IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 4 Ver. XII (Apr. 2016), PP 42-46
www.iosrjournals.org

Assessment of Postoperative Pain Intensity after Preemptive Analgesia with Nimesulide, Metamizole Sodium And Placebo In Removal Of Impacted Mandibular Third Molars

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Abstract: *Objective: Assessment of pain and analgesic efficacy can be made after extraction of a mandibular third molar. The objective of this study is to determine the effect of preemptive administration of nimesulide, metamizole sodium and placebo on the intensity of postoperative pain after extraction of impacted mandibular third molars.*
Study Design: *This is a randomized, double-blind, placebo-controlled study. 80 patients meeting the inclusion and exclusion criteria, with teeth to be extracted, were enrolled in the study. 30 minutes prior to surgery, the patients took the medication contained in a vial with an assigned number which had been provided to them earlier.*
Results*: Postoperative pain reached its peak at 6 hours after surgery in all the three groups. Lower intensity of postoperative pain in the group treated with nimesulide was found. At 24 hours, no statistically significant difference in VAS pain intensity scores was found between the treatment groups.*
Conclusion: *Pronounced effect of preemptive analgesia with nimesulide*
Keywords*: Preemptive analgesia, Third molar surgery, postoperative pain, VAS*

I. Introduction

Effective postoperative pain control is an essential component of the care of surgically treated patients. Postoperative pain is a combination of unpleasant sensory, emotional and mental experience, associated with neuroendocrine, immune and metabolic changes as the final result of tissue damage, anesthesia and psychological stress [1]. According to Macintyre and Ready [2], inadequate assessment and management of postoperative pain can have a profound effect on the patient, leading to increased levels of anxiety, sleep disturbance, restlessness, irritability and aggression. Surgical removal of mandibular third molars is a common oral surgical procedure [3, 4, 5].

According to some authors, this surgical procedure makes possible to assess central sensitization. In their studies, they concluded that even minor surgical procedures in maxillofacial surgery can result in central or peripheral sensitization. [6] Many clinical studies provide evidence of central sensitization [7, 8], and it is now considered as the main cause of post-traumatic pain hypersensitivity. Extraction of a mandibular third molar is a very good model for assessment of pain and analgesic efficacy. This model was proposed by Winter [9] in the study of the analgesic effect of ibuprofen in the postoperative period following the extraction of impacted mandibular molars.

According to Ong et al [10], pain can be pharmacologically modulated by: preventing the perception of nociceptive irritation, blocking the conduction of nociceptive signals, together with peripheral nerves, prevention of central sensitization, and multimodal analgesia.

Preemptive analgesia - the most promising direction in pain control methods. The concept of preemptive analgesia was introduced by Woolf in 1983 [11]. It is based on the principles of prevention, namely blocking the pain in the surgical site prior to the start of procedure.

Many authors, in their studies, advocate for the use of preemptive analgesia in extraction of mandibular third molars to control postoperative pain, finding a positive effect of various analgesic interventions used [12, 13, 14].Review of literature showed that multiple scales for pain assessment are used [15, 16].

According to Seymour [17], VAS is an appropriate method for recording of postoperative dental pain. The studies of Coll et al. [18] show that VAS is a good tool for objective measurement of pain in day surgery.

II. Objective

The objective of the study performed is to determine the effect of preemptive administration of nimesulide, metamizole sodium and placebo on the intensity of postoperative pain after extraction of impacted mandibular third molars.

III. Material And Methods

3.1 Design

This study involved 80 patients with impacted mandibular third molars to be extracted. This is a double-blind, randomized clinical study, conducted in accordance with the Declaration of Helsinki. The study was conducted after obtaining approval by the Ethics Committee at the Medical University of Plovdiv and informed consent of the patients.

Selection criteria: All patients in the study were aged between 17 and 45. In order to prevent discrediting the study with regard to the effect of preemptive analgesia, patients who had had pain in the respective impacted molar in the previous week, as well as those taking NSAIDs or antibiotics in the same period, were excluded from the study. A vial with a number assigned, containing 10 tablets, was randomly provided to each patient. Three groups, depending on the medication given to the patients, were formed. The first group of 30 patients received nimesulide 100 mg 30 minutes pre-operatively, and then twice daily for 5 days. The second group of 30 patients received metamizole sodium 500 mg 30 minutes prior to surgery, and then twice daily for 5 days, and the third group of 20 patients received placebo also twice daily for 5 days and 30 minutes preoperatively. To ensure comparability of results, all patients were operated on by the same surgeon, using the same surgical technique.

3.2 Pain assessment

Visual analogue scale (VAS) is a measurement tool for parameters which cannot be measured directly. Pain, being a subjective feeling, is such a parameter. VAS is usually a 100 mm line, the two ends of which are 0 mm (no pain) and 100 mm (most severe pain). Each patient was given instructions how to register (record in a diary) what his/her perception of pain was at 2, 6, 12, 24, 48 and 72 hours postoperatively. Greater frequency of entries in the first 24 hours can be explained by the fact that pain in this period is not caused by an infectious agent.

3.3 Statistical methods

The Kruskal-Wallis test was used to compare the continuous variables among the three investigated groups (treated with nimesulide, metamizole sodium and placebo). The Mann-Whitney U test was applied when only two groups were compared. The change of VAS score during the postoperative period was evaluated by the Friedman Test (several time points) and Wilcoxon Signed Rank Test (two time points). Boxplot diagrams were used for graphical visualization of the VAS scores (outliers were distinguished according the criteria 1.5 of the interquartile range). Fisher's exact test was applied for comparison of categorical variables. Calculations were made with MS Excel 2016.

IV. Results

Using descriptive statistics methods, homogeneity in terms of gender and age was found. Table 1 shows gender distribution of patients in all three groups.

Table 1. Gender distribution of the patients in the groups treated with different medications

	Medication administered		
%	**Placebo (N = 20)**	**Metamizole sodium (N = 30)**	**Nimesulide (N = 30)**
Males	35%	33%	30%
Females	65%	67%	70%

Using Fisher's Exact Test (P = 0.95) we proved that proportions by gender (Table 1) were statistically identical. Kruskal-Wallis Test (P = 0.86) was applied to the age factor, and statistical identity of results in patients in all three groups was found. Table 2 shows the characteristics of the patients in all three groups, distributed by age.

Table 2. Age distribution of the patients in the three groups.

Applied treatment	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
Placebo	20	23	4	17	36	21	22	23
Metamizole sodium	30	24	5	17	38	21	23	25
Nimesulide	30	24	6	17	43	21	23	25

VAS pain intensity scores showed a statistically significant difference in pain levels between the groups up to postoperative hour 24. At the last two time points at which scores were recorded (hours 48 and 72), no significant difference in pain intensity in all three treatment groups was found.

Application of Kruskal-Wallis Test to VAS scores at the second postoperative hour (P = 0.021) demonstrated a statistically significant difference between the three groups. Multiple comparisons of postoperative pain intensity showed significant difference between the groups treated with nimesulide and placebo - Mann-Whitney U (P = 0.007). (Fig. 2A)

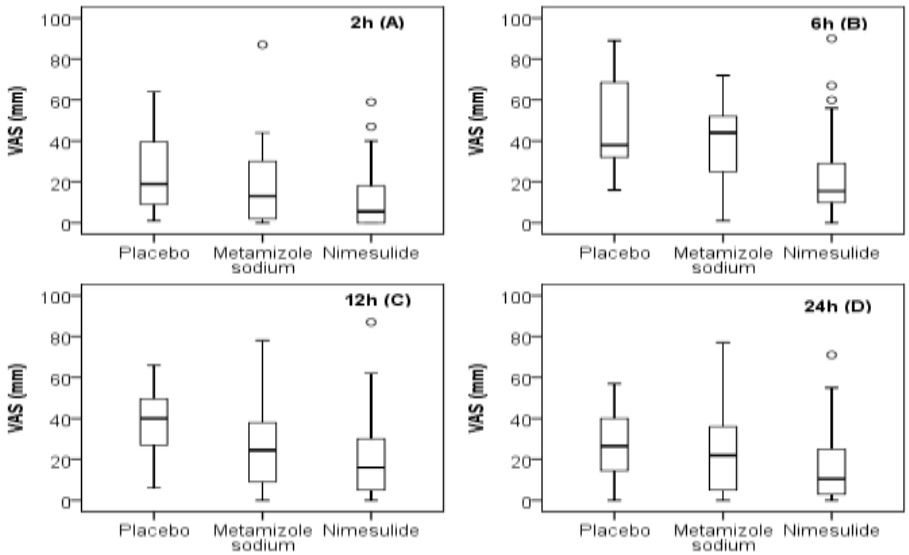

Fig. 2. VAS pain intensity at the second, sixth, twelfth and twenty-fourth postoperative hour

At the sixth postoperative hour, we also we found a statistically significant difference when comparing the three treatment groups, Kruskal-Wallis Test (P < 0.001). A significant difference was found when comparing nimesulide and placebo groups - Mann-Whitney U (P <0.001) and those treated with nimesulide and metamizole sodium - Mann-Whitney U (P = 0.002). (Fig. 2B).

At the twelfth postoperative hour, comparison between the three groups again showed a statistical difference, Kruskal-Wallis Test (P – 0.003). A statistically significant difference was found when comparing the patients who received metamizole sodium or placebo - Mann-Whitney U (P = 0.034), as well as between the groups treated with nimesulide or placebo - Mann-Whitney U (P = 0.001). (Fig. 2C).

At the twenty-fourth postoperative hour, a statistically significant difference was found only when comparing the groups treated with nimesulide or placebo - Mann-Whitney U (P = 0.013). (Fig. 2D)

Comparison between the pain intensity scores at the different time points (as a function of time) showed significant differences in all three groups (Friedman Test). The comparison between hours 2 and 6 is the most indicative (Wilcoxon Signed Rank Test), which demonstrated a statistically significant difference in all three groups (Fig. 3). In the other cases of comparison of pain intensity between two consecutive postoperative hours, it was found that the differences between the obtained VAS scores were smaller. (Fig. 3)

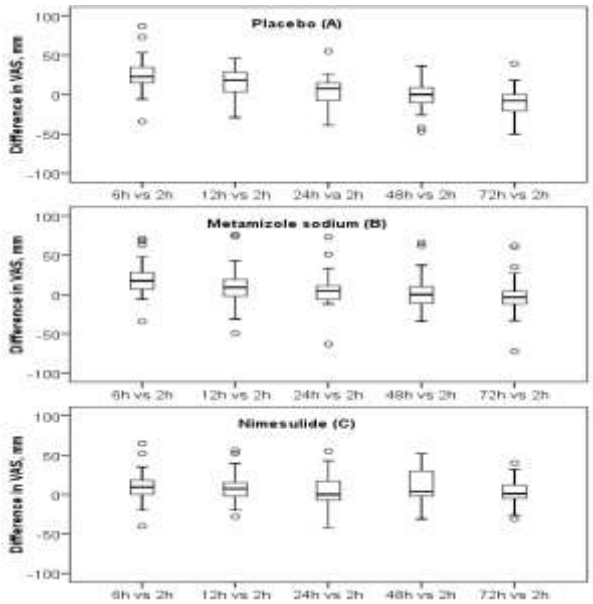

Fig. 3. Comparison of postoperative pain intensity scores as a function of time

V. Discussion

The results obtained in our study confirm the thesis of preemptive analgesia, which coincides with the results of the studies of a number of authors [12,19]. Presence of a pronounced preemptive effect in the group treated with nimesulide was found. The preemptive effect of nimesulide was particularly pronounced during the first 24 hours, when mainly the neuropathic pain component is influenced. At 24 hours, inflammatory nociceptive irritation of the surgical wound also plays role, which partly explains the lack of statistically significant differences at those time points. We found highest intensity of pain based on VAS scores at the sixth postoperative hour in all three treatment groups, which is in agreement with the studies of many authors [19, 20]. Other authors report differences in time of occurrence of pain peak in the compared groups [21], but in their studies pain intensity is highest at the sixth postoperative hour in nimesulide group. According to other studies with identical design, intensity of pain after extraction of impacted third molars is highest at the fifth postoperative hour [22]. A number of studies have demonstrated the pronounced preemptive effect of nimesulide [21, 22], while clinical studies with metamizole sodium are a relatively small number [23, 24] and they investigate its postoperative administration. The study conducted by us showed that after the sixth postoperative hour the difference in the effect on postoperative pain between nimesulide and metamizole sodium groups was not statistically significant. After reaching its maximum intensity, pain starts to lessen, and after 24 hours its intensity is low, unless a complication of inflammatory nature develops. When comparing VAS scores at the second postoperative hour and VAS scores at the next time points, a statistically significant difference in all three groups was found. In numerical values, the median for the group treated with nimesulide is the lowest compared to that of the other two groups. This comparison as a function of time shows a pronounced preemptive effectiveness of nimesulide compared to metamizole sodium and placebo.

VI. Conclusion

This comparative study of pain intensity after preemptive analgesia with nimesulide, metamizole sodium and placebo in extraction of impacted mandibular third molars demonstrated a pronounced preemptive effect in the group treated with nimesulide 100 mg twice daily. After the twenty-fourth postoperative hour, no significant difference in the effects of drugs used was found.

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