

Postoperative analgesia with nimesulide vs metamizole in appendectomies. Prospective randomized study

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SUMMARY

Antecedents: One of the techniques of preventive analgesia to treat the postoperative pain includes the use of analgesic anti-inflammatory not conventional estereoids. **Objective:** To compare the postoperative analgesic effectiveness of nimesulide in front of metamizole in appendectomy. **Material and method:** We were carried out a controlled clinical rehearsal, in the Hospital «Guillermo Luis Fernández Hernández-Baquero», Holguín, Cuba, during a period of ten months. 88 patients were selected in total, which were divided at random in two groups of 44 patients each one: Group I: nimesulide 200 mg, via oral, 120 minutes before proceeding surgical and Group II: metamizole 2 g intravenous, after the induction of the anesthesia and premedication with midazolam 0.02 mg/kg IV. Apply anesthesia general orotracheal and registered arterial pressure, heart frequency and saturation of the hemoglobin in several stages of the perioperative as well as the most frequent adverse effects. The intensity of the pain was measured in the postoperative one through the Similar Visual Scale. **Results:** A decrease of the pain was observed in the postoperative one in both groups, more marked with the patients of the Group II, not being significant at the 6 hours ($p = 0.277$). The adverse effects found in the Group I: vomits in 2 patients. In the Group II: nauseas in 8 cases and vomits in 6 patients. **Conclusions:** The nimesulide and metamizol administrations are effective when being used as preventive analgesia in surgery of patient to which was carried out appendectomy.

Key words: Preventive analgesia, nimesulide, postoperative pain, metamizole.

RESUMEN

Antecedentes: Una de las técnicas de analgesia preventiva para tratar el dolor postoperatorio incluye el uso de analgésicos antiinflamatorios no esteroideos convencionales. **Objetivo:** Comparar la eficacia analgésica postoperatoria de nimesulida frente a metamizol en apendicectomías. **Material y método:** Se realizó ensayo clínico controlado, en el Hospital «Guillermo Luis Fernández Hernández-Baquero», Holguín, Cuba, durante un período de diez meses. Se seleccionaron 88 pacientes, los cuales se dividieron al azar en dos grupos de 44 pacientes cada uno: Grupo I: nimesulida 200 mg, vía oral, 120 minutos antes del proceder quirúrgico y Grupo II: metamizol 2 g intravenoso, luego de inducción de la anestesia. Se premedicaron con midazolam 0.02 mg/kg IV. Aplicamos anestesia general orotraqueal y se registró tensión arterial media, frecuencia cardíaca y saturación de la hemoglobina en varias etapas del perioperatorio 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 observó una disminución del dolor en el postoperatorio en ambos grupos, más marcado con los pacientes del Grupo II, no siendo significativo a las 6 horas ($p = 0.277$). Los efectos adversos encontrados en el Grupo I: vómitos en 2

pacientes. En el Grupo II náuseas en 8 casos y vómitos en 6 pacientes. **Conclusiones:** La administración de nimesulida y metamizol resultaron eficaces al ser utilizados como analgesia preventiva en cirugía de apendicectomía.

Palabras clave: Analgesia preventiva, nimesulida, dolor postoperatorio, metamizol.

INTRODUCTION

Preventive analgesia was originally proposed by Patrick Wall in 1988 and introduced by Woolf in 1991 by demonstrating that administration of opioids and/or local anesthetics before a noxious stimulus was preventing the development of the medullary hyperexcitability induced by injury and an increased pain perception⁽¹⁻⁴⁾. The principle on which is based consist of blocking nociceptive pathways before a nociceptive stimulation occurs so that the central sensitization is avoided from the preoperative, achieving in this way diminish the intensity of pain and the used doses of analgesics⁽⁵⁾.

The non-steroidal anti-inflammatories (NSAIDs) form a large group of drugs sharing therapeutic actions and side effects⁽⁶⁾. They do not produce respiratory depression and do not induce tolerance or physical dependence. Their analgesic efficacy is limited and not dose dependent. They are effective for treating mild-moderate pain, and in some cases may control the acute pain of inflammatory, postoperative, and colic component^(7,8).

NSAIDs inhibit the synthesis of prostaglandins that play an important role in pain-response mediation. By reducing the production of these pain-mediating metabolites, these drugs may play an important role in the treatment of postoperative pain⁽⁹⁻¹¹⁾.

The nimesulide is a non-steroidal anti-inflammatory drug which has analgesic properties whose administration may also be orally and rectally. Peak plasma concentrations are achieved within 1.22 to 3.16 hours; its absorption is completed through gastrointestinal tract, extensive liver metabolism and renal excretion. There is no data showing which it inhibits platelet activity or produces renal function disorders, on the other hand it is less ulcerogenic than the other NSAIDs. In addition to inhibiting cyclooxygenase (COX)₂, it appears to act on the tumor necrosis factor (TNF) which is responsible for the release of other hyperalgesic cytokines⁽¹²⁻²¹⁾.

The metamizole –introduced into clinical practice in 1922– is a derivative of aminopyrine and a potent analgesic, is also widely used in clinics for its antipyretic activity. The mechanism of analgesic action is not clearly defined, but there seems to be a central component of action at the periaqueductal and gray matter or the spinal cord and its actions on the peripheral system: arginine/nitric oxide/

cGMP⁽²²⁻²⁴⁾. The metamizole seems to have a favorable profile in the control of acute postoperative pain⁽²⁵⁻³⁰⁾.

The aim of our research was to compare the postoperative analgesic efficacy of two non-opioid analgesics drugs in appendectomies: metamizole –commonly used in our environment– versus dipyrone, whose use is not common.

MATERIAL AND METHODS

A double blind, controlled clinical trial was performed in the General Teaching Hospital “Guillermo Luis Fernández Hernández-Baquero”, Moa, Holguín, Cuba, from March to January 2007, after prior authorization by the Ethics Committee and Informed Consent of patients. In total, 88 patients were selected, which were divided randomly into two groups:

- Group I: Nimesulide (n = 44) 200 mg orally 90 minutes before the surgical procedure.
- Group II: Metamizole (n = 44) 2 g intravenously after anesthetic induction.

Inclusion criteria:

- Age between 19 and 55 years old.
- Classification I and II according to the American Society of Anesthesiologists.
- Patients diagnosed with acute appendicitis.

Exclusion criteria:

- Hypersensitivity to NSAIDs (referred).
- Quantitative and qualitative disorders of coagulation.
- Hypovolaemia
- Chronic patients consuming other NSAIDs.

They were premedicated with midazolam 0.02 mg / kg (IV).

Electrodes were placed for continuous recording of electrocardiogram (ECG), blood pressure of a non-invasive (MBP), heart rate (HR), hemoglobin saturation (HbSat).

In all patients an anesthetic induction was performed with thiopental at a dose of 4 mg / kg, after administration of fentanyl 1.5 mg/ kg, vecuronium 0.1 mg/kg and 2% lidocaine 1.5 mg/kg. They were coupled to a SERVO 900D volume ventilator with a current volume of 8 to 10 mL/kg to achieve a PETCO₂ 35-45 mmHg. During maintenance a nitrous ox-

ide-oxygen mixture with a fraction of inspired oxygen (FiO_2) of 0.35-0.40 and an analgesic dose of fentanyl by continuous infusion according to patient's demand, as well as an infusion of vecuronium 1 mg/kg/ min were used. The residual muscle relaxation was treated with atropine and neostigmine.

The postoperative pain intensity was measured in the recovery room within 30 minutes, 2 hours, 4 hours, and 6 hours by visual analog scale (VAS)⁽³¹⁾:

- Mild pain (1 to 3)
- Moderate pain (4 to 6)
- Severe pain (7 to 9)
- Unbearable pain (10)

Tramadol 100 mg IV was used as the rescue medication.

The evaluated circulatory parameters HR and MBP were recorded at different times of the perioperative period with the purpose of achieving a higher objectivity of the pain degree.

The MBP was calculated according to the formula:

$$\text{MBP: SBP} + 2 \text{ DBP}/3$$

The most frequent adverse effects were recorded.

Summarized measures for qualitative (percentage) and quantitative (mean and standard deviation) variables were included for the statistical analysis. The Student's t test and analysis of postoperative analgesia with the Chi-square (χ^2) were used for comparison of the hemodynamic parameters. All p value < 0.05 was considered statistically significant.

RESULTS

In total, 88 patients were studied, which had been randomly divided in two groups. Group I (n = 44), patients treated with nimesulide 200 mg, and Group II (n = 44), patients treated with metamizole. Between the ages of 19 and 55 years. Gender: Group I: 18 women (41%) and 26 men (59%). Group II: 21 women (48%) and 23 men (52%). Weight: Group I: 73.8 ± 4.26 kg; Group II: 72.9 ± 4.25 kg. According to the classification of the American Society of Anesthesiologists; in the Group I: I = 30, II = 14. In the Group II: I = 32, II = 12.

A reduced postoperative pain in both groups, more markedly in the patients of the Group II, was observed in the VAS variable (Figure 1). However, it was not significant at six hours (p = 0.277).

The basal mean blood pressure for Group I was 92.2 ± 1.25 mmHg and mean was 85.3 ± 0.70 mmHg in the postop-

erative period. In the Group II: in the basal of 91.5 ± 1.0 mmHg and in the postoperative period of 84.0 ± 0.26 mmHg with statistical significance (p < 0.01) (Figure 2).

The changes observed in the heart rate for the Group I in the basal: a mean of 83.3 ± 2.91 beats per minute and 74.3 ± 1.02 beats per minute in the postoperative period. Group II: a HR of 78.5 ± 4.59 beats per minute in the baseline and 71.7 ± 0.95 beats per minute in the postoperative period with statistical significance (p < 0.01) (Figure 3).

Adverse effects found in the Group I were: vomiting in 2 patients (4.5 %). Nausea in eight cases (18%) and vomiting in six patients (14%) were reported in the Group II.

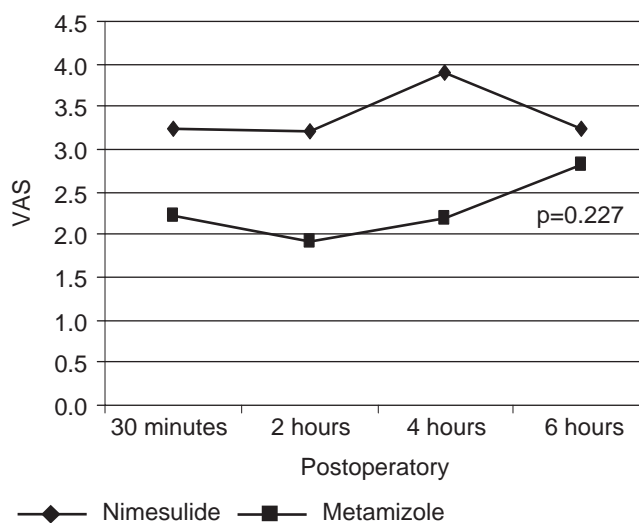


Figure 1. Temporary course of average VAS.

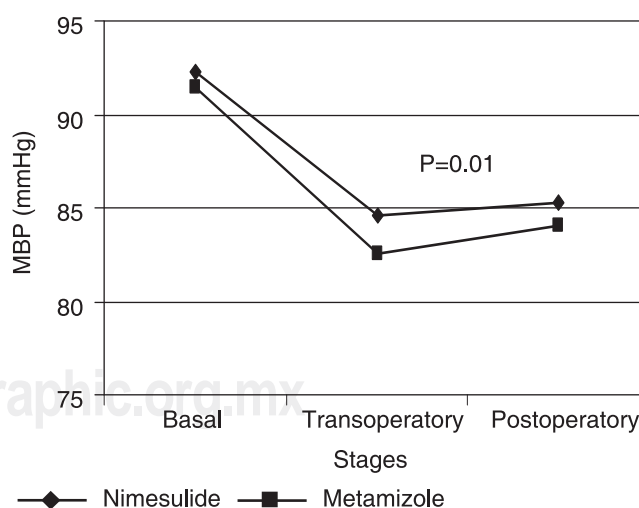


Figure 2. Behavior of the perioperative mean blood pressure in both groups.

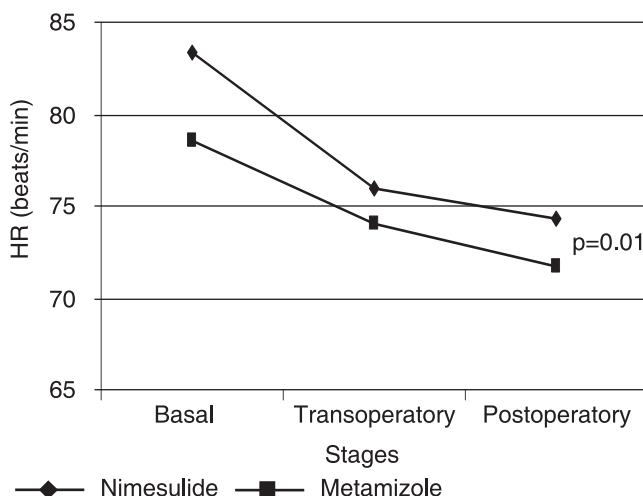


Figure 3. Behavior of perioperative mean heart rate in both groups.

DISCUSSION

The acute postoperative pain is common, severe in a high percentage of the cases, and managed poorly, causing suffering to the sick patient, and it is associated with complications in the respiratory, cardiovascular, digestive, as well as endocrine-metabolic function.

In our research, a favorable outcome was observed in relation to analgesia in the patients receiving both drugs, but better results were obtained with the use of metamizole in the different stages of the perioperative period. Kempe et al⁽³²⁾ in his randomized, double blind study including 40 ASA I-III patients who underwent surgery for breast cancer, compared dipirone 1 g vs paracetamol 1 g, administered 30 min before transferring the patient to recovery room, as well as every six hours for the first 24 hours, obtaining well results. However, five of the patients receiving metamizole showed hypotension; this complication was not seen in the

patients of our study, despite the administration of 2 g of such medication, but there was nausea in 18% and vomiting in 14% of the cases.

Rawal et al⁽³³⁾ reported few adverse effects with 120 patients undergoing to hand surgery. In our work, gastrointestinal disorders were not seen, by which we not agree with Torres et al⁽³⁴⁾ studies performed in 151 women undergoing abdominal hysterectomy, where 20.2% of the patients showed this adverse effect in comparison to tramadol 42.1%.

In other studies related to metamizole, the results have not been encouraging as our result, having other analgesics a higher efficacy such as the work of Yilmaz et al⁽³⁵⁾ where showed that naproxen and meloxicam were more effective, and the information reported by Kaufmann⁽³⁶⁾ where the oxycodone was better.

On the other hand, despite the controversial results with the use of nimesulide, which is associated with a higher risk of inducing hepatic injury in comparison with other NSAIDs⁽³⁷⁾, in our series, a 200 mg dose administered to adult patients in the preoperative period, we don't observed this complication. However, the results for the analgesia were good with a VAS not higher than 3. But in the case of metamizole, the quality was better; studies such as Alotti et al⁽³⁸⁾ when it was administered to 100 patients who underwent cardiopulmonary bypass surgery presented the same analgesic efficacy than COX-1 inhibitors such as naproxen.

Previous pharmacodynamic studies carried out with nimesulide⁽⁶⁾ have shown that this drug inhibits the synthesis of prostaglandins, very important biochemical mediators involving in the pain production, reason complementing our results supported by the hemodynamic parameters, although the results obtained with metamizole ($p = 0.01$) were significant in the postoperative period.

We concluded that both metamizole and nimesulide provide a well postoperative analgesia in appendectomies, with VAS values not higher than 3, although metamizole shown to be better in the administration regimen of the study's design.

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