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## Preventive effect of 100 mg tramadol in postoperative pain

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### SUMMARY

**Objective:** To evaluate the analgesic effectiveness of tramadol in the prevention of postoperative pain in patients who underwent acute appendicitis. **Material and methods:** It harpvenedention of theyrned i by ultrasound was carried out a controlled, double-blind, and randomized clinical study, on, patients who have been operated due to acute appendicitis at the hospital «Guillermo Luis Fernández Hernández-Baquero», Moa, Holguín, Cuba, during the months going from October 2005 to May 2006; 86 patients were selected. They were divided into two groups of 43 patients each. Group I: tramadol 100 mg and; Group II: intravenous metamizol 2 g, both 30-minutes treatments were given before the surgery. General anesthesia was applied; and systolic blood pressure, cardiac rate and hemoglobin saturation (HbSat) were recorded during several stages of the anesthetic process: basal, transoperative, and at the first 180 minutes of the postoperative, as well as the most frequent adverse effects. Pain intensity was measured in the postoperative period through the Analogous Visual Scale (AVS). **Results:** Pain significantly decreased through the use of tramadol when compared with the placebo ( $p < 0.05$ ); nausea was prevailing (16.3%), followed by vomits in the 13% of the patients who used tramadol. **Conclusions:** Tramadol at a dosage of 100 mg in the preoperative period contributes to the reduction of the intensity of postoperative pain.

**Key words:** Tramadol, preventive analgesia, post-operative pain.

### RESUMEN

**Objetivo:** Evaluar la eficacia analgésica de tramadol en la prevención del dolor postoperatorio en pacientes intervenidos de apendicitis aguda. **Material y métodos:** Se realizó un ensayo clínico controlado, doble ciego, aleatorio en pacientes intervenidos de apendicitis aguda en el Hospital "Guillermo Luis Fernández Hernández-Baquero", Moa, Holguín, Cuba, durante los meses de octubre 2005 a mayo de 2006; se seleccionaron 86 pacientes, los cuales se dividieron en dos grupos de 43 cada uno. Grupo I: tramadol 100 mg y grupo II: metamizol 2 g, intravenoso, 30 minutos antes de la intervención. Aplicamos anestesia general orotraqueal y se registró tensión arterial sistólica, frecuencia cardíaca y saturación de la hemoglobina (SatHb) en varias etapas del acto anestésico: basal, transoperatorio, y primeros 180 minutos del postoperatorio así como los efectos adversos más frecuentes. Se midió la intensidad del dolor en el postoperatorio a través de la Escala Visual Análoga. **Resultados:** Se obtuvo un descenso significativo del dolor con el uso de tramadol comparado con metamizol ( $p < 0.05$ ); predominaron las náuseas (16.3%) seguido de vómitos en el 13% de los pacientes que usaron tramadol. **Conclusiones:** El tramadol a dosis de 100 mg en el preoperatorio contribuye a la reducción de la intensidad del dolor postoperatorio.

**Palabras clave:** Tramadol, analgesia preventiva, dolor postoperatorio.

## INTRODUCTION

The pain causes anxiety for those who suffer it, inducing responses that may involve physiological changes that modify normal patterns in organs and systems of the economy.

The term "preventive analgesia" suggests that an antinociceptive intervention, carried out preoperatively, could prevent or reduce postoperative pain, as this intervention would prevent the central sensitization, thus possibly reducing the analgesic dose used in the postoperative period and its side effects, and therefore improving its efficacy and safety<sup>(1-7)</sup>.

Tramadol is a synthetic analogue of the opioid family, it has been studied and produced in 1977 in Germany, where extensive experience in its clinical use was developed. Its introduction in Latin America and U.S. data from 1993 and 1995, respectively<sup>(8)</sup>. The chemical structure corresponds to a piperidine related to the phenanthrene group of the opium alkaloids, including the codeine and the morphine. The chemical structure corresponds to a piperidine related to the phenanthrene group of the opium alkaloids, including codeine and morphine. The mechanism of action is mixed, opioid and non-opioid<sup>(9)</sup>. Its affinity for the m receptors has been confirmed by studies of selective block with naloxone, and on the other hand, the effect on increasing the reuptake of norepinephrine and 5-hydroxytryptamine has been demonstrated through inhibition with yohimbine and ritanserin. The analgesic potency of tramadol in relation to morphine is considered of 1/6 and 1/10<sup>(10-12)</sup>.

Its mean analgesic effect by oral route is of 6 hours at single doses and its latency is approximately 30 minutes. The effect of tramadol on anesthetic requirements is given by its analgesic action that positively influences a reduction of minimum alveolar concentration required to achieve an adequate anesthetic level in patients who received the drug<sup>(13)</sup>.

The metamizol, a derivative of aminopyrine and potent analgesic, is also often used in clinic due its antipyretic action. In its analgesic action appears to exist a central component of action.

The pyrazolones, as compared to other nonsteroidal anti-inflammatory drugs, appear to be less aggressive on the gastric mucosa and they do not cause bleeding complications<sup>(14,15)</sup>. The metamizole seems to have a favorable profile in acute postoperative pain control in major outpatient surgery<sup>(16,17)</sup>.

Considering this, the objective of this study was to evaluate the analgesic efficacy of 100 mg tramadol in postoperative pain management in patients who underwent acute appendicitis.

## MATERIAL AND METHODS

A randomized, double blind, controlled clinical trial in patients who underwent surgery for acute appendicitis at the

Hospital "Guillermo Luis Fernández Hernández-Baquero", Moa, Holguín, Cuba from October 2005 to May 2006 was performed, prior authorization from the Research and Ethics Committee and informed consent of patients. Individuals aged between 18 and 60 years and with ASA physical status I and II were included in this study. In total, 86 patients were selected, they were divided into two groups of 43 each:

Group I: 100 mg Tramadol

Group II: 2 g Dipyrrone

Both dissolved in 100 mL of 0.9% saline solution were administered intravenously 30 minutes before the intervention.

The patients were premedicated with 0.02 mg/kg IV midazolam in the preoperative room. Electrodes were placed for continuous recording of electrocardiogram (ECG), systolic blood pressure (SBP), heart rate (HR), and saturation of hemoglobin (HbSat) in various stages of anesthesia: baseline, transoperative, and first 180 minutes after surgery, as well as the most common side effects.

Anesthesia was induced with propofol at 2 mg/kg dose, prior administration of 1.5 µg/kg fentanyl, 0.1 mg/kg vecuronium and 1.5 mg/kg 2% lidocaine in all patients. They were coupled to a volume ventilator SERVO 900D with a tidal volume from 8 to 10 mL/kg to achieve a PETCO<sub>2</sub> of 35-45 mmHg. Nitrous oxide-oxygen mixture with an inspired oxygen fraction (FiO<sub>2</sub>) of 0.35-0.40 and analgesic dose of fentanyl by continuous infusion according to patient demand, as well as 1 µg/kg/min vecuronium by infusion were used during maintenance.

At the conclusion of surgery, the intensity of pain was measured in the recovery room, within 30 minutes and in the first 180 minutes using the Visual Analog Scale (VAS)<sup>(18)</sup> from 0 to 10, where 0 = no pain and 10 = most intense pain. Before initiating the study, patients were instructed on how to use the VAS to indicate the intensity of pain.

HR and SBP hemodynamic parameters and VAS will be compared in order to assess the quality of analgesia of both drugs.

Summary measures for qualitative (percentages) and quantitative (arithmetic mean and standard deviation) variables were included for the statistical analysis. Student's t test was used for comparison of hemodynamic parameters. All results with  $p < 0.05$  were considered statistically significant.

## RESULTS

In total, 86 patients were studied, they were divided into two groups randomly. The patients' mean age in the group I was  $42.5 \pm 15.4$  years. Group II:  $39.6 \pm 14.2$  years. In group

I there were 26 women (60.5%) and 17 men (39.5%), and group II there were 18 women (41.9%) and 25 men (58.1%). In group I, 28 (65.1%) and 25 patients (58.1%) were classified as ASA I and ASA II, respectively. In group II, 31 (72%) and 12 (28%) patients were classified as ASA I and ASA II, respectively.

Systolic blood pressure was recorded at different perioperative periods; values of  $115.33 \pm 2.97$  mmHg were observed in group I within the first 60 minutes of perioperative period, and values of  $120.61 \pm 6.30$  mmHg were observed in group II, which established a statistically significant difference of 5.28 with  $p = 0.004$ . By comparing the results within 180 minutes, we obtained values of  $118 \pm 2.08$  mmHg in group I, and values of  $123.41 \pm 6.21$  mmHg in group II, being the difference of 5.41, which established a statistically significant difference ( $p = 0.001$ ) (Figure 1).

Heart rate variations in postoperative period are shown in Figure 2. Regarding the assessment of pain, significant decrease of VAS was obtained in recovery period and the first 60 minutes after surgery in group I as compared to group II ( $p = 0.001$ ), and these results were maintained up to 180 minutes (Figure 3).

In group I, the predominant side effect was nausea (16.3%), followed by vomiting in 13% of patients. In group II, the percentage of adverse effects was nausea in 11.6%.

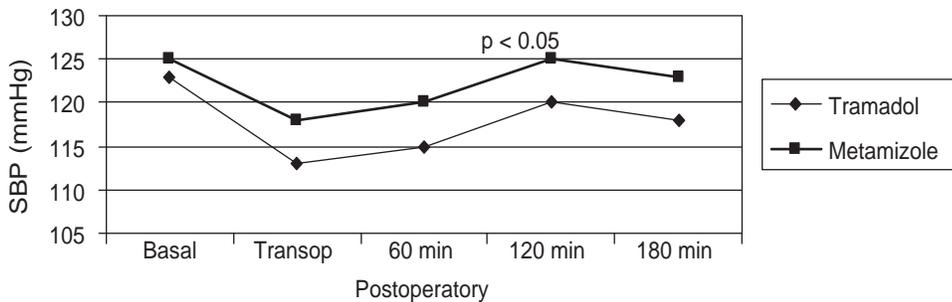
## DISCUSSION

In the results of our investigation, significant decrease in the intensity of postoperative pain was observed in patients receiving tramadol ( $p = 0.05$ ) as compared to placebo. There are reports indicating that this opioid is a good alternative for different types of even chronic and acute pain<sup>(19-21)</sup>.

Lehmann (22), in his double-blind study, reported adequate analgesia by administrating 50 mg IV tramadol in the postoperative period and getting a similar effect to 5 mg morphine or 150 mg clonidine, in our case we administered 100 mg preoperatively and the results were acceptable.

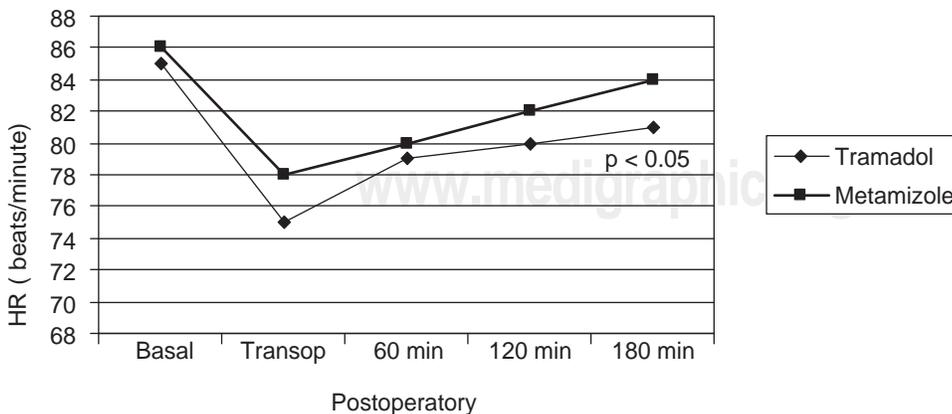
Various reported studies, such as study by McQuay et al<sup>(23)</sup>, which used this opioid in the prevention of postoperative analgesia, as well as work by Edwards et al.<sup>(24)</sup> using the oral route for combining it with paracetamol, have obtained higher results as compared to other analgesics, such as the administration of 400 mg ibuprofen. Good analgesia was obtained in our investigation, without combining it with another analgesic, only comparing it with an active placebo such as metamizol which is used in research.

We observed significant differences in hemodynamic parameters ( $p < 0.05$ ) which we used as a indicator of the analgesic state.



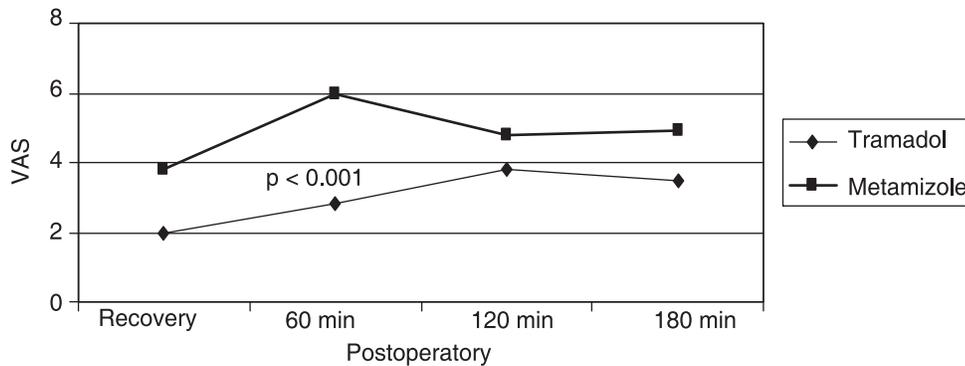
Transop = transoperatory

**Figure 1.** Systolic blood pressure with tramadol vs metamizole in preventive analgesia of patients operated of acute appendicitis.



Transop = transoperatory

**Figure 2.** Behavior of heart rate with tramadol vs metamizole in preventive analgesia of patients operated of acute appendicitis.



**Figure 3.** VAS pain at different times of evaluation.

In our case, tramadol showed 16.2% of prevalent nausea, a result that does not match what has been published by Aygun<sup>(25)</sup> et al, who compared the effects of intravenous tramadol with intravenous fentanyl and epidural tramadol, where the incidence of nausea and vomiting was 40%. In general, both results support the literature which describes

the occurrence of these side effects in patients treated with this drug.

By the results observed in our study, we conclude that the use of tramadol at 100 mg doses in the preoperative period helps to reduce the intensity of postoperative pain.

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