of oedema between the two pharmacological protocols administered, at the different postoperative time points. statistically significant differences between the groups (paired t-test) found at day 1 (P=0.001) and day 2 (P= 0.002). Table 4 shows the comparison of the reduction in mouth opening between the two pharmacological protocols administered, at the different postoperative time points. statistically significant differences between the groups at day 1 (P= 0.004) and day 2 (P= 0.003) (paired t-test and Wilcoxon test).

Patient satisfaction assessed using the Likert scale showed that comfort and satisfaction were greater for the dexamethasone + nimesulide protocol (26.99+ 3.60) than for the nimesulide + placebo protocol (26.99+ 2.19), the difference was statistically significant (paired t-test, P = 0.022).

Fig 2 and fig 3 showing Comparison of swelling and mouth opening in group A and group B at day 2 and day 7 follow up.

Table 1: Gender wise comparison of mean age (years)

	Gender	N	Mean	Std. Deviation	P value
age	Males	11	30.36	4.802	0.504, NS
	Females	9	28.67	6.344	

Table 2: Comparison of pain (NRS) between protocols (nimesulide + placebo and dexamethasone + nimesulide) at different postoperative time

Intergroup comparison of pain						
	N	Gr A		Gr B		P value
		Mean	Std. Deviation	Mean	Std. Deviation	
At 0.5 hr	20	2.00	.725	1.70	.470	**0.034, S**
At 2 hrs	20	2.40	.598	2.00	.459	**0.033, S**
At 4 hrs	20	2.70	.801	2.25	.851	**0.048, S**
At 6 hrs	20	3.15	.988	2.60	.821	**0.022, S**
At 8 hrs	20	3.50	1.192	2.70	.801	**0.002, S**
At 12 hrs	20	3.75	1.552	2.90	.968	**0.003, S**
At 16rs	20	3.05	.887	2.60	1.046	0.059, NS
At 24 hrs	20	2.60	1.188	2.20	1.056	0.070, NS
At 48 hrs	20	2.40	1.095	1.90	1.165	0.135, NS
At 72 hrs	20	1.70	.801	1.25	.639	0.058, NS

Table 3: Comparison of oedema (millimetres) between protocols (nimesulide + placebo and dexamethasone + nimesulide) at different postoperative time points.

Intergroup comparison of swelling						
	N	Gr A		Gr B		P value
		Mean	Std. Deviation	Mean	Std. Deviation	
At day 1	20	5.65	1.663	2.55	3.017	0.001, S
At day 2	20	5.10	2.382	2.60	3.530	0.002, S
At day 3	20	3.60	2.741	2.05	3.456	0.06, NS
At day 7	20	1.05	1.701	0.40	2.963	0.297, NS

Table 4: Comparison of mouth opening reduction (millimetres) between protocols (nimesulide + placebo and dexamethasone + nimesulide) at different postoperative time.

Intergroup comparison of Trismus						
	N	Gr A		Gr B		P value
		Mean	Std. Deviation	Mean	Std. Deviation	
At baseline	20	37.315	5.6259	37.595	6.8879	0.420, NS
At day 1	20	26.345	7.6234	30.795	6.0592	**0.004, S**
At day 2	20	27.460	7.6709	31.975	5.8949	**0.003, S**
At day 3	20	30.550	6.8542	33.000	6.0764	0.088, NS
At day 7	20	35.390	5.6599	38.190	5.3848	0.052, NS

Fig 1. Armamentarium for surgical extraction of impacted mandibular third molar.

Fig 2. Orthopantomogramof a patient having bilaterally symmetrical impacted mandibular third molars

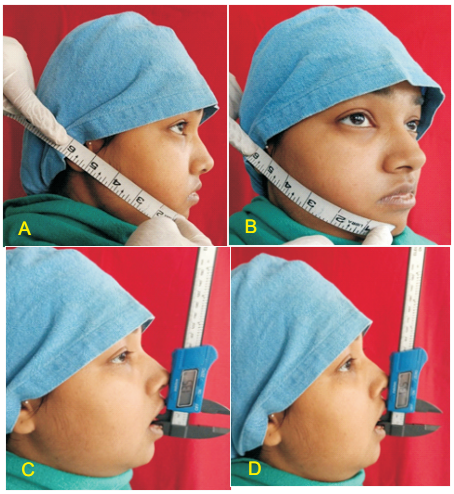

Fig 3. Comparison of swelling and mouth opening in the group A at day 2 and day 7 follow up(i) & (ii) swelling at day 2 & day 7, (iii) & (iv) mouth opening at day 2 & day 7.

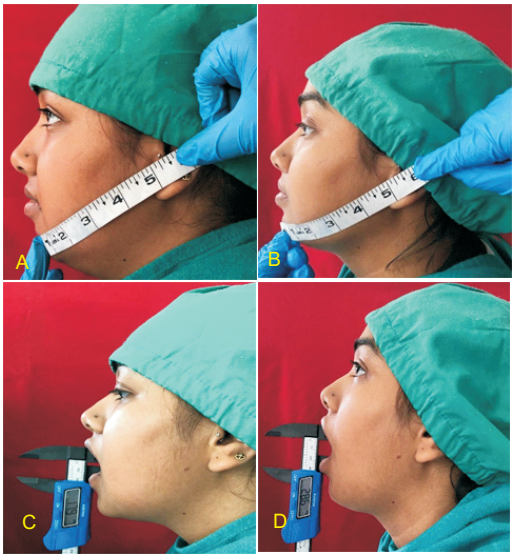

Fig 4. Comparison of swelling and mouth opening in the group B at day 2 and day 7 follow up(i) & (ii) swelling at day 2 & day 7, (iii) & (iv) mouth opening at day 2 & day 7.

Discussion:

The aim of this study was to compare the preemptive analgesic effects of nimesulide and dexamethasone administered preemptively in third molar surgery. Postoperative pain is related to alterations in the central and peripheral nervous systems induced by surgical trauma.

Nimesulide, the NSAID employed in the study, has an impact on pain due to its capacity to suppress COX-2. Nimesulide blocks the release of hydroxyl radicals, superoxide radicals, and hypochlorous acid generation by activated polymorphonuclear neutrophils, as well as the release of histamine from mast cells and basophils.

Dexamethasone inhibits the inflammatory process through two distinct mechanisms. The first is a slow-acting genomic mechanism, where corticosteroid molecules diffuse through the cell membrane and bind to cytosolic receptors GR-α and GR-ß. These complexes are then transported to the nucleus, where they bind to specific DNA sequences, promoting the expression of mRNA and the synthesis of anti-inflammatory proteins. The second mechanism is fast-acting and non-genomic, involving the binding of dexamethasone to cell membrane receptors. This interaction leads to the formation of second messengers like cAMP or protein kinases, which inhibit the expression of phospholipase-A2 and COX-2 enzymes [10].

Bauer et al. [4] evaluated the efficacy of a combination of ibuprofen and dexamethasone in patients undergoing tooth extraction surgery. Patients consumed fewer rescue analgesics in the group that used a combination of dexamethasone and ibuprofen ($p < 0.05$) and felt more comfortable after surgery.

The findings of this study support this assertion because the combination of dexamethasone and nimesulide significantly reduced pain following third molar surgery. It showed that at 0.5hr, 2hr, 4hr, 6hr, 8hr & 12hr follow-ups, the mean pain score differs significantly among Group A & Group B.

Markiewicz et al., in a systematic review and meta-analysis, also advocated the potent effects of corticosteroids on trismus and edema, but found no reduction in pain [11].

A possible explanation for the lack of efficacy of steroids for pain lies in the fact that these drugs inhibit the release of betaendorphin by the anterior pituitary. Betaendorphin is known to be a potent endogenous analgesic present in the peripheral circulation.

A study by Buyukkurt et al. compared the administration of prednisolone alone with the administration of prednisolone + diclofenac and found that the latter combination was more effective with respect to pain, edema, and postoperative trismus. In this study on intergroup comparison, significantly

lower swelling was observed with the nimesulide and dexamethasone group at post-operative 1st: (5.65 ± 1.66 and 2.55 ± 3.01), 2nd (5.25 ± 2.33 and 2.60 ± 3.53), and 3rd day: (3.95 ± 3.03 and 2.05 ± 3.45) respectively [12].

Trismus is also a common complication following third molar extraction and can have a negative impact on quality of life by hampering eating and speaking. A significant increase in mouth opening in the postoperative period was observed with the use of dexamethasone. However, the difference between drugs was only significant on the second day of evaluation. This finding may be explained by the biological half-life of the drugs, as dexamethasone is considered a long-acting steroid (36–54 h).

The meta-analysis by Markiewiczt al. confirmed the potent effect of corticosteroids on trismus during the first 7 days postoperative. The current study corroborates the data from this meta-analysis as reduced values were observed in nimesulide and dexamethasone group on day 1, day 2 and day 7 (26.34 ± 7.623 and 30.79 ± 6.05), (27.46 ± 7.67 and 31.97 ± 5.89), (34.74 ± 7.21 and 38.19 ± 5.38) respectively which decreased over time during the 7 days after surgery.

Complications of surgery may be associated with certain risk factors, which, if not examined, can influence the results and lead to research bias; these include patient age, the use of oral contraceptives, and the duration of surgery etc. The average age of the patients in both groups in this study was under 35 years. Baqain et al. stated that a prolonged duration of surgery can lead to greater pain, swelling, and trismus due to the increased release of inflammation products and that this could have a consequent influence on research results [13]. There were, however, no patient exclusions based on that criterion. Mean POSSE (postoperative symptom severity scale) scores among Group B sites were found to be significantly lower than that as compared to Group A sites at 1st, 3rd, 5th and 7th day.

This study suggests that dexamethasone and nimesulide used as preoperative therapy before third molar surgery show favorable effects in the management of postoperative swelling and trismus compared to placebo. The results of this preliminary study are encouraging; however further research is required to provide a better understanding of the potential benefits of dexamethasone in postoperative therapy following impacted third molar surgery

Conclusion:

Preemptive analgesia using oral dexamethasone 8 mg combined with nimesulide100 mg has been shown to effectively control postoperative pain, reducing the need for additional analgesic medication, minimizing postsurgical edema, and decreasing the reliance on rescue analgesics compared to nimesulide alone. This study included 20 patients with symptomatic bilateral impacted mandibular third molars, consisting of 11 males and 9 females, with an average age of 30.36 ± 4.802 years and 28.67 ± 6.344 years, respectively. Further randomized, controlled clinical studies are necessary to provide more conclusive evidence of its efficacy.

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