Analgesic Efficacy of the Intra-Articular Administration of High Doses of Morphine in Patients Undergoing Total Knee Arthroplasty

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INTRODUCTION

It is known that the postoperative period of total knee arthroplasty is very painful, and patients often require analgesics and present elevated pain scores resulting in important morbidity[1-3]. Several approaches for adequate pain control in patients undergoing knee surgeries have been investigated, from the systemic administration of non-hormonal anti-inflammatories (NSAIDs) to systemic and spinal opioids, and patient-controlled analgesia, exposing the patient to the inherent risks of invasive procedures and adverse effects of systemic analgesics[2,4-6].

The intra-articular administration of opioids, which arose when experimental studies identified mobilization of opioid receptors in peripheral tissues induced by anti-inflammatory stimuli, whose effects are reversible by the administration of the specific opioid antagonist, is a therapeutic option. Anti-inflammatory effects on the synovial tissue, producing analgesia similar to that of dexamethasone, as well as the reduction in the number of leukocytes in the chronically inflamed joint, were also observed[7,8].

Due to the possibility of using the IA administration of morphine, several clinical assays have compared doses of 1 mg of morphine with placebo with controversial results, especially regarding analgesia in the immediate postoperative (PO) period (0 to 2 hours). On the other hand, they are important by demonstrating a positive late effect (6 to 24 hours) of this therapy[9-12]. This discovery encouraged subsequent studies using higher doses of morphine, which observed progressive reduction in postoperative pain scores and analgesic consumption with increasing doses of the opioid, characterizing a dose-dependent effect[13].

In the case of total knee arthroplasty (TKA), few authors have evaluated the use of morphine doses higher than 5 mg combined or not with local anesthetics with controversial results[1,14-17].

Due to the lack of knowledge on the effects of elevated doses of IA morphine in the control of postoperative pain in TKA, this study was undertaken to assess the analgesic efficacy of intra-articular morphine 10 mg in patients undergoing this procedure.

METHODS

This protocol was approved by the Ethics on Research Committee of the Hospital Universitário Presidente Dutra, and patients signed an informed consent before the first evaluation. Fifty patients undergoing total knee arthroplasty (TKA) were included in the study and randomly divided into two groups: Treatment Group and Control Group. Patients who refused to participate, classified as ASA IV or ASA V according to the American Society of Anesthesiologists, with psychiatric disorders, drug addiction, with known allergy to morphine, and who were discharged from the hospital before the first 24 postoperative hours were excluded from the study.

All procedures were performed under spinal block with 15 mg of 0.5% hyperbaric bupivacaine without opioids. Benzodiazepines were allowed for sedation when the anesthesiologist deemed necessary.

A pneumatic tourniquet applied to the root of the thigh was used for the surgery, which consisted of a median incision for the approach to the knee, followed by luxation and lateral displacement of the patella. Cemented prosthesis was used, with or without patellar prosthesis, according to the orthopedic indication. The inclusion of patellar prosthesis was not considered an exclusion criterion.

At the end of the surgery, local hemostasia was performed followed by placement of a suction drain through a different opening than the surgical wound, and synthesis of the wound planes. Before complete skin closure, the solution specified for the case was injected in the intra-articular space. In all patients, the drain was opened after 15 minutes.

Patients were divided in groups by random drawing without participation of the evaluator, surgeon, or patient. The solution was prepared by the Pharmacy, identified only by the case number, and transported to the operating room. One card for each patient, containing the group he/she belonged to, was prepared and placed on a sealed envelope identified only by the case number to be opened only at the end of the intervention. The treatment group received 10 mg (1 mL) of morphine diluted in 19 mL of NS (total of 20 mL), while the control group received 20 mL of NS.

All patients were granted access to rescue analgesia with the administration of 5 mg of morphine upon request, and a minimal four-hour period between doses was established. Additional 5-mg doses could be administered in case of pain. Patients were clearly instructed to request analgesics in case of pain, and the nursing staff was trained accordingly.

Data regarding age, gender, race, weight, and height, preoperative pain scores, and duration of the surgery were recorded. Systematic pain evaluations, with the patient at rest, were performed in the following moments: 2 hours after the IA injection (M1), 6 hours after IA injection (M2), 12 hours after IA injection (M3), and 24 hours after IA injection (M4). The numeric scale (NS) was used for pain evaluation after properly explained to the patients. This scale has an axis numbered from 0 to 10, in which one extremity (zero) indicates the absence of pain and the other (ten) indicates the worse pain possible.

The use of rescue medication, the time (Tr) between the intra-articular injection of the solution and the first dose of analgesic, besides the total analgesic consumption in the first 24 postoperative hours were recorded. Side effects, such as: dizziness, nausea, vomiting, pruritus and/or urticaria, agitation, disorientation, depression, and somnolence, were recorded.

Results were tabulated on an electronic database program and exported to the BIO STAT 4.5 software[18] for statistical analysis. To detect whether parameters had a normal distribution, the Shapiro-Wilks test, followed by parametric tests for parameters with normal distribution was used, and non-parametric test for the others.

As for anthropometric data, the Student *t* test was used to compare weight and height, and the Mann-Whitney test for age and duration of the surgery. Fisher's exact test was used to compare both groups according to gender.

The Friedman test was used to compare intragroup NS scores among moments (M), and the Mann-Whitney test was used to compare intergroup NS scores. The latter was also used to compare analgesic consumption and the intergroup interval until the first request for analgesic.

Spearman test was used to determine whether preoperative pain correlated with the increase in Tr and reduction in analgesic consumption. To evaluate the significance of the side effects, the Chi-square test was used. A level of significance of 5% was adopted in all tests.

Calculation of the sample size was based on total analgesic consumption. It was determined that 25 patients per group would be enough to detect a difference of approximately 50% in mean analgesic consumption in each group with 98% power and type one error of 0.01.

RESULTS

Both groups did not differ regarding age, gender, height, and weight. The surgery had a mean duration of 150 minutes that was similar in both groups. Table I shows the demographic data of the patients in the study.

Table II shows NS scores (median and variation) in the different moments (M). Figure 1 shows mean NS scores over 24 hours, comparing both groups. A statistically significant difference was observed only in M1 (p = 0.0215) and M2 (p = 0.0059), with lower scores in the treatment group.

Comparing moments in each group over 24 hours, the treatment group showed statistically significant differences in pain severity in the following moments: preoperative and M3 (PreOP > M3; p = 0.0051) and preoperative and M4 (PreOP > M4; p = 0.0051). In the control group, statistically significant differences were observed between preoperative and M4 scores (PreOP > M4; p = 0.0093); M1 and M4 (M1 > M4; p = 0.0051); and M2 and M4 (M2 > M4; p < 0.0001).

When rescue medication was compared between both groups, consumption was significantly lower in the treatment group (p = 0.0001). Mean analgesic consumption in 24 hours was 12.2 mg of morphine in the treatment group, and 20.6 mg in the control group. Figure 2 shows total consumption during the study.

The time for the first request for rescue medication was significantly lower in the control group (p = 0.0166), 3.5 hours in the treatment group and 2 hours in the control group. Figure 3 shows medians, and maximal and minimal values in hours for the first request for rescue medication.

Table I – Demographic Data (Mean ± Standard Deviation)

Parameters	Group		p
	Treatment (n = 25)	Control (n = 25)	
Age (years)*	66.16 ± 7.39	64.44 ± 9.91	ns
Weight (kg)*	73.36 ± 13.82	68.92 ± 13.97	ns
Height (cm)*	160.52 ± 7.56	159.32 ± 7.64	ns
Gender			ns
Male	10	8	
Female	15	17	

**Results expressed as Mean ± Standard Deviation
ns = non-significant; Mann-Whitney test; Student t test; Fisher's exact test.

Table II – Pain Severity According to the Numeric Scale (NS)

Parameters	Group		p
	Treatment (n = 25)	Control (n = 25)	
Preoperative	5 (3-9)	7 (5-9)	ns
M1	0 (0-8)	8 (5-10)	0.0215*
M2	5 (2-8)	8 (7-9)	0.0059*
M3	2 (0-6)	4 (0-7)	ns
M4	2 (0-4)	2 (0-6)	ns

Results expressed as median (minimal – maximal)
M1 = 2 h after IA morphine; M2 = 6 h after IA morphine; M3 = 12 h after IA morphine; M4 = 24 h after IA morphine;
ns = non-significant; (*) = significant (p < 0.05) – Mann-Whitney test.
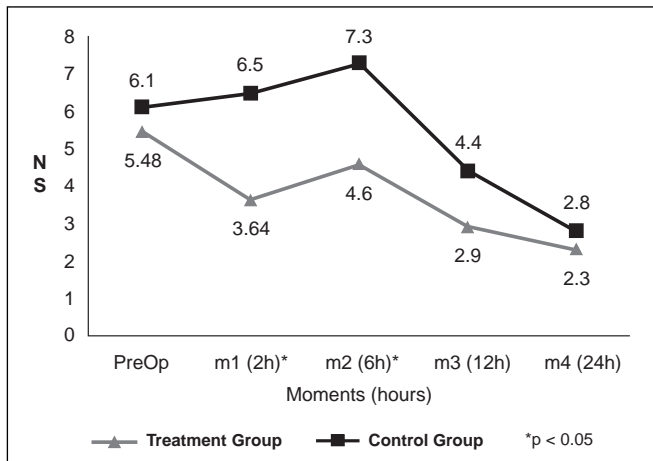

Figure 1 – Comparison of Pain Scores in Both Groups in the First 24 Postoperative Hours.
Data presented as means. Friedman test.

A correlation between preoperative pain and time until the first request for rescue medication was not observed in the treatment group (p = 0.8627) and control group (p = 0.8952). Similarly, a statistically significant correlation between the severity of preoperative pain and analgesic consumption was not observed in the treatment group (p = 0.8904) and control group (p = 0.4044).

Some adverse events were observed during the study, but without statistically significance between the groups: somnolence (treatment group: 4/25; control group: 4/25), nausea (treatment group: 10/25; control group: 13/25), and vomiting (treatment group: 7/25; control group: 7/25) were the most common.
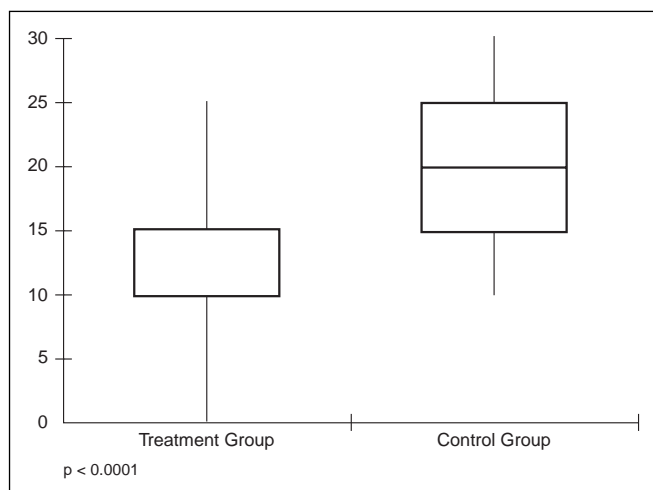
Figure 2 – Comparison of Rescue Analgesic Consumption between Both Groups.

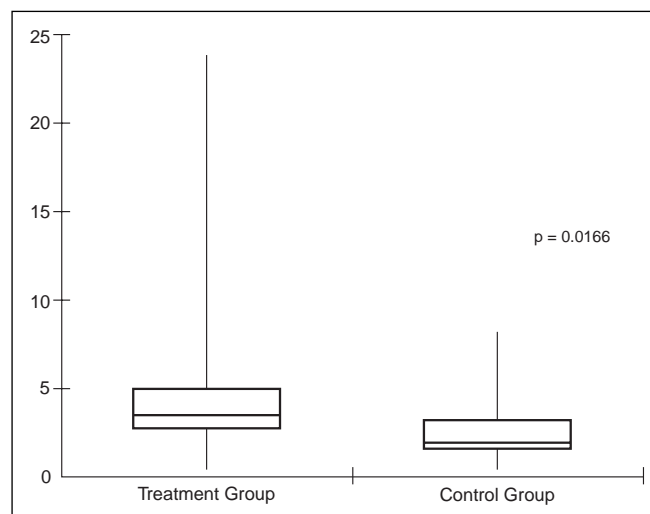Results presented as median and variation (maximal and minimal). Mann-Whitney test.

Figure 3 – Comparison of the Time Interval Until the First Request of Rescue Analgesic.

Data presented as median and variations (minimal and maximal). Mann-Whitney test.

DISCUSSION

The sample size of the present study was in conformity with the recommendations of some authors in systematic reviews, who indicate that this factor as an important cause of failure of the random distribution of patients with moderate to severe pain, leading to misinterpretation of the results by increasing the risk of false-positives. They also state that populations with more than 40 patients (20 per group) are recommended to minimize this problem[19].

In the present study, a pneumatic tourniquet that was deflated 15 minutes after the IA injection to allow greater time for the binding of morphine to its receptors was used in all procedures. A study suggested that tissue binding and, therefore, the efficacy of the local anesthetic, could be increased by maintaining longer the tourniquet in place after the IA injection. The author demonstrated, when evaluating the pharmacokinetics of this drug, an increase in plasma concentration with a reduction in the time between the intra-articular injection and the release of the tourniquet, possibly by increasing local blood flow, leading to greater systemic absorption of the drug[20].

Based on this evidence, Whitford investigated the contribution of the duration of the use of the pneumatic tourniquet for analgesia of patients undergoing knee arthroscopy. Patients received the intra-articular injection of 5 mg of morphine in 25 mL of NS and the tourniquet remained inflated for 10 minutes, in the first group, while in the second group it was removed immediately after the administration of the drug. A significant reduction in pain and analgesic consumption, besides an increase in the time until the request of the first dose of rescue analgesic, was observed in the first group. The author attributed this phenomenon to the removal of morphine from its receptors due to an increase in local blood flow secondary to post-ischemic reperfusion with the early release of the tourniquet[21].

The choice of the dose of morphine (10 mg) in the present study was based on the analysis of two known aspects from studies with patients undergoing arthroscopy. First, it has been demonstrated, and reaffirmed in a systematic review of the subject, a reduction in postoperative pain when doses higher than 5 mg of the opioid are used, characterizing a dose-dependent analgesic effect[13,22].

Second, total knee arthroplasty, which differs from arthroscopy, is associated with greater tissue trauma and pain; therefore, the doses recommended for arthroscopy could not be used in the present study. This problem has been indicated since the first studies on TKA[23], when it was suggested that the addition of morphine to IA bupivacaine was not effective in reducing postoperative pain due to the low dose of opioid used.

Regarding safety, contraindications to the IA administration of morphine for postoperative analgesia do not seem to exist. In an *in vitro* study, Jaureguito cultivated human cartilage removed during TKA of patients with osteoarthritis. He added different concentrations of morphine in NS (0.04, 0.2, and 0.4 mg.mL^{-1}) and morphine associated with 0.25% bupivacaine to the culture, besides incorporating radionucleotides (10 mCi.mL^{-1} $^{35}SO_4$) at the end of the incubation period to evaluate the synthesis of proteoglycans. Serial histologic slides stained with hematoxylin/eosin and electron microscopy were used to evaluate structural and cellular abnormalities, as well as histologic integrity. The author demonstrated a dose-dependent reduction in the incorporation of the radio sulfate in the samples after 12 hours. However, normalization was observed after 72 hours, even when higher doses of morphine were used. Those results indicated a transitory reduction in the synthesis of proteoglycans, changes in metabolism, and cellular damage, which reverted after the third day. Besides, histologic or ultrastructural damages of the cartilage were not observed on microscopy when it was exposed to morphine[24].

The method of rescue analgesia chosen for the present study was the subcutaneous administration of 5 mg of morphine,

which was enough to promote satisfactory postoperative analgesia in the control group in M3 and M4. In M1 and M2, in which this group showed higher NS scores, additional doses of subcutaneous morphine were administered until adequate pain control was achieved. The decision to use the same drug as co-intervention was aimed at trying to avoid masking the effect of the study treatment by the synergistic effects of another class of drug. The subcutaneous route, which is largely used in the control of pain exacerbation, was chosen since its safety and efficacy are similar to that of the intravenous route, with minimal side effects[25,26].

In the present study, assessment of the analgesic efficacy was direct and indirect: the first was based on the comparative analysis of the intergroup and intragroup pain scores in the different moments (M); in the second, the time (Tr) until the first request of rescue medication and total analgesic consumption between both groups was evaluated. This type of analysis was used in a review[22] article and follows the general tendency of most studies on the subject. It is believed that this is the best way to assess treatment efficacy since considering that the effects of the co-intervention with rescue analgesic shows a tendency to homogenize NS scores analysis of the indirect data can be a more reliable mean of characterizing the efficacy of IA morphine.

The possibility that pain reduction and the decreased need of analgesics after IA morphine was secondary to a systemic effect was investigated by several authors who demonstrated that the IA was superior than the intravenous route in pain reduction and, in some cases, the intragroup difference did not achieve statistical significance. However, the superiority of the intravenous over the IA route was not demonstrated when similar doses were used[10,27,28].

It was also suggested that the effects of IA morphine were more prolonged that that of the intravenous administration. It has been postulated that this difference would be related with the intra-articular glucuronidation, which would produce morphine-6-glucuronide, a metabolite with longer half-life that would be responsible for the longer time of action. In that study, the same author demonstrated plasma levels of morphine after the IA injection of 5 mg of morphine lower than 10 mg.mL^{-1}, which are not enough according to the author to produce systemic analgesia[29].

In another study, the plasma levels of morphine after the administration of 5 mg of this drug reached a mean concentration of 3.5 ng.mL^{-1} two hours after the IA administration, and 6.5 ng.mL^{-1} after the intravenous administration[27]. Despite the greater plasma concentration in the IV group, intergroup differences in numeric scale (NS) scores in the early (1, 2, and 4 postoperative hours) were not observed, but the IA group had lower NS scores at 6 and 24 hours[27].

When 10 mg of morphine were administered IA and IV, the IA group showed a significant reduction in pain scores and analgesic consumption, but intragroup differences in the plasma concentration of morphine in the different moments (15 minutes, 1, 2, 4, and 24 hours) were not observed; however, the group that received the IA medication had lower NS scores at 6 and 24 h[27].

When IA and intramuscular morphine 10 mg were compared the IA group showed significant reduction in pain scores and consumption of analgesics, but serum levels of morphine (at 15 minutes, 1, 2, 4, and 24 hours) did not differ between both groups. Serum levels remained constantly low and never achieved the minimal effective concentration. The author suggested that the results were due mainly to the peripheral actions of the opioid[30].

Postoperative assessment can be divided in three moments: early phase (0 to 2 hours), in which the residual effect of intraoperative anesthesia/analgesia could lead to a bias; intermediate phase (2 to 6 hours), in which the effects of those medications would normally start to decrease; and late phase (6 to 24 hours), in which the analgesic effect would be predominantly local[22]. In the present study, patients were evaluated in the preoperative period, and at 2 (M1), 6 (M2), 12 (M3), and 24 (M4) hours after the IA injection of morphine.

To reduce the influence of the anesthesia on M1 evaluation, we decided to use spinal block with 15 mg of bupivacaine without the addition of opioids, and local anesthesia was not used during the procedure. Intra- and postoperative analgesic drugs were not used.

Direct assessment demonstrated a reduction in NS scores in the treatment group in all studies moments, but statistically significant differences were observed only in M1 and M2. Another author observed similar results using 5 mg of morphine, but with statistically significant differences only four hours after the IA injection[32].

The efficacy of the reduction in pain scores with IA morphine after arthroscopies remains controversial. So far, four systematic reviews on the subject were undertaken without conclusions on its efficacy[19,22,31,32]. Several authors state the presence of evidence that this route of administration would be effective in the reduction of the pain scores and reduction in the consumption of analgesics[33,34].

However, those results were questioned recently based on the fact that few controlled studies with good methodological quality exist. The author also stated that clinical assays of better quality and larger study population demonstrated that IA morphine would not be an effective analgesic method, questioning the evidence of assays favorable to the use of this route of administration[22].

In the present study, evaluation of pain scores demonstrated a tendency for the reduction in pain along time between M2 and M4 in both groups. When the mean evolution of pain severity between the preoperative evaluation and M2 was investigated, a tendency for increasing pain was observed in the control group from M1 on, with a peak after six hours, while the morphine group showed a decreasing tendency. Besides this divergence in scores, differences among the different moments, from M1 on, were not observed in the treatment group; differences were only seen among preoperative pain scores and M3 (12 hours) and M4 (24 hours). In the control group, statistically significant differences were observed between M1 (2 hours) and M4 (24 h); M2 (6 h) and M4 (24 h); and preoperative evaluation and M4 (24 h). This behavior observed in both groups can be attributed to the residual effects of

bupivacaine used in the spinal block, which, along with IA morphine, would show more important reduction in pain scores in the first two hours, but it would not have such an important repercussion in the control group.

In the indirect assessment, the first parameter evaluated was the time until the first request for rescue analgesic (Tr), which was significantly different, longer in the treatment group with median of 3.5 hours *vs.* 2 hours in the control group. This result was similar to that of another study, in which the authors observed a longer time until the first dose of analgesic in the group that received 5 mg of morphine associated with bupivacaine, with means of 5.5 and 5 hours for the rheumatoid arthritis and osteoarthritis groups, respectively[1]. Those results were also similar to those of another author who compared IA morphine, tramadol, and placebo and observed a significantly longer time in the opioid groups, with a mean of 34 and 33 minutes for morphine and tramadol, respectively. However, a significant difference was not observed between the treatment groups[36].

This type of assessment seems to be the best way to analyze the efficacy of IA morphine, since it is based on the period the patient is not under the effects of the anesthetic and before the use of any other type of intervention, allowing the assessment of the effect of the local opioid. This method has been suggested as a mean to increase the sensitivity of the study, as well as the quantification of the analgesic used by the patient in the postoperative period[32].

The second parameter investigated was analgesic consumption in the first 24 hours, which was significantly higher in the control group, with comparable results to those of a similar study[1]. However, other authors did not observe a significant reduction in analgesic consumption, but those results can be attributed to the low doses of IA morphine used[14,23].

Evaluating the hypothesis that low postoperative scores and reduced inflammation would be responsible for the inconclusive results on the efficacy of the IA administration, the use of IA morphine in arthroscopic surgery was analyzed in a clinical assay dividing patients in two groups: "surgery with little inflammation" and "very inflammatory surgery", followed by the random allocation of the patients in subgroups that received morphine, bupivacaine, or placebo. In the second group (very inflammatory surgery) the author observed statistically significant differences among the subgroups regarding the reduction in pain scores and analgesic consumption, especially in the morphine group. In the first group, bupivacaine was more effective with significant reduction in pain scores despite the lack of difference in analgesic consumption among the subgroups. Based on those results, the author[26] suggested that the lower expression of opioid receptors in the joint would be responsible for the reduced efficacy of morphine in the "little inflammatory" group[37].

In the present study, a different approach was used to evaluate this hypothesis. Preoperative pain scores were correlated with postoperative analgesic consumption in 24 hours and with Tr, parameters that seem to have a better correlation with the local effects of morphine. However, a significant correlation was not observed, and this result contradicts the hypothesis that greater level of preoperative pain and, possibly, more inflammation, would imply better control with the use of IA morphine.

Some side effects were observed during the study, and the most common included nausea (40% in the control group; 35% in the treatment group) and vomiting (28% in both groups). Those symptoms were self-limited and did not compromise the continuity of the study. Mild somnolence without further repercussions was observed in only four patients (16%) in each group. None of the patients included in the study requested to be excluded due to the side effects. In previous studies, the development of side effects was not a limiting factor for the use of IA morphine, both in arthroscopies and TKA[1,13,14,37,38].

When the side effects of this analgesic technique are compared to that of other techniques, similar percentage of episodes of nausea and vomiting are observed. In a study comparing epidural patient-controlled analgesia (PCA) with sufentanil for postoperative pain after TKA, the author observed a percentage ranging from 38% to 40% in the study groups. In another study in which the author investigated the use of 250 µg of spinal morphine, isolated or in association with clonidine, he observed a 20% incidence of nausea and vomiting in the different groups[3,4,39].

The predominance of female patients in all groups is a limitation of the present study, since this was indicated in clinical assays as a possible confounding factor[4]. It was observed that the incidence of complaints of postoperative pain is higher in female patients undergoing knee arthroscopies, considering that the relative risk of postoperative pain in those procedures is 1.47, for mild to moderate pain, although a difference in the incidence of severe pain in males and females does not exist[40].

It was possible to conclude that 10 mg of intra-articular morphine increased the time until the first request for rescue analgesic and reduced analgesic consumption in the first 24 postoperative hours, and it also decreased postoperative pain scores at 2 and 6 hours.

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RESUMEN

Garcia JBS, Barbosa Neto JO, Vasconcelos JW, Ferro LSG, Silva RC – Eficacia Analgésica del Uso de Dosis Alta de Morfina Intra-articular en Pacientes Sometidos a la Artroplastia Total de Rodilla.

JUSTIFICATIVA Y OBJETIVOS*: A pesar de que la eficacia de la morfina intra-articular (IA), permanece como algo controvertido, ha quedado demostrado que las dosis mayores generan mejores resultados y consecuentemente, un menor consumo postoperatorio de analgésico, caracterizando así, el efecto dosis-dependiente en la acción periférica. Fue realizado un estudio controlado, aleatorio y doble ciego para evaluar la eficacia de 10 mg de morfina por vía intra-articular en pacientes sometidos a la artroplastia total de rodilla.*

MÉTODO*: Se evaluaron 50 pacientes sometidos a la artroplastia total de rodilla, distribuidos aleatoriamente en dos grupos: el grupo tratamiento recibió 10 mg (1 mL) de morfina por vía intra-articular diluido en 19 mL de solución fisiológica al 0,9% (SF), mientras que el grupo control recibió una inyección intra-articular con 20 mL de SF, ambos después del cierre de la cápsula articular, al final de la operación. La morfina subcutánea bajo demanda, estuvo disponible para el dolor residual. Se evaluaron las siguientes variables: intensidad del dolor graduada en la Escala Numérica (EN) a las 2h (M1), 6h (M2), 12h (M3) y 24h (M4), después de la inyección IA; tiempo para la primera solicitación de analgésico; y consumo de analgésicos y efectos adversos.*

CONCLUSIONES*: El grupo tratamiento presentó menores valores en la EN que el grupo control en M1 y M2, mientras que en los otros momentos, no se registró ninguna diferencia significativa. El intervalo para la primera solicitación de analgésicos fue significantemente mayor en el grupo tratamiento y el consumo de analgésicos en las primeras 24 horas fue menor en ese grupo. No hubo diferencia entre la incidencia de efectos adversos entre los grupos. Llegamos a la conclusión, de que 10 mg de morfina redujeron el dolor del postoperatorio entre 2 y 6 horas después de aplicada la inyección IA, y se generó un periodo mayor sin analgésico de rescate reduciendo su consumo en las primeras 24 horas.*