

## A Comparative Study of the Effect of Preemptive Analgesia with Nimesulide, Metamizole Sodium or Placebo on Postoperative Edema After Extraction of Impacted Third Molars

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**Abstract:** *Objective: Comparing the effectiveness of preemptive analgesia with nimesulide, metamizole sodium or placebo in terms of postoperative edema in surgical removal of impacted mandibular third molars.*

*Material and methods: 80 patients with impacted mandibular third molars requiring surgical treatment were enrolled in the study. This is a randomized, double-blind, placebo-controlled study. The patients were given vials marked with numbers, containing nimesulide, metamizole sodium or placebo; the patients had to take the medication 30 minutes prior to surgery.*

*Results: Postoperative edema was most pronounced in the groups treated with metamizole sodium or nimesulide. The distances measured in the study showed varying degrees of involvement by postoperative inflammation. The distances from the angle of the mandible to the labial commissure and to the pogonion, respectively, were most affected by postoperative edema ( $P < 0.05$ ).*

*Conclusion: The edema was most pronounced at the first 48 hours in all three treatment groups. Preemptive analgesia with nimesulide or metamizole sodium did not appear to have any effect on postoperative edema.*

**Keywords:** *preemptive analgesia, third molar surgery, edema, non-steroidal anti-inflammatory drugs*

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### I. Introduction

Development of postoperative pain is typical after each surgical procedure. Clinical (nociceptive) pain can be divided into two types, namely, inflammatory and neuropathic. The first type is associated with an injury of peripheral tissues during a surgical procedure, and the second type is associated with an injury of the nervous system [1].

Injury of tissue and peripheral nerves results in local inflammatory reactions, together with elevated levels of various bioactive mediators, incl. prostaglandins, bradykinins, SP, CGRP and cytokines at the site of injury [2].

Surgical removal of mandibular third molars is a common oral surgical procedure. According to Troullos et al [3], this surgical procedure allows measuring the pain, edema, loss of function and hyperthermia, as well as their suppression in the first 2-3 days after surgery. According to Meechan and Seymour [4], the immediate postoperative sequelae - pain, edema and trismus - provide a useful clinical model for evaluating the efficacy of analgesics and anti-inflammatory drugs. Postoperative edema can be controlled by different methods which are based on the use of different drug classes - corticosteroids, NSAIDs, antibiotics [5, 6, 7, 8]. Another part of the studies conducted focus on the route of administration of the drug (9). A third group of authors focus on the timing of the drug administration - pre- and postoperatively [10, 11].

Preemptive analgesia is an up-to-date drug intervention based on the prevention of central sensitization [1]. The use of NSAIDs for preemptive treatment has an effect on peripheral sensitization in the early postoperative period, thereby suppressing the release of prostaglandins, cytokines and other bioactive substances. COX1 and COX2 are assumed as important enzymes in terms of postoperative pain and inflammatory edema [12]. Various NSAIDs affect postoperative pain and inflammation to different degrees. Some of them have an effect mainly on the inflammatory process, while others have an effect on the pain [13]. The effect on the postoperative edema in maxillofacial region is of social importance, and it also reduces complications and contributes to faster recovery of the patient [14]. Nimesulide is a medication commonly used to control the postoperative pain and the reactive inflammatory process after extraction of impacted mandibular third molars [15, 16]. Another drug commonly used in many parts of the world for pain relief is metamizole sodium [17]. The use of metamizole sodium for control of inflammation after extraction is limited due to the fact that its mechanisms of action are not completely understood. A clinical study demonstrated that metamizole

sodium has an effect on COX1 and COX2, without causing any gastrointestinal problems typical of other NSAIDs, which makes it a good option for analgesia [18].

## II. Objective

The objective of this study was to compare the effectiveness of preemptive analgesia with nimesulide, metamizole sodium or placebo in terms of postoperative edema in surgical removal of impacted mandibular third molars.

## III. Material and Methods

The study was conducted in compliance with the Declaration of Helsinki, and after obtaining approval by the Ethics Committee at the Medical University of Plovdiv. This is a randomized, double-blind, placebo-controlled study. 80 patients with impacted mandibular third molars were randomized to receive vials marked with numbers, containing nimesulide, metamizole sodium or placebo. To be included in the study, the patients had to meet all the inclusion and none of the exclusion criteria.

**Inclusion Criteria:** clinically healthy patients aged between 16 and 45, with indications for an extraction of a mandibular third molar; with no evidence of pain associated with the mandibular third molar to be extracted; Pell and Gregory class 1 or 2.

**Exclusion criteria:** pregnancy; allergy to nimesulide, metamizole or lactose - the main ingredient of the placebo; acute inflammation in the region of the tooth to be extracted; taking antibiotics or NSAIDs in the past seven days; patients needing antibiotic prophylaxis.

Three groups were formed: 30 patients received nimesulide 100 mg (Enetra – “Actavis”), 30 patients received metamizole sodium 500 mg (Algozone – “Elder”) and 20 patients (control group) received placebo. Each vial contained 10 tablets of the medication. 30 minutes prior to the surgical procedure, each patient took 1 tablet from the vial which was given to him/her. The next administration of the drug took place 12 hours after the surgical procedure. The patients had to take 1 tablet at every 12 hours for five days.

### 3.1 Control of postoperative edema

To measure the degree of postoperative edema, reference points were selected and distances to be measured were determined. The reference points were the angle of the mandible, the tragus, the external canthus, the sidewall of the nose, the labial commissure and the pogonion. The distances measured were from the angle of the mandible to the other five points (for convenience, distances were designated with D). D1 – from the angle of the mandible to the tragus, D2 – to the external canthus, D3 - to the sidewall of the nose, D4 - to the labial commissure, and D5 - to the pogonion.

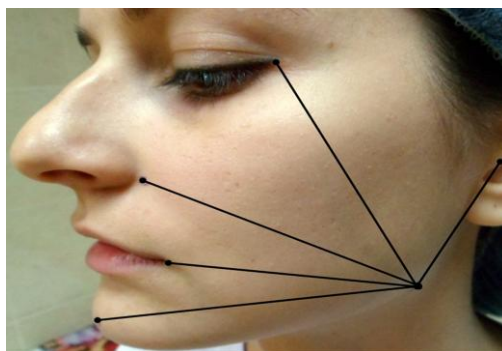


Fig. 1. Distances measured to find changes in postoperative edema

All measurements and surgical procedures were performed by the same investigator in order to reduce the probability of error. Measurements were made prior to surgery (baseline) and at 24, 48 and 72 hours postoperatively.

### 3.2 Statistical Methods

The Kruskal-Wallis Test was used to compare the distances (D1, D2, D3, D4 and D5) among the three treatment groups (treated with placebo, metamizole sodium or nimesulide). The change of the value of each distance during the postoperative period was evaluated using the Friedman Test (several time points) and Wilcoxon Signed Rank Test (two time points). Boxplot diagrams were used for graphical visualization of D1, D2, D3, D4 and D5 (outliers were distinguished according to the criteria 1.5 of the interquartile range). The correlation between a given couple of distances  $D_i - D_j$  ( $i, j = 1, 2, 3, 4$  and  $5; i \neq j$ ) was assessed by the

Kendall's tau b correlation coefficient. Fisher's exact test was applied for comparison of categorical variables. Calculations were made with MS Excel 2016.

#### IV. Results

Gender distribution of patients in each of the three treatment groups was as follows: in the nimesulide treatment group - 70% females: 30% males, in the metamizole sodium treatment group - 67% females: 33% males, in the placebo group - 65% females: 35% males. Using Fisher's Exact Test ( $P = 0.95$ ), statistical identity between genders was found in the three treatment groups.

Comparison between the three treatment groups in terms of age showed statistical identity, confirmed by Kruskal-Wallis Test ( $P = 0.86$ ).

The results of the comparison of the measured distances between the three groups at each of the hours studied showed no statistically significant difference.

The analysis of the results of comparing the distances as a function of time between the three groups showed statistically significant changes in the groups treated with nimesulide or metamizole sodium. No statistically significant difference was found in the first studied distance D1 when comparing the measurements at baseline and at 24, 48 and 72 postoperative hours.

A significant difference in the second distance D2 as a function of time was found in the group treated with metamizole sodium vs. the other two groups. This was confirmed by Friedman Test ( $P = 0.007$ ). Another statistically significant difference in this distance was found when comparing the values measured at baseline to those measured at 24 postoperative hours in the metamizole sodium group - Wilcoxon Signed Rank Test ( $P = 0.011$ ). The results of the comparison between the three treatment groups with regard to D2 are presented in Figure 2.

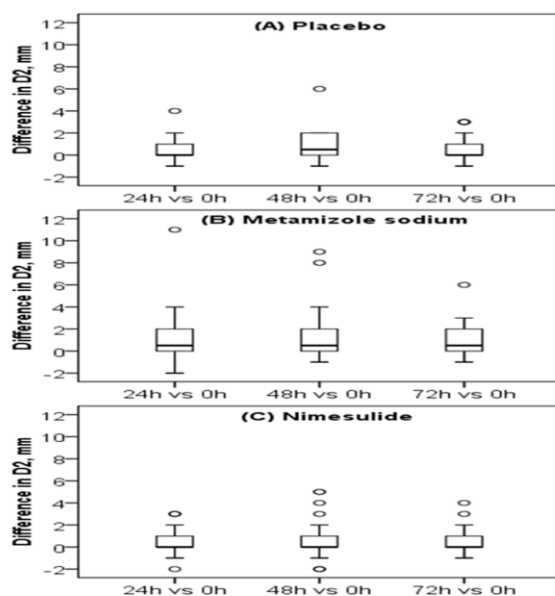
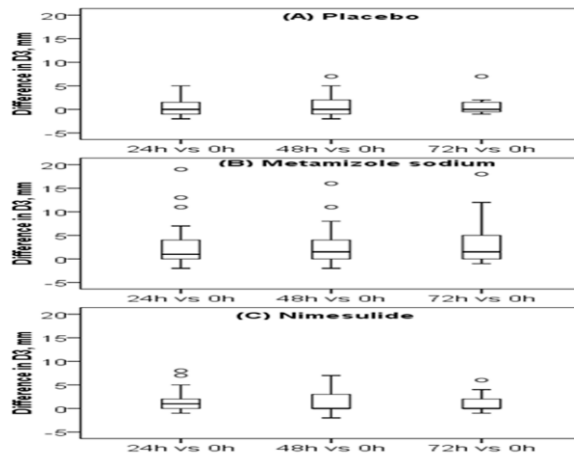


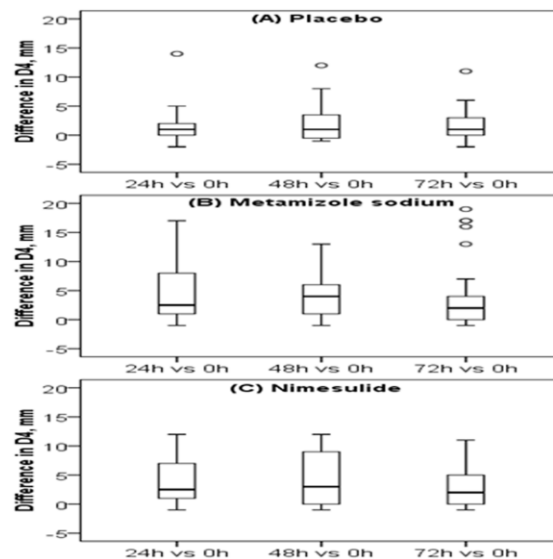
Fig. 2. Changes in D2 in the three groups when comparing the baseline values to those at 24, 48 and 72 postoperative hours

The comparison with regard to D3 at all studied hours found statistically significant difference in the groups treated with nimesulide and metamizole sodium. This difference was positive (increased edema in these two groups). The applied Friedman Test for the nimesulide group resulted in ( $P = 0.003$ ), and for the metamizole sodium group ( $P < 0.001$ ). Comparison of the baseline values of D3 to the values of D3 at the next studied hours showed significant difference at 24 hours in the nimesulide and metamizole sodium groups. The result of the applied Wilcoxon Signed Rank Test was ( $P < 0.001$ ) for the metamizole sodium group, and ( $P < 0.001$ ) for the nimesulide group. Figure 3 shows the changes in D3, as a function of time.



**Fig. 3.** Changes in D3 in the three groups when comparing the baseline values to those at 24, 48 and 72 postoperative hours

The comparison between the values of D4 measured at all the studied hours showed that there was a statistically significant difference in the nimesulide and metamizole sodium groups. The data showed increased edema in these two groups. The result of the applied Friedman Test for the nimesulide group and the metamizole sodium group was ( $P < 0.001$ ) and ( $P < 0.001$ ), respectively. The comparison of the baseline values of D4 to the values at the next studied hours showed that there was a statistically significant difference (increased edema) between hour 0 and hour 24 in the nimesulide and metamizole sodium groups, and between hour 48 and hour 72 in the nimesulide group. The result of the applied Wilcoxon Signed Rank Test was ( $P < 0.001$ ) for the nimesulide group, and ( $P < 0.001$ ) for the metamizole sodium group, respectively, for the comparison between the baseline and postoperative hour 24. For the comparison between hour 48 and hour 72 in nimesulide group, the result of the Wilcoxon Signed Rank Test was ( $P = 0.011$ ). Figure 4 shows the changes in D4 as a function of time.

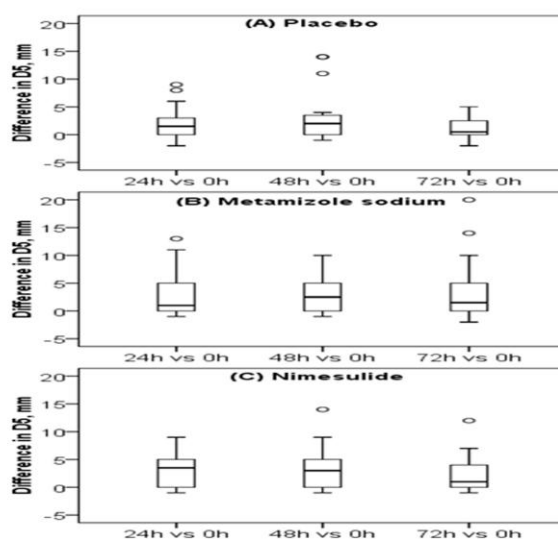


**Fig. 4.** Changes in D4 in the three groups when comparing the baseline values to those at 24, 48 and 72 postoperative hours

With regard to the last studied distance D5, a statistically significant difference was found when comparing the values measured at all studied hours in all three groups. This difference is also positive - increased edema. The result of the applied Friedman Test for nimesulide, metamizole sodium and placebo groups was ( $P < 0.05$ ). A significant difference was found when comparing the preoperative measurements to those at postoperative hour 24 in all three groups. The result of the applied Wilcoxon Signed Rank Test was ( $P <$

0.05). A statistically significant difference was also found when comparing the placebo group and the nimesulide group at 48 and 72 hours.

Figure 5 shows the changes in D5 in the three treatment groups.



**Fig. 5.** Changes in D5 in the three groups when comparing the baseline values to those at 24, 48 and 72 postoperative hours

For the three groups of patients, the correlations between each couple  $D_i - D_j$  ( $i, j = 1, 2, 3, 4$  and  $5; i \neq j$ ), at each time point after extraction, were evaluated by calculation of the non-parametric Kendall's tau b correlation coefficient and by testing the hypothesis of its difference from zero. It was found that for all groups and each time point the following correlations between couples were statistically significant: D1-D2; D1-D3; D2-D3; D3-D4; D3-D5 and D4-D5. A correlation between D1 and D4 was evident for the entire period (0h, 24h, 48h and 72h) within the placebo group, meanwhile there was no correlation between this couple of distances for the patients treated with metamizole sodium or nimesulide. On the opposite, correlations which were statistically significant in the last two groups (metamizole sodium – for the 48h and 72h, and nimesulide – for the 0h, 24h, 48h and 72h) but not observed in the placebo group (for the 0h, 24h, 48h and 72h) were found for the couples D2-D4; D1-D5 and D2-D5. The statistically significant correlations which were present in the group treated with metamizole sodium but absent in the placebo group were: at the time of extraction (0h) - D2-D5 and at the 24h after the surgical procedure - D2-D4 and D2-D5.

## V. Discussion

This study makes an attempt to add to our current knowledge of the benefits of preemptive analgesia in terms of early postoperative edema at the first 72 hours after surgery.

The objective of the study conducted was to investigate the effectiveness of preemptive analgesia with nimesulide, metamizole sodium or placebo in terms of postoperative edema after surgical removal of impacted third molars, as well as to compare the effects of the three medications as a function of time. The results of the comparison of the values of each distance at specific time points did not show a statistically significant difference in all three groups. The comparison of the results of the measurement of the five distances as a function of time showed a statistically significant difference in nimesulide and metamizole sodium groups, with increased postoperative edema. The edema was most pronounced during the first 48 hours after surgery, and our results are similar to the results of the studies of other authors [5, 13]. Pronounced edema was demonstrated by the measurement of D4 (between the angle of the mandible and the labial commissure), and this result is identical to the results of similar studies [13]. D1 remained unchanged, which, in our opinion, is due to the great distance from the surgical site. The comparison of the values of D2 between the three groups showed that there was a statistically significant difference only in the metamizole sodium group (increased edema), which, in our opinion, is due to the peripheral mechanisms of relief of pain and inflammation by the medication used [18], as well as to the probability of errors when recording the results (valid for all measurements made due to minor differences of 1-2 mm between the baseline and follow-up measurements). Significant changes in the third measured distance D3 were observed in the nimesulide and metamizole sodium groups (increased postoperative edema); the results of our study are identical to the results of other studies with a similar design [13, 19]. A

statistically significant difference was found when comparing the baseline levels of D3 to those at postoperative hour 24, which is identical to the results of other studies [19]. Data analysis for D4 showed similar results to those for D3; only in the nimesulide group the comparison between hours 48 and 72 showed statistically significant difference, which may be due to a secondary inflammatory process. Our results are identical to the results of other studies [19, 20]. There were statistically significant differences in the last studied distance D5 in all three groups at the first 24 hours after surgery. In our opinion, this is due to the proximity of this distance to the surgical field, as well as to the postoperative reactive inflammation.

Analyzing the results of the non-parametric Kendall's tau<sub>b</sub> correlation coefficient, a correlation of the distances studied in all three groups was found. The correlation was most pronounced in the nimesulide group, less pronounced in the metamizole sodium group, and the weakest in the placebo group. There is evidence of strong correlation between D5 and the other studied distances. We found no objective factors influencing the relationship between the medication administered and the change in the distances studied.

## VI. Conclusion

The edema was most pronounced at the first 48 hours in all three treatment groups. No statistically significant anti-inflammatory effect of preemptive analgesia with nimesulide or metamizole sodium was observed in comparison with the placebo group.

## References

- [1]. Woolf CJ, Chong Mun-Seng. Preemptive analgesia-Treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993; 77:362-79.
- [2]. McMahon SB, Cafferty WB, Marchand F. Immune and glial cell factors as pain mediators and modulators. *Exp Neurol* 2005; 192: 444-462
- [3]. Troullos ES, Hargreaves KM, Butler DP, Dionne RA. Comparison of non-steroidal anti-inflammatory drugs, ibuprofen and flurbiprofen, to methylprednisolone and placebo for acute pain, swelling, and trismus. *J Oral Maxillofac Surg*. 1990; 48:945-52.
- [4]. Meechan JG, Seymour RA. The use of third molar surgery in clinical pharmacology. *British Journal of Oral and Maxillofacial Surgery* 1993; 31(6): 360-365.
- [5]. Filho JRL, Maurette PE, Allais M, Cotonho M, Fernandes C. Clinical comparative study of the effectiveness of two dosages of Dexamethasone to control postoperative swelling, trismus and pain after the surgical extraction of mandibular impacted third molars. *Med Oral Patol Oral Cir Bucal*. 2008 ;1:13(2):E129-32.
- [6]. Kim K, Brar P, Jakubowski J, Kaltman S, Lopez E. The use of corticosteroids and nonsteroidal antiinflammatory medication for the management of pain and inflammation after third molar surgery: a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2009 ;107(5):630-40.
- [7]. Simone JL, Jorge WA, Horliana ACRT, Canaval TG, Tortamano IP. Comparative analysis of preemptive analgesic effect of dexamethasone and diclofenac following third molar surgery. *Braz Oral Res*. 2013; 27(3):266-71.
- [8]. Monaco G, Tavernese L, Agostini R, Marchetti C. Evaluation of antibiotic prophylaxis in reducing postoperative infection after mandibular third molar extraction in young patients. *J Oral Maxillofac Surg*. 2009 ;67(7):1467-72.
- [9]. Chaudhary P, Rastogi S, Gupta P, Indra N, Thomas R, Choudhury R. Pre-emptive effect of dexamethasone injection and consumption on post-operative swelling, pain, and trismus after third molar surgery. A prospective, double blind and randomized study. *J Oral Biol Craniofac Res*. 2015; 5(1): 21-27.
- [10]. Campbell WI, Kendrick RW, Ramsay-Baggs P, McCaughey W. The effect of pre-operative administration of bupivacaine compared with its postoperative use. *Anaesthesia*. 1997 ;52(12):1212-6.
- [11]. Yamaguchi A, Sano K. Effectiveness of preemptive analgesia on postoperative pain following third molar surgery: Review of literatures. *Japanese Dental Science Review* 2013; 49: 131-138
- [12]. Cottrell J, O'Connor J. P. Effect of Non-Steroidal Anti-Inflammatory Drugs on Bone Healing. *Pharmaceuticals* 2010, 3, 1668-1693.
- [13]. De Menezes S. A. F., Cury P. R. Efficacy of nimesulide versus meloxicam in the control of pain, swelling and trismus following extraction of impacted lower third molar. *Int. J. Oral Maxillofac. Surg*. 2010; 39: 580-584.
- [14]. Sortino F, Cicciù M. Strategies used to inhibit postoperative swelling following removal of impacted lower third molar. *Dent Res J*. 2011; 8(4): 162-171.
- [15]. Pierleoni P, Tonelli P, Scaricabarozzi I. A double-blind of nimesulide and ketoprofen in dental surgery I. *Drugs* 1993; 46(Suppl. 1):168-170.
- [16]. Pouchain EC, Costa FW, Bezerra TP, Soares EC. Comparative efficacy of nimesulide and ketoprofen on inflammatory events in third molar surgery: a split-mouth, prospective, randomized, double-blind study. *International Journal of Oral and Maxillofacial Surgery*. 2015; 44(7):876-884
- [17]. Kötter T, da Costa BR, Fässler M, Blozik E, Linde K, Jüni P, Reichenbach S, Scherer M. Metamizole-associated adverse events: a systematic review and meta-analysis. *PLoS One*. 2015, 13;10(4): e0122918. doi: 10.1371
- [18]. Hinz B, Cheremina O, Bachmakov J, Renner B, Zolk O, Fromm MF, Brune K. Dipyrone elicits substantial inhibition of peripheral cyclooxygenases in humans: new insights into the pharmacology of an old analgesic. *FASEB J*. 2007; 21(10):2343-51.
- [19]. Costa FW, Soares EC, Esses DF, Silva PG, Bezerra TP, Scarparo HC, Ribeiro TR, Fonteles CS. A split-mouth, randomized, triple-blind, placebo-controlled study to analyze the pre-emptive effect of etoricoxib 120 mg on inflammatory events following removal of unerupted mandibular third molars. *Int J Oral Maxillofac Surg*. 2015 ;44(9):1166-74.
- [20]. de Sousa Santos JA, da Silva LC, de Santana Santos T, Menezes Júnior LR, de Assunção Oliveira AC, Brandão JR. Comparative study of tramadol combined with dexamethasone and diclofenac sodium in third-molar surgery. *J Craniomaxillofac Surg*. 2012; 40(8):694-700.