Intraarticular Morphine after Knee Arthroscopy. A Prospective, Randomized and Double-blind Study

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Introduction. Knee arthroscopy is a usual procedure in orthopedic surgery, which currently tends to be performed on an ambulatory basis. This underscores the need to provide the patient with efficient and safe analgesia.
Purpose. To assess the analgesic effect of intraarticular morphine after knee arthroscopy, as well as whether this effect is dose-dependent or whether, on the contrary, it is influenced by the patient's body mass index (BMI) or the duration of the procedure.
Materials and methods. The study analyzed 45 patients subjected to a knee arthroscopy at the Castelló General Hospital. They were randomly distributed across 3 groups (saline solution, 1 mg morphine chloride, 4 mg morphine chloride). For pain control, the visual analog scale (VAS) and the demand of rescue analgesia (metamizole 2 gr i.v.).In addition, a note was made of the time at which side effects occurred that could be attributed to the morphine chloride.
Results. Significant differences were found between the two morphine chloride groups and the control group regarding VAS scores at 24 hours. There were no significant differences in the remaining AVS measurements or in the demand of rescue analgesia. We did not observe a dose-dependent effect. There were no side effects that could be attributed to the intraarticular morphine chloride.
Conclusions. The use of morphine chloride as an analgesic for patients undergoing knee arthroscopy is an effective and safe method. Larger study groups are necessary to find other statistically significant differences.

Key words: *knee, arthroscopy, analgesia, pain, intraarticular, morphine.*

Morfina intraarticular tras artroscopia de rodilla. Estudio prospectivo, aleatorizado y doble ciego

Introducción. La artroscopia de rodilla es una intervención frecuente en cirugía ortopédica, y últimamente se realiza sin ingreso, debiéndose proporcionar una analgesia eficaz y segura.
Objetivo. Valorar el efecto analgésico de la morfina intraarticular tras artroscopia de rodilla, así como si este efecto es dosis dependiente o está influenciado por el índice de masa corporal del paciente o por la duración de la intervención.
Material y método. Se han incluido 45 pacientes intervenidos por artroscopia de rodilla en un hospital general. Se distribuyeron aleatoriamente en 3 grupos (suero fisiológico, 1 mg de cloruro mórfico, 4 mg de cloruro mórfico). Para el control del dolor se empleó la escala visual analógica (EVA) y la demanda de analgesia de rescate (metamizol 2 g intravenosos). También se recogió la hora a la que se presentaron efectos secundarios que podrían deberse al cloruro mórfico.
Resultados. Se encontraron diferencias significativas entre los dos grupos con cloruro mórfico respecto al grupo control en las puntuaciones de la EVA a las 24 horas. No se apreciaron diferencias significativas en el resto de las mediciones de la EVA ni en la demanda de analgesia de rescate. No observamos efecto dosis dependiente. No aparecieron efectos secundarios que puedan asociarse al cloruro mórfico intraarticular.
Conclusiones. El uso del cloruro mórfico como analgesia en pacientes sometidos a artroscopia de rodilla es un método eficaz y seguro. Hacen falta grupos de estudio más numerosos para encontrar otras diferencias estadísticas.

Palabras clave: *rodilla, artroscopia, analgesia, dolor, intraarticular, morfina.*

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Knee arthroscopy is one of the most frequent procedures in orthopedic surgery. Lately this procedure has also been applied without hospitalization, so analgesia must be safe and must appropriately control pain.

The use of morphine post-knee-arthroscopy has increased in recent years, especially due to studies that show the migration of opioid receptors from the dorsal horn ganglia in the spine to sensitive peripheral nerve-endings in the knee. A local accumulation of immature cells that contain endogenous opioid peptides is formed in the same way. Both of these phenomena are especially common in arthroscopies that generate a significant inflammatory reaction[1-4]. These receptors are the ones in charge of mediating the local analgesic effect of morphine, and decreasing the systemic analgesic effect, which means that less secondary effects could be expected[5]. These data are seen in many studies[6-9] that conclude that the analgesic effect of intraarticular morphine begins at 4-6 hours after surgery and lasts for a period of time as yet not clearly defined. Two recent reviews claim that the duration of analgesic effect is of 24-30 hours[8-10]. In spite of this, we can find studies that conclude that intraarticular morphine has no analgesic effect[11-14].

In this prospective, randomized, double blind study we analyze the analgesic effect of intraarticular morphine after knee arthroscopy, its degree of dose-dependence[15] and its level of safety. Another of the objectives of this study is to determine if the pain suffered by patients after surgery is related to the duration of ischemia[16] in the operated limb and the patient's BMI.

MATERIALS AND METHODS

In this study we included 45 patients that underwent knee arthroscopy in a general hospital. They were randomly assigned to 3 groups of 15, using a pre-designed list of random numbers. Group A, the control group, received 10 cc of intraarticular saline (placebo) at the end of arthroscopy, group B received 1 mg of morphine chloride, and group C received 4 mg of morphine chloride in a total volume of 10 cc of saline. In all cases the administration of the drug was carried out immediately after the suspension of the ischemia. Both randomization to a certain treatment and the preparation for the treatment were carried out by nursing staff that anesthetize patients for surgery, so that neither the patients nor the medical staff knew what treatment had been applied.

The Visual Analog Scale (VAS) and the demand for rescue analgesia were used to measure pain intensity. Previously, VAS had been explained to all the patients, who understood it. Pain was measured once before surgery, and 5 times after surgery (at 0, 2, 6, 12 and 24 hours). The demand for rescue analgesia (metamizole 2 g IV) was also recorded, both the quantity used and time of request. Patients that underwent knee arthroscopy, either for diagnostic reasons or for meniscectomy were also included, when this was carried out with subarachnoid spinal anesthesia with 12 ml of bupivacaine 0.5%, and they were ASA I or II. Amongst the exclusion criteria were age over 65 years, chronic knee pain (more than 1 year), use of chronic steroid, nonsteroid antiinflammatory drugs (NSAIDS) and/or opioids, or allergy to morphine. All patients were informed orally before their inclusion in the study.

The appearance of secondary effects that could be due to morphine chloride was also assessed (nausea-vomiting, excessive sedation, pruritus, respiratory depression), as also their timing.

A statistical study was carried out using version 3.3.2 of the Epi Info® software. Qualitative variables were analyzed using chi square (sex, side, ASA before surgery), and the Fisher test was used when necessary. Quantitative variables (age, BMI, time of ischemia and VAS score) were compared with qualitative variables (type of treatment, demand of analgesic rescue) by means of ANOVA and Student's 't' test. When appropriate non-parametric tests were applied (Kruskal-Wallis and Mann-Withney U). The possible association between quantitative variables was analyzed by means of linear regression techniques. Results where $p < 0.05$ were considered significant.

RESULTS

No significant differences were found between the groups in demographic data (age, sex or BMI), clinical data (preoperative ASA) or time of ischemia during knee arthroscopy (Table 1).

No significant differences were found between the 3 groups in preoperative VAS values (Table 1).

No significant differences were found between the 3 groups in the postoperative VAS results at 0, 2, 6 and 12 hours (Table 2). Although not significant, the values ob-

Table 1. Preoperative Data

	Saline	1 mg morphine chloride	4 mg morphine chloride	p
Age	41.4667	44.2667	43.8667	0.7322[a]
Sex (F:M)	10:5	9:6	7:8	0.5285[b]
BMI	28.8667	29.4667	27.3333	0.5040[a]
ASA (I:II)	11:4	7:8	8:7	0.3060[b]
Ischemia (min)	55.4000	55.2667	50.0000	0.6498[a]
Side (R:L)	8:7	8:7	7:8	0.9149[b]
Previous VAS	29.7333	26.9333	38.1333	0.2734[a]

[a]ANOVA; bchi square; M: male; F: Female, BMI Body mass index; R: right; L: left; VAS: Visual Analog Scale.

Table 2. Comparison of VAS scores obtained in the three groups

	Saline	1 mg morphine chloride	4 mg morphine chloride	p
Previous VAS	29.7333	26.9333	38.1333	0.2734[a]
VAS 0 h	3.2000	3.6667	3.6000	0.8935[a]
VAS 2 h	7.4000	11.0667	7.8667	0.4389[a]
VAS 6 h	18.0667	12.4667	11.3333	0.1376[a]
VAS 12 h	21.4667	16.4000	18.6000	0.5783[a]
VAS 24 h	23.2000	12.0667	10.5333	0.0001[a]

[a]ANOVA; VAS: Visual Analog Scale.

tained in the control group at 6 and 12 hours post-surgery were higher than those seen in the groups that received morphine chloride.

On the other hand, if we take results seen 24 hours after surgery, there are significant differences in VAS scores, with higher results in the control group in comparison with the other two groups together (p = 0.0001, ANOVA) (Figure 1). Similarly, significant differences are seen in VAS scores at 24 hours, if we compare the control group with each of the other groups individually, and with the 1 mg group we find p = 0.0002 in comparison with the 4 mg group with p = 0,0001.

To assess whether the VAS score, whatever the treatment received, is related to the duration of surgery (time of ischemia), linear regression was carried out (Table 3). The correlation coefficient obtained was not significant.

Similarly, if we analyze the results of the VAS score independently from the type of treatment assigned, with reference to BMI previous to surgery, the values obtained do not show a direct association between both variables (Table 4).

Table 3. Relationship between the duration of ischemia and different pain measurements

	Ischemia/ VAS 2 h	Ischemia/ VAS 6 h	Ischemia/ VAS 12 h	Ischemia/ VAS 24 h
Correlation Coefficient r^2	0.07	0.10	0.02	0.06

VAS: Visual Analog Scale.

Rescue analgesia was demanded by 5 patients in the control group, and was requested at 9.4 ± 5.6 hours post-surgery. In the group that received 1 mg of morphine chloride 4 patients demanded it (7.5 ± 3.7 hours), and in the group that received 4 mg 2 patients demanded it (7.5 ± 3.5 hours). These differences in the number of patients that requested rescue analgesia are not statistically significant when we compare the 3 groups simultaneously (p = 0.4307, chi square), nor when we compare them two by two; between groups A and B we find p = 0.3567, and between A and C, p = 0.1174. None of the patients in this study required more than one dose of rescue analgesia.

The demand for analgesia, whatever treatment was given, is not associated with a significant difference in the duration of the surgical procedure (Table 5), although it is seen that the surgical procedure was of longer duration in those patients that required analgesia (61.5 minutes) than in those that did not require it (50.9 minutes).

Furthermore. whatever the treatment given, it is not possible to state that the cause of the request for rescue analgesia is a certain BMI, since its level is similar in both groups, nor can the demand for analgesia be associated with a different ratio of patients with a certain preoperative VAS score (Table 5).

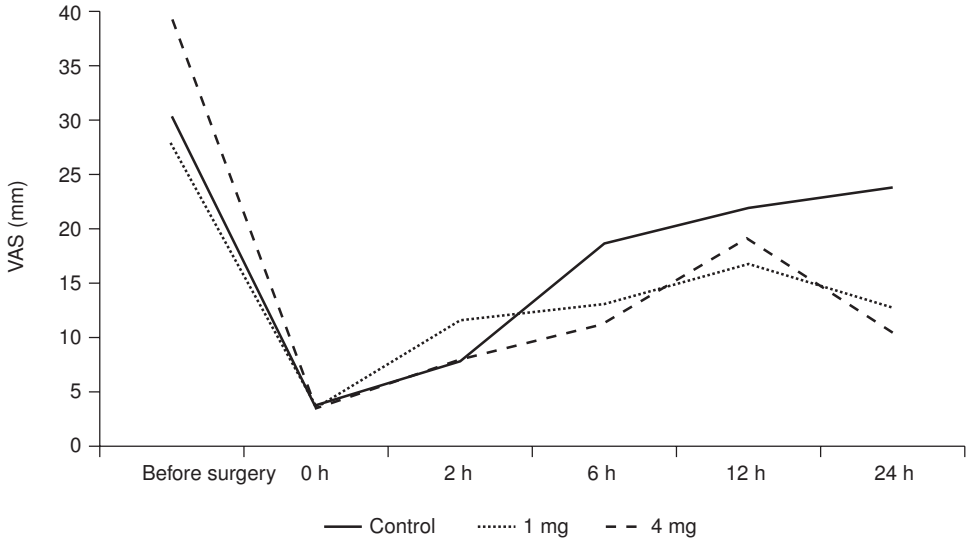

Figure 1. *Evolution in the VAS score over time in the different study groups. VAS: Visual Analog Scale.*

Table 4. Relation between BMI and different pain measurements

	BMI/VAS 2 h	BMI/VAS 6 h	BMI/VAS 12 h	BMI/VAS 24 h
Correlation coefficient r^2	0.01	0.09	0.02	0.00

BMI Body mass index; VAS: Visual Analog Scale.

Table 5. Comparison between patients demanding and not demanding analgesia

	Demand analgesia (n = 11)	Do not demand analgesia (n = 34)	p
Duration (min)	61.54	50.97	0.0876[a]
BMI	29.54	28.23	0.4626[a]
ASA (I:II)	6:5	20:14	0.4044[b]

aStudent's «t» test; b chi square; BMI: Body mass index.

Table 6. Comparison of VAS scores between groups that received 1 and 4 mg of morphine chloride

	1 mg morphine chloride	4 mg morphine chloride	p
Prior VAS	26.9333	38.1333	0.1432[a]
VAS 0 h	3.6667	3.6000	0.9482[a]
VAS 2 h	11.0667	7.8667	0.2755[a]
VAS 6 h	12.4667	11.3333	0.7332[a]
VAS 12 h	16.4000	18.6000	0.6853[a]
VAS 24 h	12.0667	10.5333	0.6285[a]

[a]Student's «t» test; VAS: Visual Analog Scale.

To assess whether the analgesic effect of morphine chloride is dose-dependent, we compared the results obtained in the two groups of 1 and 4 mg. When the VAS scores are compared no significant differences are seen (Table 6).

The possible dose-dependent analgesic effect cannot be assessed if we analyze the demand for analgesia in these two groups, since, although there are differences between both (4 and 2 patients), these are not significant (p = 0.2049). Although plasma concentrations of morphine have not been analyzed in this study, there has been monitoring of any secondary effects that could be attributed to the central effect of opioids, such as nausea or coughing, pruritus or respiratory failure. In this study, as in the Drosos[13]study, these secondary effects were not detected in any patient.

DISCUSSION

Peripheral opioid receptors are activated only in the presence of inflamed tissue; furthermore, these opioid receptors have been identified in the synovial membrane of the knee and the analgesic effect of intraarticular morphine can be neutralized with intraarticular naloxone, therefore indicating that analgesia is achieved by local mediation[17-21].

The duration of the analgesic effect of morphine is more prolonged than if it were administrated intravenously or epidurally. In spite of this, studies on the analgesic efficacy of intraarticular morphine chloride after arthroscopic knee meniscectomy are very different. In the metaanalysis published by Gupta8 it is possible to see an important variability, not only between different studies, but also within studies, showing a significant lack of consistency.

This lack of consistency makes it difficult to obtain valid conclusions from many of these metaanalysis, which is the conclusion come to by Rosseland14. This author states that most of the published studies are of poor quality, and those considered of good quality conclude that there are no differences between the control group and the morphine chloride group.

In a previous study, Rosseland[2] did not find any differences between the placebo and intraarticular morphine groups when morphine was given to patients with significant pain after arthroscopy, thus taking a different stand to those authors that maintain that morphine is effective especially in the subgroup of patients who suffer pain immediately after surgery. In this study, significant differences are only seen between the groups 24 hours alter surgery. Furthermore, there is also improvement of pain, although not significant, at 6 and 12 hours. No significant differences between groups are seen when the demand for rescue analgesia is analyzed.

Other factors, that have been associated with pain after knee arthroscopy and which could cause a study bias, are the degree of pain before surgery, the degree of surgical aggression and the residual effects of anesthesia[12,16,22,23].

In this study VAS was used to measure pain prior to surgery, and patients relate the mean intensity of knee pain during daily activities. We found no differences in preoperative VAS in the 3 groups, even when compared 2 by 2.

Surgical aggression in this study is limited by the inclusion criteria, whereby only patients undergoing isolated meniscectomy or diagnostic arthroscopy were included, and patients with condropathy and those that underwent anterior cruciate ligament (ACL) reconstruction were excluded.

Therefore, surgical aggression has been assessed based on ischemia time of the operated limb. Therefore, like Joshi[24] we must say that we have not found any association between a more prolonged time of ischemia and greater subsequent pain.

The anesthetic technique used for all patients in the study has been the same, thus preventing any bias. In this study, no association was found between patient BMI and pain after surgery, either in the VAS score or in the demand for rescue analgesia.

As to the possibility of the effect being dose-dependent, the literature shows different results, Since some studies do determine this effect to be dose-dependent, whereas others do not[15,25,26]. In this current series we did not determine a dose-dependent effect of intraarticular morphine chloride after knee arthroscopy. Furthermore, some previous studies found a phenomenon of hyperalgesia in some patients that received a higher dose of morphine chloride[25,26]. It is thought that higher doses of morphine may cause a local release of histamine. We did not see any cases of hyperalgesia in our series.

In conclusion, this study only shows the analgesic effect of intraarticular morphine chloride after knee arthroscopy determined by VAS scores at 24 hours. We found no significant differences between the groups at 6 and 12 hours after surgery. We believe that to find any differences it would be necessary to increase the size of the sample and include patients that suffer a high degree of postoperative pain.

No results were found to support a dose-dependent effect of morphine, since the results obtained with 1 mg and 4 mg are similar. We found no association between postoperative pain and prior BMI or the duration of ischemia in the operated limb.

REFERENCES

1. Likar R, Mousa SA, Philippitsch G, Steinkellner H. Increased numbers of opioid expressing inflammatory cells do not affect intra-articular morphine analgesia. Br J Anaesth. 2004; 93:375-80.
2. Rosseland LA, Stubhaug A, Grevbo F. Effective pain relief from intra-articular saline with or without morphine 2 mg in patients with moderate-to-severe pain after knee arthroscopy: a randomized, double-blind controlled clinical study. Acta Anaesthesiol Scand. 2003;47:732-8.
3. Marchal JM, Delgado-Martínez AD, Poncela M. Does the type of arthroscopic surgery modify the analgesic effect of intraarticular morphine and bupivacaine? A preliminary study. Clin J Pain. 2003;19:240-6.
4. Janson W, Stein C. Peripheral opioid analgesia. Review. Curr Pharm Biotechnol. 2003;4:270-4.
5. Ho ST, Wang TJ, Tang JS. Pain relief after arthroscopic knee surgery: intravenous morphine, epidural morphine, and intra-articular morphine. Clin J Pain. 2000;16:105-9.
6. Kalso E, Tramer MR, Carroll D, McQuay HJ, Moore RA. Pain relief from intra-articular morphine after knee surgery: a qualitative systematic review. Review. Pain. 1997;71: 127-34.
7. Richardson MD, Bjorksten AR, Hart JA, McCullough K. The efficacy of intra-articular morphine for postoperative knee arthroscopy analgesia. Arthroscopy. 1997;13:584-9.
8. Gupta A, Bodin L, Holmstrom B, Berggren L. A systematic review of the peripheral analgesic effects of intraarticular morphine. Anesth Analg. 2001;3:761-70.
9. De Andres J, Valia JC, Barrera L. Intra-articular analgesia after arthroscopic knee surgery: comparison of three different regimens. Eur J Anaesthesiol. 1998;15:10-5.
10. Kalso E, Smith L, McQuay HJ, Andrew Moore R. No pain, no gain: clinical excellence and scientific rigour–lessons learned from IA morphine. Review. Pain. 2002;98:269-75.
11. Dierking GW, Ostergaard HT, Dissing CK, Kristensen JE, Dahl JB. Analgesic effect of intra-articular morphine after arthroscopic meniscectomy. Anaesthesia. 1994;49:627-9.
12. Rosseland LA, Stubhaug A, Skoglund A, Breivik H. Intra-articular morphine for pain relief after knee arthroscopy. Acta Anaesthesiol Scand. 1999;43:252-7.
13. Drosos GI, Vlachonikolis IG, Papoutsidakis AN, Gavalas NS, Anthopoulos G. Intra-articular morphine and postoperative analgesia after knee arthroscopy. Knee. 2002;9: 335-40.
14. Rosseland LA. No evidence for analgesic effect of intra-articular morphine after knee arthroscopy: a qualitative systematic review. Reg Anesth Pain Med. 2005;30:83-98.
15. Likar R, Kapral S, Steinkellner H, Stein C, Schafer M. Dose-dependency of intra-articular morphine analgesia. Br J Anaesth. 1999;83:241-4.
16. Whitford A, Healy M, Joshi GP, McCarroll SM, O'Brien TM. The effect of tourniquet release time on the analgesic efficacy of intraarticular morphine after arthroscopic knee surgery. Anesth Analg. 1997;84:791-3.
17. Stein C, Millan MJ, Yassouridis A, Herz A. Antinociceptive effects of mu- and kappa-agonists in inflammation are enhanced by a peripheral opioid receptor-specific mechanism. Eur J Pharmacol. 1988;155:255-64.
18. Stein C, Comisel K, Haimerl E. Analgesic effect of intraarticular morphine after arthroscopic knee surgery. N Engl J Med. 1991;325:1123-6.
19. Khoury GF, Chen AC, Garland DE, Stein C. Intraarticular morphine, bupivacaine, and morphine/bupivacaine for pain control after knee videoarthroscopy. Anesthesiology. 1992; 77:263-6.
20. Lawrence AJ, Joshi GP, Michalkiewicz A, Blunnie WP, Moriarty DC. Evidence for analgesia mediated by peripheral opioid receptors in inflamed synovial tissue. Eur J Clin Pharmacol. 1992;43:351-5.
21. Stein C, Pfluger M, Yassouridis A, Hoelzl J, Lehrberger K, Welte C, et al. No tolerance to peripheral morphine analgesia in presence of opioid expression in inflamed synovia. J Clin Invest. 1996;98:793-9.
22. Aasbo V, Raeder JC, Grogaard B, Roise O. No additional analgesic effect of intra-articular morphine or bupivacaine compared with placebo after elective knee arthroscopy. Acta Anaesthesiol Scand. 1996;40:585-8.
23. Ruwe PA, Klein I, Shields CL. The effect of intraarticular injection of morphine and bupivacaine on postarthroscopic pain control. Am J Sports Med. 1995;23:59-64.

24. Joshi GP, McCarroll SM, Cooney CM, Blunnie WP, O'-Brien TM, Lawrence AJ. Intra-articular morphine for pain relief after knee arthroscopy. J Bone Joint Surg Br. 1992;74: 749-51.
25. Björnsson A, Gupta A, Vegfors M. Intraarticular morphine for postoperative analgesia following knee arthroscopy. Reg Anesth. 1994;19:104-8.
26. Tetzlaff JE, Dilger JA, Abate J. Preoperative intra-articular morphine and bupivacaine for pain control after outpatient arthroscopic anterior cruciate ligament reconstruction. Reg Anesth Pain Med. 1999;24:220-4.

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