

# Comparative Prospective Study of the Management of Preventive Analgesia in Patients Undergoing Primary Total Knee Arthroplasty

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## ABSTRACT

**Background and Objective:** Preventive analgesia is one that is administered hours or days before a total knee arthroplasty in order to reduce postoperative pain. The objective of this study was to compare and analyze the clinical efficiency of the use of preventive analgesia in patients undergoing total knee replacement. **Methods:** Ninety-six patients, divided into two groups of 48 patients, were evaluated prospectively and comparatively between November 2018 and March 2019. Group A received preoperative analgesia with a combination of etoricoxib, tramadol, and paracetamol, orally, 2 hours before surgery. Control group B did not receive anything. The postoperative pain of the patients was evaluated according to their own records on a visual analog scale at 12, 24, 48, 72 hours and one week after surgery. **Results:** A significant difference was observed at 24 hours between both groups, pain was significantly less for group A ( $p = 0.001$ ), at 48 hours the difference was statistically lower than at 24 hours ( $p = 0.016$ ). It was also observed that the control group required a greater number of rescues, although the difference was only significant at 24 hours ( $p = 0.047$ ). **Conclusion:** The combination of etoricoxib, tramadol and paracetamol is effective, safe, cost-effective and easy to administer, with a low rate of adverse effects; which represents an adequate scheme for the management of preventive analgesia.

**Key words:** Knee arthroplasty; pain; preemptive analgesia.

**Level of Evidence:** IIb

## Estudio prospectivo comparativo del manejo de la analgesia preventiva en pacientes sometidos a artroplastia total de rodilla primaria

## RESUMEN

**Introducción:** La analgesia preventiva es aquella que se administra horas o días antes de una artroplastia total de rodilla con el fin de reducir el dolor posoperatorio. El objetivo de este estudio fue comparar y analizar la eficacia clínica de la analgesia preventiva en los pacientes sometidos a un reemplazo total de rodilla. **Materiales y Métodos:** Sesenta y seis pacientes, divididos en dos grupos de 33 pacientes, fueron evaluados prospectivamente y comparados entre noviembre de 2018 y marzo de 2019. El grupo A recibió analgesia preoperatoria con una combinación de etoricoxib, tramadol y paracetamol, por vía oral, 2 horas antes de la cirugía. El grupo B de control no recibió analgesia. El dolor posoperatorio de los pacientes se evaluó de acuerdo con sus propios registros en una escala analógica visual a las 12, 24, 48, 72 h y una semana después de la cirugía. **Resultados:** Se observó una diferencia significativa a las 24 h entre ambos grupos, el dolor fue significativamente menor en el grupo A ( $p = 0,001$ ), a las 48 h la diferencia fue estadísticamente menor que a las 24 h ( $p = 0,016$ ). También se observó que el grupo de control requirió más cantidad de rescates, aunque la diferencia solo fue significativa a las 24 h ( $p = 0,047$ ). **Conclusión:** La combinación de etoricoxib, tramadol y paracetamol representa es eficaz, segura, económica y fácil de administrar, y la tasa de efectos adversos de la analgesia es baja; por lo tanto, representa un esquema adecuado para el manejo de la analgesia preventiva.

**Palabras clave:** Artroplastia de rodilla; dolor; analgesia preventiva.

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## INTRODUCTION

Total arthroplasty is the procedure par excellence to treat degenerative knee disease. In the second half of the last century, this surgery was considered one of the most relevant advancements in surgery. In Argentina, it has become one of the most performed procedures in orthopedic surgery. However, up to 30% of the patients who undergo this procedure do not report significant improvements in their quality of life a year post-surgery. Postoperative pain is one of the main challenges faced by the surgeon. Studies show that patients who experience high levels of pain before the surgery will have worse outcomes and feel dissatisfied after the procedure. Many times, this implies a prolonged hospital stay, a torpid postoperative rehabilitation and a disturbance in the doctor-patient relationship.<sup>1</sup>

Several methods are used to prevent and treat postoperative pain: spinal anesthesia, peripheral nerve block, intra-articular injection, opioids, NSAIDs and corticosteroids during the postoperative period.<sup>2-4</sup>

We can define preventive analgesia as analgesia administered hours or days before a surgical procedure in order to reduce perioperative pain.<sup>5</sup>

The purpose of using analgesics immediately before the procedure to diminish postoperative pain and analgesic requirements is clear: to diminish acute pain caused by the injury, prevent pathological modulation of pain in the nervous system, prevent analgesic consumption, inhibit persistent postoperative pain and prevent chronic pain.<sup>3-5</sup>

Animal studies confirm that using analgesics before tissue aggression is more effective for pain management than using them after the procedure; however, its real clinical effectiveness is a controversial topic.<sup>6</sup>

Some clinical trials show that the timing of analgesia does not affect postoperative pain management, regardless of the analgesic method. Nevertheless, this conclusion may be wrong, since these trials are based on a short-term assessment of pain and there may be differences depending on the type of surgery.<sup>7,8</sup>

The objective of this study is to compare and analyze the clinical effectiveness of preventive analgesia in patients who undergo total knee replacement and its impact on the use of postoperative analgesia, rehabilitation and length of stay.

## MATERIALS AND METHODS

This study took place in the Hospital Británico, located in the Autonomous City of Buenos Aires. We conducted a prospective study protocol. 96 patients treated by two surgeons of our institution between November 2018 and March 2019 were randomized and evaluated.

Data collection and posterior evaluation were performed by V.D and I.S, physicians in the same Service, who were independent from the treating surgeons.

Two groups of 48 patients were formed: group A, which received a preoperative analgesic plan, and control group B.

Patients who presented moderate to intense unilateral knee pain with chronic degenerative knee disease (Ahlback classification equal to or greater than 3) and who had an indication for total knee replacement (TKR) were included in the protocol. Patients with 1) a previously known pathology or allergy contraindicating any of the drugs used in the protocol; 2) prosthetic revision surgery; 3) psychiatric history; 4) bilateral knee pain; and/or 5) chronic pain in a different joint were excluded from the protocol.

Both groups received the same type of anesthesia (spinal block and saphenous nerve block) as well as the same postoperative analgesic plan. In all cases, an internal parapatellar approach was performed and in no cases was a wound suction unit used. In 20 cases from group A and 5 from group B a tourniquet cuff was used during surgery. Its use depended on the treating surgeon's decision, based on the patient's history and/or surgical indication.

Both groups received the same postoperative analgesic plan during the first two days:

- 1) 2 ampoules of morphine, diluted in 500 ml saline, administered intravenously with a drip rate of 21 mL/hour;
- 2) Diclofenac 75 mg, administered intravenously every 2 hours;
- 3) 1 rescue ampoule of morphine, administered intravenously as needed by the patient.

After 48 hours, the analgesic plan was delivered orally in the following way (the patients continued the scheme after discharge):

- 1) Diclofenac 75 mg taken orally every 12 hours
- 2) Tramadol 100 mg taken orally as a rescue as needed (up to 100 mg every 8 hours)

All patients received omeprazole before meals for gastric protection, metoclopramide as rescue in case of nausea or vomiting and once-daily enoxaparin as DVT prophylaxis for 21 days post-surgery (40 mg taken subcutaneously).

Rehabilitation started immediately after surgery, and included isometric exercises in bed and standing and walking with aid (walker or canadian crutches) 12 to 24 hours after surgery depending on the patient's possibilities according to pain. Patients were asked to record their pain levels 12, 24, 48, 72 hours and a week after surgery according to a visual analog scale (VAS), as well as the number of opioid rescues used after hospital discharge. They were also asked about their level of satisfaction with the treating surgeon, side effects of the prescribed drugs and rehabilitation.

Data regarding opioid rescues during hospital stay, side effects of analgesia and length of stay were collected from the nursing report sheets and health records.

A statistical analysis was conducted with the data collected, using Mann-Whitney U test for two samples.

### Preventive analgesia protocol

All the patients received the corresponding preoperative indications 48 hours before surgery.

Only those in group A were asked to comply with the following orally-administered preventive analgesic plan:

- 1) Paracetamol 1g
- 2) Etoricoxib 90 mg
- 3) Tramadol 100 mg in tablets

The patients in this group were asked to take the medication 2 hours before surgery with a sip of water.

Both groups received a routine corticosteroid at induction by the anesthesia team.

## RESULTS

All data were collected and evaluated by two of the study authors.

In group A the average age was 73.4 years (40 to 89 years) and in group B (control) it was 72.5 years (42 to 87 years).

In group A 20 right knees and 28 left knees were operated, in group B 29 right knees and 19 left knees were operated.

Of the 48 knees in group A, 12 had valgus misalignment and 36 had varus misalignment; in group B, 10 had valgus and 38 had varus.

Group A was composed of 30 women and 18 men; group B was composed of 27 women and 21 men.

According to the analysis of data from the VAS (on a scale of 0 to 10) completed by the patients (Figure 1):

- 1) 12 hours after surgery, the difference between the two groups was statistically insignificant ( $p=0.716$ );
- 2) the greatest difference between group A and group B was observed 24 hours after surgery; pain levels were significantly lower for group A ( $p=0.008$ );
- 3) 48 hours after surgery, the difference was statistically lower than 24 hours after surgery, remaining statistically significant ( $p=0.019$ ).

In regard to the number of morphine rescues, we observed that the control group required a greater number of rescues, although the difference was statistically significant only after 24 hours ( $p=0.083$ ) (Figure 2).



Figure 1. Visual analog scale over time for the group with preventive analgesia and the control group.

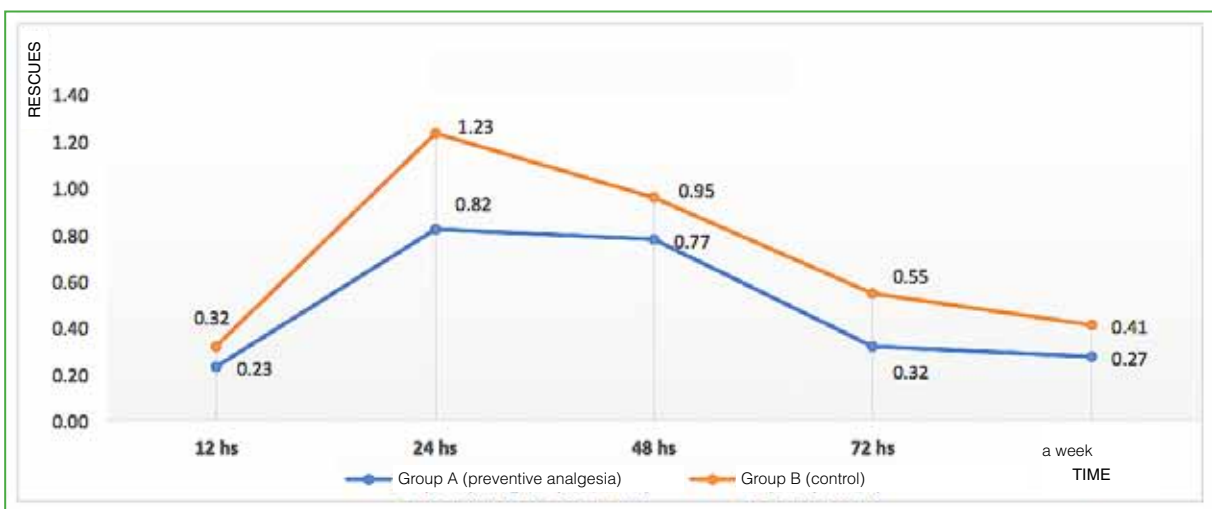


Figure 2. Rescue administrations over time.

All patients in group A started walking rehabilitation within the postoperative 24 hours, whereas group B did not start walking until 48 hours post-surgery, performing only sedestation and isometric exercises 24 hours post-surgery. 20 patients in this group reported they had only managed to do that due to postoperative pain. Therefore, patients in group A could start intrahospitalary rehabilitation earlier on and had shorter stays (Figure 3). In group A the average stay was 3.68 days and in group B it was 4.029 days ( $p=0.055$ ), which was statistically significant.

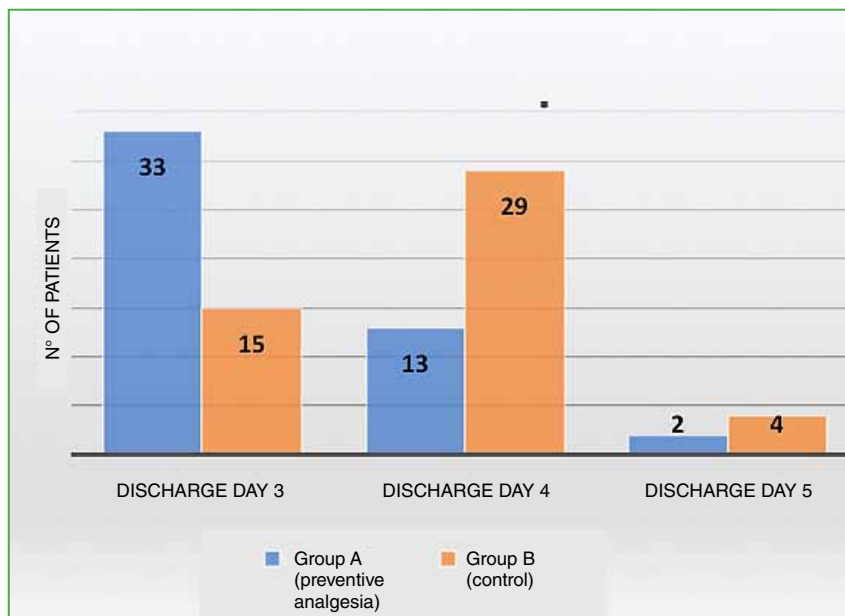
The patients were also asked about their level of satisfaction with their treating physician after surgery, on a scale of 1 to 5 (1=dissatisfied; 5=very satisfied). The average score in group A was 4.68 points and, in group B, 4.52 points, which was statistically insignificant ( $p=0.103$ ).

Regarding complications, we can mention the following: out of the 96 evaluated patients, 20 suffered minor complications: 9 (group A: 6 and group B: 3) suffered from gastrointestinal complications (diarrhea, nausea and/or vomiting); 4 (group A: 2 and group B: 2) suffered from fever in the immediate postoperative period ( $>38^\circ$ , one isolated episode); 3 (group A: 2 and group B: 1) presented abundant and prolonged ( $>3$  days) discharge from the

wound, without further complications, and were discharged from hospital with a dry dressing after remaining under observation for more than 48 hours since the last soiled dressing; 2 patients in group A had intense headaches and 2 patients in group B had an episode of desaturation which improved with oxygen at 100% administered in the general ward; they did not suffer further complications.

Within severe complications, a patient in group A and a patient in group B suffered a deep vein thrombosis in the immediate postoperative period which required medical treatment. They remained hospitalized until coagulation test values were normal. A patient from group B suffered an acute prosthetic infection which required a surgical toilet and treatment with antibiotics. The prosthetic material did not need to be removed.

None of the complications were directly related to the administered medication.



**Figure 3.** Distribution of patients according to the day of discharge, by group.

## DISCUSSION

Total knee arthroplasty produces moderate to intense pain in the first postoperative day in 75% of patients and, after two weeks, in 30-40% of the cases.<sup>9</sup> This can not only bring discomfort, but also alter the normal rehabilitation process and generate joint stiffness, chronic residual pain and dissatisfaction in the doctor-patient relationship.<sup>10</sup>

When used before surgery, NSAIDs, both Cox-1 and Cox-2 inhibitors, have proved effective for pain management. A metaanalysis by Ong et al. evidenced that in multiple types of surgery, NSAIDs, administered alone or combined, reduced analgesic consumption in the postoperative period and delayed the first request for opioid rescue.<sup>11</sup> Another study published by Alexander et al. found that preoperative administration of 75 mg of intravenous diclofenac or 60 mg of ketorolac before a TKR significantly reduced morphine requirements and their associated side effects.<sup>12</sup> In an 11-patient study, performed by Renner et al., the administration of etoricoxib 2 hours before surgery was shown to allow an effective concentration of the drug in critical tissues, a reduction in the production of proinflammatory mediators and an improvement in pain management in the immediate postoperative period. Although the study was based on patients who underwent a hip arthroplasty, we believe the results are applicable to TKR.<sup>13</sup> In our study, we chose to use the aforementioned NSAID since Cox-2 inhibitors present the advantage of not producing alterations in platelet aggregation, thus preventing hemorrhagic complications; moreover, they have less gastrointestinal side effects.

Opioids have also proved effective as preventive analgesia. Hendolin et al. conducted a study with 41 patients who were administered 0.14 mg/kg of intramuscular morphine an hour before the TKR; this reduced pain in the immediate postoperative period.<sup>14</sup> In our study, we used tramadol, for its posology and presentation in 100 mg tablets facilitates administration.

No literature was found on the isolated administration of paracetamol to prevent pain; however, it was found to have a beneficial effect in combination with other drugs. In a study by Skinner and Shintani, the administration of paracetamol combined with rofecoxib, tramadol and dexamethasone was found to significantly improve postoperative pain.<sup>15</sup>

In our study, the combination of Etoricoxib 90 mg, Paracetamol 1 g and tramadol 100 mg, administered orally 2 hours before surgery, was found to improve postoperative pain management in the first 24 hours, with a reduction in the requests for morphine rescue. This translates into comfort for the patient, a faster rehabilitation and a shorter hospital stay.

Other groups of pain medications have proved useful: among corticosteroids, both dexamethasone and methylprednisolone may be beneficial when administered hours before joint replacement surgery.<sup>14,16,17</sup> These medications are routinely administered by the anesthesia team during induction to reduce the inflammatory effect of surgery.

The literature is conclusive about the benefits of multimodal analgesia for preventive pain management; we have found numerous studies which support it.<sup>15,18-21</sup> Multimodal analgesia can be defined as the combination of different analgesics with different action mechanisms in different sites of pain transmission in order to increase analgesic potency while lowering drug dosage and thus reducing side effects.<sup>22</sup>

Numerous strategies can be applied to minimize postoperative pain; however, these strategies depend on the treating surgeon's experience, for there are no studies providing enough evidence, nor clinical guidelines determining the superiority of an analgesic protocol over others to prevent pain after a knee arthroplasty. Nevertheless, there are metanalysis and expert consensus on some guidelines and recommendations for the management of preventive analgesia.<sup>5,23</sup>

The use of tourniquet cuff is controversial. A study published by Liu et al. showed that patients who had not received a tourniquet felt less pain in the early postoperative period when compared to those who had received a tourniquet.<sup>24</sup> However, in another study published by Kim et al. there were no significant findings on the link between tourniquet use and pain.<sup>25</sup> In our study, patients in group A presented less pain than patients in group B, who had received a tourniquet.

The limitations of our study are: a low number of patients, lack of long-term follow-up of patients to assess pain and rehabilitation a week post-surgery, and a sample with heterogeneous diagnoses (all patients with painful degenerative knees were included). We highlight as strengths: the prospective and randomized design and the comparison between two similar populations.

## CONCLUSION

We believe our study provided representative results which are comparable to the consulted literature. The analgesic protocol administered before surgery (etoricoxib, tramadol and paracetamol) provided a significant improvement in postoperative pain management, which in turn improved rehabilitation and reduced hospital stays. At the same time, it proved to be a good drug combination, for it is safe, cost-effective and easy to administer, with a low rate of side effects.

It is important to highlight that preventive analgesia does not constitute an isolated tool. It is necessary to combine it with a correct anesthesia and an adequate postoperative analgesic plan in order to achieve a significant improvement in patient comfort and its associated outcomes.

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Conflict of interests: Authors claim they do not have any conflict of interest.

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