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## ORIGINAL ARTICLE

# The preemptive effect of tramadol and metamizole on the intensity of postoperative pain

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### ABSTRACT

**Aim** To demonstrate the analgesic effect of preemptively administered tramadol and metamizole on the postoperative pain severity, after an elective operative hysterectomy with adnexectomy.

**Methods** There were three groups with 30 patients in each group. Patients included in the study were between 45 to 67 years old. They were all in the ASA group II. Randomization was performed in random order according to the regular elective operating program. Patients in Group I received i. m. tramadol 1mg/kg, and in Group II 30mg/kg of metamizole, five minutes before anaesthesia induction. Patients did not receive preemptive analgesia in Group III (control). All patients underwent the same induction anaesthesiology procedure with propofol, fentanyl, tracrיום, supplemented with O<sub>2</sub>, N<sub>2</sub>O, and sevoflurane at an appropriate dose until MAC 1 was reached. Surgeries lasted for 80-120 minutes. Every patient performed a resting pain assessment 30 minutes after an extubation by Numerical Pain Scale (NPS).

**Results** We found out that tramadol had a better effect in preemptive analgesia and that the average pain score for Group I was 6.10 (p=0.043). In Group II, it was 7.93 (p=0.022). There is significant difference in pain intensity between patients in the control group, (pain intensity was 9.16), and those who received tramadol and metamizole. There was no significant difference in the intensity of pain when using these two analgesics (p=0.733).

**Conclusion** The effect of preemptively administered tramadol prior to the introduction of general anaesthesia in postoperative pain is significantly more favourable than the effect of metamizole.

**Key words:** analgesia, general anaesthesia, hysterectomy, pain assessment

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## INTRODUCTION

By the definition of the International Association for Study of Pain (IASP), pain is described as “unwanted sensory, motor, and emotional experience connected with an actual or threatening tissue damage, or described from patient perspective with terms that indicates that kind of damage” (1). It is an obligation for every doctor in the Intensive Care Unit (ICU) to eradicate pain, or to lower its intensity to a bearable level. Taking into consideration that pain is an individual feeling, it is difficult to estimate it, and the commonly used option is to ask a patient to self-assess the pain level by using the pain scales which are used in every day practice (2). Mostly used scale for pain assessment of older patients is a numerical pain scale (NPS) (3). These days analgesic offer gives us a wide range in cupping postoperative nociceptive pain. In that sense there are many guides that are directing the schemes in postoperative treatment of pain, all to the extent of preemptive or preoperative application of analgesics (4). In many studies it was proven that administration of analgesics before anaesthesia induction allowed more favourable postoperative analgesic score (5). In preemptive approach to postoperative analgesia, it is possible to use different analgesics and techniques, but in many studies tramadol was confirmed as a primary and most adequate analgesic (6,7).

Because we often use metamizole and tramadol in our clinical practice, we wanted to compare their preemptive effect on pain in our patients.

The aim of this study was to investigate the effect of tramadol and metamizole in preemptive application in terms of decreasing postoperative pain after hysterectomy and adnexectomy.

## PATIENTS AND METHOD

### Patients and study design

This prospective, randomized, comparative, blinded (the patients did not know in which group they would be) study was conducted at the Clinic for Gynaecology and Obstetrics at the Clinical Centre in Sarajevo (tertiary-level hospital serves a population of half a million) over a six-month period. It included three groups of patients, 30 in each group, who were prepared for elective operative hysterectomy with adnexectomy. The patients were ASA (American Society of Anaesthesiologi-

sts) group II (8), 45-67 years old, with a body mass index (BMI) of 18.5-24.9. Exclusion criteria were: a BMI below 18.5 or above normal body weight (24.9), a history of allergic manifestations to one of the analgesics used, and the patients whose surgery lasted longer than 120 minutes. Randomization was performed consecutively according to the regular elective operative program.

The patients were explained the procedure for participation in the study and their consent was obtained. All patients agreed to the trial with the prior knowledge of the study design and the possibility of withdrawing from the study whenever they wished. Post-operative pain assessment of patients was performed 30 minutes after extubating and being placed in the Intensive Care at bed rest. We did not determine the intensity of pain in the movement because our patients were encouraged to move 2 hours after surgery.

An approval of the Scientific Committee of the Clinical Centre in Sarajevo was obtained for this research.

### Methods

There were 30 patients in the Group I who received, 1 mg/kg tramadol i. m., 5 minutes before induction of anaesthesia. In the Group II patients received i. m. metamizole at a dose of 30 mg/kg, 5 minutes before the induction of anaesthesia. In the Group III (control group) there were 30 patients who underwent the same operative procedure but without preemptively administered analgesia.

All patients underwent the same induction anaesthesiology procedure with pre-induction with spontaneous ventilation of 100% O<sub>2</sub> of 5 L/min, and i. v. application of 1% propofol 2mg/kg, fentanyl 3 µg/kg, and atracurium besilate 0.5 mg/kg. After intubation, anaesthesia was managed with supplementation of O<sub>2</sub>, N<sub>2</sub>O (50/50%), sevoflurane in the appropriate volume percentage for the achieved minimum alveolar concentration (MAC 1).

The operative course went neatly in all patients. All surgeries took 80-120 minutes. After awakening from anaesthesia and intensive care placement that happened within 30 minutes of extubation, all patients underwent pain evaluation and were instructed to report pain on the 11-point numerical pain scale (NPS) with zero equalling “no pain” and 10 indicating “the worst imaginable pain“ (6).

## Statistical analysis

Data were entered into previously prepared tables with patients initials, age, length of surgery, and pain intensity recorded. The obtained results were statistically analysed with ANOVA analysis of variance of small samples (to test the equality of multiple groups), Levene's test (to analyse variance equality) and Student t- test (the confidence intervals and hypotheses about the equality/difference of arithmetic means of the compared groups) were applied. Statistical significance was set up at  $p < 0.05$ .

## RESULTS

The average pain score in the Group I where tramadol was administered was 6.10. In the Group I 14 patients reported feeling pain with a score of 6. In the Group II with metamizole administration, the average pain score was 7.93; the highest number of pain ratings being given number 8 occurred in 15 patients. In the control Group III the average pain score was 9.17; a score of 10, which reflects the most severe pain, was obtained in 16 patients of this group. There was a significant difference of the average values of pain intensity in the individual groups ( $p < 0.05$ ).

By comparing the control group and the group which received tramadol preemptively, it was found that the average pain score in tramadol group was lower ( $< 9.17$  and  $6.10$ , respectively). These two groups did not have the same variance based on the Levene's test ( $p = 0.043$ ).

The average pain score of patients who received metamizole was lower than the pain of patients in the control group ( $7.93$  and  $< 9.17$ , respectively). These two groups did not have the same variance, based on the Lavene's test ( $p = 0.022$ ) (Table 1).

The pain intensity score in the patients who received metamizole or tramadol showed the same variance with 95% significance (based on the Levene's test) ( $p = 0.733$ ). It is also evident that there was no statistically significant difference in pain intensity when using these two analgesics.

The average age in the Group I was 57.9 years, in the Group II 59.4 years and in the Group III 57.1 years. The average duration of operations in the Group I was 102.4 min, in the Group II 103.8 min, and in the Group III 98.7 min (Table 1). There was no statistically significant difference in the age of the patients in the tramadol

**Table 1. Number of patients, average age and duration of surgery according to the patient groups**

Patient group	No of patients	Pain scores	Average age (years)	Average surgery duration (min.)
I (n=30)	7	5	58.5	110.1
	14	6	55.4	105.0
	8	7	55.5	99.7
	1	8	67.0	95.0
	30	6.10	57.9	102.4
II (n=30)	9	7	61.7	103.5
	15	8	58.5	102.4
	5	9	56.4	99.4
	1	10	66.0	110.0
	30	7.93	59.4	103.8
III (n=30)	3	7	59.0	95.6
	5	8	58.0	98.8
	6	9	53.5	96.3
	16	10	58.0	104.1
	30	9.17	57.1	98.7

Group I, Tramadol; Group II, Metamizole; Group III, control

( $p = 0.635$ ) and metamizole ( $p = 0.154$ ) group comparing to the control group, as well as between the tramadol and metamizole groups ( $p = 0.326$ ).

There was no statistically significant difference in the length of the surgery when comparing the duration of the tramadol ( $p = 0.155$ ) and metamizole ( $p = 0.722$ ) group with the control group, as well as between the tramadol and metamizole groups ( $p = 0.269$ ).

Levene's test for three groups showed equal ( $p = 0.057$ ), which is bigger than 0.05 (evaluation mistake); therefore, the variances of these three samples did not differ statistically (if the Levene's test is significant, than the variances are not equal). It was confirmed that variability between the groups was bigger than variability inside the groups (Table 1).

Based on the number of the patients included in the study, we calculated the possibility of 99% that the study will reveal the difference in the treatment on double-sided level of  $p = 0.05$  significance, considering that the real difference between the treatments was 1.833 times bigger than the standard deviation.

## DISCUSSION

Our study investigated the effect of metamizole and tramadol in preemptive analgesia in patients from Sarajevo Canton. Patients received analgesics via intramuscular (i.m.) application on the operating table before the induction into anaesthesia. All patients underwent the same anaesthesia induction procedure and had the same balanced anaesthesia. The well-known fact is that movement of patients

immediately postoperatively enhances the feeling of pain due to tightening of the abdominal muscles, so that was not our interest at that moment (8). We did not perform additional measurements of pain intensity (12h or 24h) (8) because our goal was to determine the effect of a single preemptively given dose of tested analgesic, and not the prolonged analgesic effect of the same analgesic, as well as the effect of repeated doses that are moving out of the scope of preemptive administration. Since the research was in accordance with the methodology foreseen, we did not need to develop a separate flow chart of the study. The NPS scale was used, according to which all patients evaluated their pain. In the control group, postoperative pain was the strongest. In the patients who received metamizole we found out that the effect of preemptive analgesia was significant in 15 of them who evaluated pain with a score of 8. Patients receiving preemptive tramadol showed significantly lower intensity pain. Tramadol is a more pharmacologically potent analgesic in the opioid group, which in our patients also showed a significant analgesic effect in preemptive analgesia (9). The effects of tramadol are not well known. Its pharmacological effect is achieved by different actions at multiple receptors; it stimulates „mu“ opioid receptors and releases serotonin (10). Tramadol also blocks NMDA, muscarinic and nicotinic acetylcholine receptors (10). Its specific analgesic effect is also confirmed by the partial antagonistic effect of naloxone, which only partially eliminates the effect of tramadol (11). Unlike tramadol, metamizole is a long-used analgesic for various types of pain, including postoperative pain (11). The mechanism of action of metamizole is based on the inhibition of prostaglandin synthesis in peripheral tissues and in the central nervous system (CNS) (12). Its analgesic effect is rather weaker than the one of tramadol (12), as shown by our study.

We could not find the same design studies online, and therefore we compared similar studies which used metamizole and tramadol separately in comparison with other analgesics in preemptive analgesia in hysterectomy (12) or similar or other operative procedures (12). In a study that covered 60 patients for elective operations, tramadol i. v. 2mg/kg and paracetamol 15mg i. v. were used 15 minutes before the induction to general anaesthesia; significantly better pain reduction was displayed in the paracetamol group, than in the tramadol group

postoperatively, as well as a lower need for extra dosage of analgesics postoperatively (13).

Also, in the study in which the preemptive diclofenac and metamizole were used in the gynaecological operations of 108 patients divided into two groups, analgesia was given immediately after the induction to general anaesthesia showing the positive preemptive analgesic effect of diclofenac and metamizole, with precedence of diclofenac effects, but without significant difference 6 hours after the application of the analgesic ( $p=0.13$ ) (14).

Preemptive use of analgesics in surgery is a known method of analgesia and it is used in various fields of surgery (15). Analgesics can be administered preemptively in a variety of ways (15). Oral administration of analgesics also produces good results in reducing pain. A study in which gabapentin and tramadol were used orally, showed a satisfactory postoperative effect (16). Application of i. v. dexketoprofen trametamol is also a favourable option for preemptive pain therapy in dental surgery (17). Some studies favour the preventive multimodal approach to the treatment of postoperative pain over preemptive analgesia (18). In a study where tramadol was administered subcutaneously preemptively, the need for opioids was decreased postoperatively (19). In the study by Sittl et al. the success of preemptive analgesia was shown in postoperative period, but to prevent chronic pain, prevention is proposed on a multimodal basis (20). Wang et al. in a study of preemptive i.v. application of 100mg tramadol with the application of a bolus dose of 0.5mg/kg of tramadol immediately after surgery with a continuous infusion of 0.1mg/kg/h of tramadol for 48h period with a PCA application of morphine 0.02mg/kg, found a significantly more beneficial effect in the reduction of pain, reduction of side effects and patient satisfaction, than in the placebo control group (21). In the study of Lu et al. a significantly better effect was found in the flurbiprofen axetil group comparing to the tramadol group (22). A study that investigated the effect of i. v. administered ketorolac and metamizole preemptively in children under various operations with inhaled anaesthesia, showed a satisfactory analgesic effect (23). A study analysing the preemptive effect of ibuprofen and metamizole on diabetic retinopathy laser surgery showed a satisfactory effect of both analgesics during sur-

gery (24). Many studies confirm the preemptive analgesic effect of metamizole and tramadol, as well as other analgesics in the postoperative period in terms of reduced opioid use postoperatively. These studies should be continued in order to find out which analgesics, individually or in combination, produce the best results in terms of analgesia and in terms of reducing side effects.

In conclusion, preemptive administration of analgesics has a beneficial analgesic effect on

postoperative pain. The effect of tramadol administered preemptively prior to the introduction of general anaesthesia in immediate postoperative analgesia is significantly more favourable than the effect of metamizole.

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## TRANSPARENCY DECLARATIONS

Competing interests: None to declare.

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