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Comparative Study between Tramadol and Placebo in Knee Surgery under Local Anesthesia

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SUMMARY

Objective: To evaluate the analgesic effect of the hydrochlorate of tramadol epidural compared with placebo in the postoperative of patients programmed for knee surgery. **Material and methods:** we was carried out a controlled clinical rehearsal, blind double, in the hospital «Guillermo Luis Fernández Hernández-Baquero», Holguín, Cuba, during the months of february to august of the 2006; 84 patients were selected, which were divided at random in two groups of 42 patients each one; we apply anesthesia lumbar epidural and catheter was placed. The agent anesthetic employee went mepivacaine to 2% 5 mg/kg. We was administered by the catheter: Group I: tramadol 100 mg dissolved in 10 mL of solution saline physiologic 0.9% and Group II: solution saline physiologic 0.9%. It was valued heart frequency and tension arterial half transoperative and postoperative. The evaluation of the pain was carried out with Similar Visual Scale. The mensurations were carried out in three occasions: recovery, at the 2 and 4 hours of the postoperative one. They registered the most frequent secondary effects. **Results:** The evaluation at the 4 hours of the postoperative one reported slight pain in the group placebo: 16%; moderate pain with tramadol in 21% and in the placebo 67% of the cases ($p < 0.05$); 23.8% only presented severe pain in the group placebo. The opposing adverse effects were in the Group I nauseas and vomits in a 31 and 21%, respectively. **Conclusions:** The analgesia epidural with tramadol prolongs the anesthetic time with good analgesic quality.

Key words: Tramadol, epidural analgesia, postoperative pain.

RESUMEN

Objetivo: *Evaluar el efecto analgésico del clorhidrato de tramadol epidural, comparado con placebo en el postoperatorio de pacientes programados para cirugía de rodilla.* ***Material y métodos:*** *Se realizó ensayo clínico controlado, doble ciego, en el hospital «Guillermo Luis Fernández Hernández-Baquero», Holguín, Cuba, durante los meses de febrero a agosto del 2006; se seleccionaron 84 pacientes, los cuales se dividieron al azar en dos grupos de 42; aplicamos anestesia epidural lumbar y se colocó catéter. El agente anestésico empleado fue mepivacaína al 2% 5 mg/kg. Se administró por el catéter: Grupo I: clorhidrato de tramadol 100 mg disuelto en 10 mL de solución salina fisiológica 0.9% y Grupo II: solución salina fisiológica 0.9%. Se valoró frecuencia cardíaca y tensión arterial media transoperatoria y postoperatoria. La evaluación del dolor se realizó con Escala Visual Análoga. Las mediciones se realizaron en tres ocasiones: recuperación, a las 2 y 4 horas del postoperatorio. Se registraron los efectos secundarios más frecuentes.* ***Resulta-***

dos: *La evaluación a las 4 horas del postoperatorio reportó dolor ligero en el grupo placebo: 16%; dolor moderado con tramadol en el 21% y en el placebo un 67% de los casos (p < 0.05); sólo el 23.8% presentó dolor severo en el grupo placebo. Los efectos adversos encontrados en el Grupo I, náuseas y vómitos en un 31 y 21%, respectivamente.* ***Conclusiones:*** *La analgesia epidural con clorhidrato de tramadol prolonga el tiempo anestésico con buena calidad analgésica.*

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

INTRODUCTION

During the last years, it has been observed another way to control pain through the epidural route. Therefore, it has been given a wide range of drugs, among which there are: local anesthetics, opiates, α agonists, among others, which occasionally have been used together[1-6]. The analgesic technique, as well as the proper drug, should be individualized in every patient, taking into account the patient's psychological features, the type of surgery, or the type of pain to which the patient is being subjected, the pharmacokinetics of each medicine, as well as the selection of the most proper administration route, and the adverse effects.

To provide post-surgical analgesia with minimal or no side effects will keep on being a great challenge. Nowadays, post-operative analgesia is one of the most studied topics and of a great concern for anesthesiologists. The route of pain and the drugs used to eliminate it, make it responsible for the charge of managing it[5].

Epidural route, as a choice for post-operative pain management, presents the advantage that it may be given to patients that have been subjected to thorax surgery[7], upper and low abdominal surgery[8], and in gynecologic-obstetric patients[9,10], as well as in those patients subjected to orthopedic surgeries[11]. Epidural route presents minimal undesirable effects, early ambulation and diminution of factors that alter the residual functional capacity, and therefore, a quick recovery. Tramadol hydrochloride is an opiate analgesic that acts centrally. It is a pure and non-selective agonist in opiate μ, δ and κ receptors, with a great affinity for m receptors. Other mechanisms contributing to its analgesics effect are: inhibition of neuronal recapture and improvement of serotonin release.

Over the 90% of this compound is absorbed when being administered through oral route. Absolute availability fluctuates around the 70%, independently from the concomitant ingestion with food. The average elimination time, $t^{o}\beta$, is of around six hours, independently from the administration route. This drug is metabolized by N and O demethylation and the conjugation of the products from O-desmethyl tramadol with gluconic acid. Only O-desmethyl tramadol is pharmacologically active[12]. Tramadol offers a safe choice for opiate epidural administration[4,8,13].

The objective of the present study is to evaluate the analgesic efficacy of tramadol hydrochloride through epidural route, comparing it against a placebo in the immediate post-operative period of patients programmed for knee surgery.

MATERIAL AND METHODS

It was carried out a clinical, controlled, double blind study at the "Guillermo Luis Fernández Hernández-Baquero" Hospital, in Moa, Holguín, Cuba, during the months of February to August 2006, with the previous authorization from the Committee of Ethics and Research and under the patients' informed consent. Eighty-four patients were selected, who were randomly divided into two groups of forty-two patients each.

It was included patients with elective knee surgery, with ages ranging from 18 to 55 years old, with a classification of the American Society of Anesthesiology (ASA) I in the groups I and II. Those patients with blockade contraindications or having received opiates before, were excluded from the study.

The monitoring consisted of Mean Blood Pressure (MBP) measurement though the indirect method by means of a sphygmomanometer (systolic arterial tension + 2 [diastolic arterial tension/3]), heart rate (HR) and pulse oximeter.

The patients were medicated with midazolam at a dose of 30 μg/kg IV in the immediate pre-operative period.

Both groups were practiced a previous hydration with 10 mL/kg of Ringer Lactate solution; patients were placed in lateral decubitus position. Besides this, asepsis and antisepsis of the lumbar-sacrum area was practiced and it was performed a puncture at the level of L2-L3 o L3-L4 with Touhy diameter 18 needle. The epidural space was localized through resistance loss, and through it, a catheter with cephalic direction was placed. The anesthetic agent was 2% mepivacaine 2% at a dose of 5 mg/kg.

After 10 minutes of the beginning of the surgery, it was administered through the catheter:

- Group I: *100 mg* of *tramadol hydrochloride* in 10 mL of 0.9% physiological saline solution
- Group II: *0.9% physiological saline solution*

Pain evaluation was performed through the Visual Analog Scale (VAS) with figures from 0 to 10[14].

- Light pain (1 to 3)
- Moderate Pain (4 to 6)
- Severe pain (7 to 9)
- Intense pain (10)

According to pain intensity, 2 g of IV metamizol was given to the patients suffering from light to moderate pain, and 50 mg of IM (intramuscular) meperidine (demerol) to those patients who presented severe pain.

The measurement was performed in three occasions, the first record was taken in the recovery room, the second record to hours after the first, and the third one 4 hours after the post-operative period.

It was evaluated the HR (heart rate), the (trans-operative and after the drug administration) basal MBP, as well as the side effects.

The obtained data was recorded in a record sheet. For the statistical analysis of the hemodynamic constants, it was used mean, standard deviation, and the Student's "t" test. For the analysis of the post-operative analgesia through the Chi-square (χ^2) test (distribution), the values of $p < 0.05$ were considered as significant.

RESULTS

Eighty-four patients were studied. They were divided into two groups in a randomized way. Age showed a mean of 34.84 ± 13.2 years old for Group I; and 40.2 ± 13.3 years old in el Group II. Sex in Group I: 14 women (33%) and 28 men (67%). Group II: 18 women (43%) and 24 men (57%). The mean surgical time was of 76 ± 18 minutes. The times between the first tramadol administration and the 1st, 2nd y 3rd pain evaluation were of 64 ± 12, 183 ± 04 and 306 ± 32 minutes, respectively.

Figure 1 shows the variations of MBP, with a value of 85.56 ± 2.28 mmHg for Group I, and 91.65 ± 2.21 mmHg for Group II, with statistical significance ($p = 0.014$).

The changes observed in HR at four hours of the post-operative period for Group I were: 77.36 ± 1.75 beats per minute.

For Group II: 91.34 ± 0.96 beats per minute, presenting statistical significance ($p = 0.0001$) (Figure 2).

In the Unit of Post-anesthetic Care, the 19% and 26% of the patients from Groups I y II, respectively, presented light pain; moderate pain in Group II in a 14.2%; and severe pain, in this same group in the 19% of the cases. The evaluation at 4 hours showed light pain only in Group I, in the 16% of the patients; moderate pain in Group I for the 21% of the patients, and in the 67% of the patients of Group II ($p < 0.05$) (Figures 3 y 4).

The most frequent adverse effects were nausea and vomits in Group I, with a 31% and a 21%, respectively.

DISCUSSION

Through the results obtained by the present study, it is demonstrated that there is a lengthening of the analgesic time when combining tramadol with local anesthetics. These results match to several publications[15-17].

Sekar *et al*[18], in a work carried out on 82 patients, using preventive analgesia, performed a comparative study using tramadol *versus* a placebo, through caudal epidural route in a spinal lumbar-sacrum surgery. They reported several cases

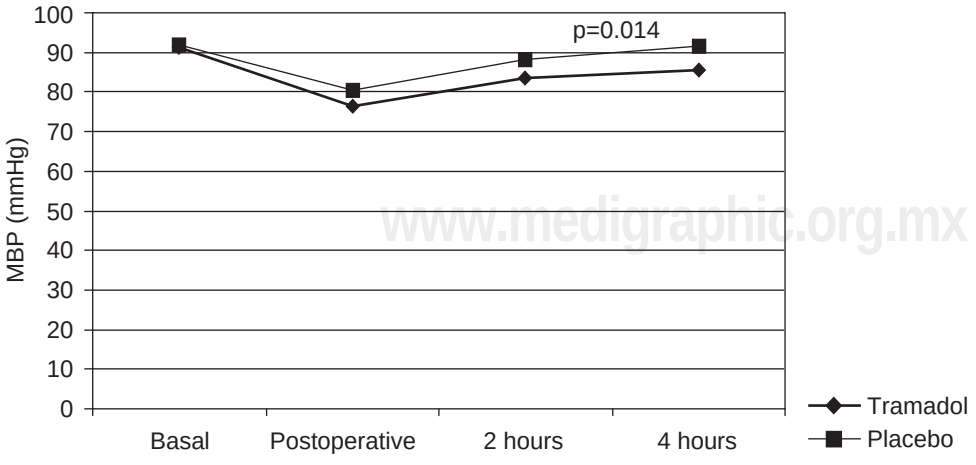

Figure 1. Behavior of mean blood pressure with epidural tramadol *vs* placebo in knee surgery

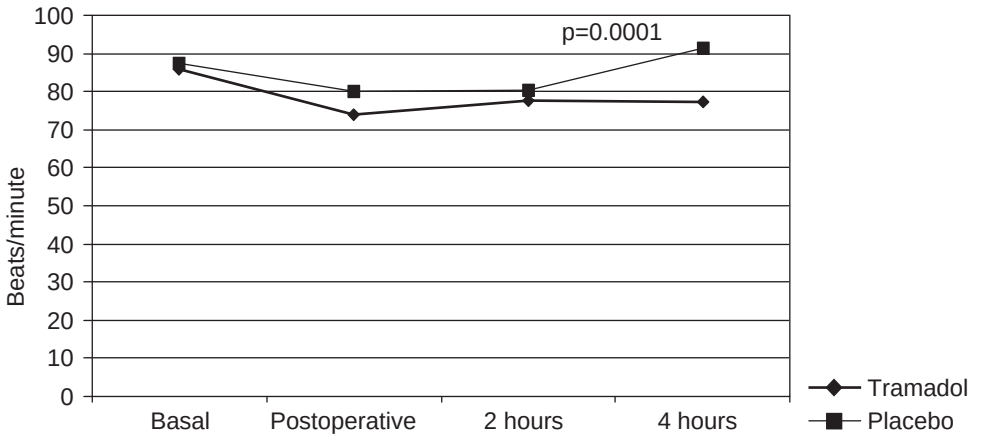

Figure 2. Behavior of heart rate with epidural tramadol *vs* placebo in knee surgery

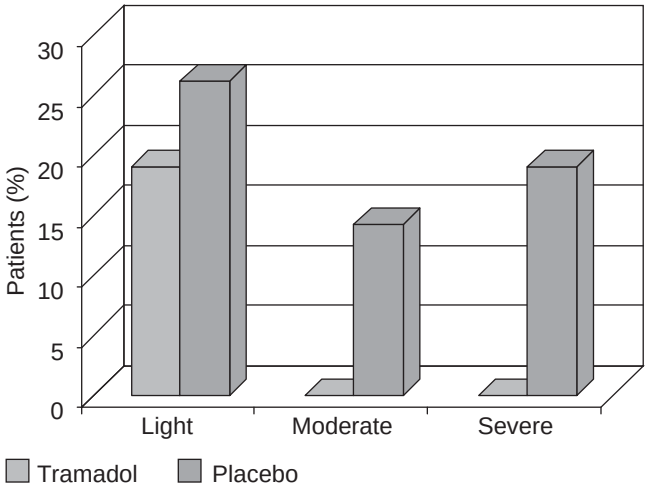

Figure 3. VAS in recovery of patients with epidural tramadol *vs* placebo in knee surgery.

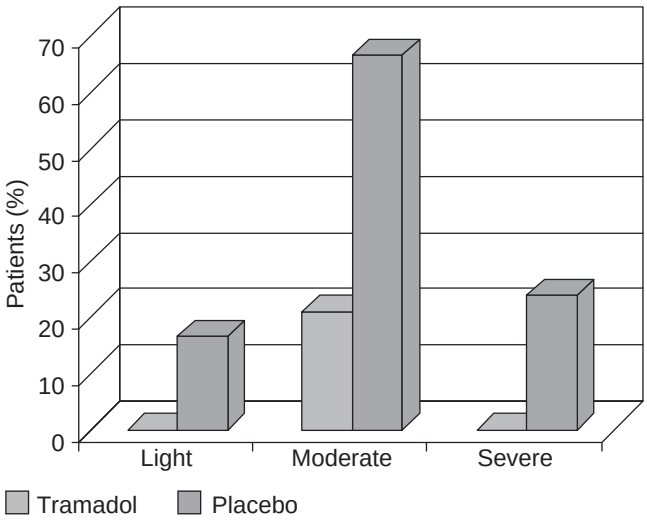

Figure 4. VAS 4 hours after surgery with epidural tramadol *vs* placebo in knee surgery.

presenting post-operative urinary retention, which was solved by means of a catheter. When compared with this study, we did not find this complication in ours.

Turker *et al*[19], in a clinical study on 40 patients to compare 100 mg of tramadol against 4 mg of morphine (both drugs given through epidural route), evaluated the beginning and the length of the analgesic effect. They found a few sedated patients and with decrease in oxygen saturation with the use of tramadol with respect to this last group. We did not observe this adverse effect in our study. In it, the most common adverse effects were nausea (31%) and vomits (21%).

In our research, the results of the post-operative hemodynamic parameters with the use of tramadol were significant regarding the MBP ($p = 0.014$) and the HR ($p = 0.0001$). This fact confirms the observations taken by other authors, who obtained satisfactory results[20].

In the study by Lin *et al*[17], using tramadol and epidural morphine, besides the combination of both drugs, they concluded that the analgesic efficacy is similar, but it changes from patient to patient; therefore, the dose of tramadol should be individualized. These authors, when combining the mentioned drugs, improved the efficacy and diminished the incidence of nausea and vomits.

Through the results obtained by our study, we can conclude that epidural analgesia produced by tramadol, in bolus and combined with local anesthetics, lengthens the anesthetic period with a good analgesia quality.

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