

## Klinik Araştırma

# Postoperative Effectiveness of Three Routes of Morphine in Arthroscopic Knee Surgery

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### SUMMARY

**Aim:** The aim of this study was to investigate postoperative analgesic effectiveness of intraarticular (IA), intramuscular (IM) or intrathecal (IT) administration of morphine in arthroscopic knee surgery.

**Materials and Methods:** Seventy-six patients with ASA physical status I-II, aged 18 to 65 years, undergoing arthroscopic knee surgery were included in the study. Morphine (10 mg) was given via IA and IM in groups IA (n:21) and IM (n:16), respectively, at the end of the surgical procedure. IT 0.1 mg morphine was administered together with the local anesthetic in Group IT (n:21). Morphine was not applied to 18 control patients (Group C). Visual analogue scale scores for pain were analyzed. Additional analgesic requirement, side effects of morphine and hemodynamic parameters were compared between the groups.

**Results:** None of the patients in Group IT needed additional analgesic treatment in the first 24 hours, whereas 14.3 %, 25.0 % and 72.2 % of the patients needed additional analgesic administration in the groups IA, IM and C, respectively ( $p<0.001$ ). There was no difference in nausea or vomiting between groups ( $p=0.07$ ). Fifteen patients in Group IT and 3 patients in Group IA experienced itching.

**Conclusion:** Morphine in three administration routes provides similar analgesic effect and better analgesia in comparison to the control group. Due to the higher incidence of side effects in the IT group, either IA or IM route may be chosen for an adequate postoperative analgesia at the dose used in the present study.

**Key words:** Intrathecal, intraarticular, intramuscular, morphine, knee surgery, postoperative pain

### ÖZET

#### Artroskopik Diz Cerrahisinde Üç Farklı Yolla Verilen Morfinin Postoperatif Etkinliği

**Amaç:** Bu çalışmada üç farklı yolla intraartiküler (İA) intratekal (İT) veya intramüsküler (İM) verilen morfinin postoperatif analjezik etkinliği araştırıldı.

**Gereç ve Yöntem:** Artroskopik diz cerrahisi uygulanacak 18-65 yaş arası 76 ASA I-II hasta çalışmaya alındı. İA (n:21) ve İM (n:16) grubunda cerrahi işlemin sonunda morfin 10 mg İA ve 10 mg İM yolla, İT (n:21) grubunda ise 0.1 mg morfin lokal anesteziyle birlikte İT yolla verildi. Kontrol grubuna (Grup C, n:18) morfin verilmedi. Ağrı görsel analog skalası ile değerlendirildi. Gruplar ek analjezik gereksinimi, morfinin yan etkileri ve hemodinamik parametreler açısından karşılaştırıldı.

**Bulgular:** İlk 24 saatte IT gruptaki hiçbir hastada ek analjezik gereksinimi olmadı. Buna karşılık İA, İM ve C grubunda sırasıyla % 14.3, % 25.0 ve % 72.2 oranlarında ek lornoksikam gereksinimi oldu ( $p<0.001$ ). Gruplar arasında bulantı ve kusma açısından anlamlı fark bulunamadı ( $p=0.07$ ). IT grubundan 15 hastada, IA grubundan da 3 hastada kaşıntı gözlemlendi.

**Sonuç:** Kontrol grubuyla karşılaştırıldığında İA, İM ve İT uygulanan morfinin daha iyi analjezik etki sağladığı gözlemlendi. Morfinin kullanılan dozlarında İT grubunda daha yüksek yan etki insidansı oluşturması nedeniyle, benzer şekilde yeterli postoperatif analjezi sağlayan İA ya da İM uygulama yolu tercih edilebilir.

**Anahtar kelimeler:** İntratekal, intraartiküler, intramüsküler, morfin, diz cerrahisi, postoperatif ağrı

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## INTRODUCTION

Adequate postoperative analgesia in arthroscopic knee surgery is important for a good clinical outcome, early hospital discharge and patient satisfaction. Local or systemic application sites of analgesics have been used to manage postoperative pain in arthroscopic knee surgery.<sup>(1-7)</sup>

Intrathecal (IT) or intraarticular (IA) injection of opioids has been reported to provide adequate pain control after arthroscopic knee applications.<sup>(1-2)</sup> The peripheral analgesic effect of morphine has been widely studied and compared with other analgesics, local anesthetics and placebo for about 20 years.<sup>(2)</sup> IA injection of morphine with a range of 1 mg to 10 mg has been reported to achieve sufficient analgesia in many studies.<sup>(2,3)</sup> Overall evaluation of the literature in systematic reviews suggested a beneficial analgesic effect of morphine compared to placebo.<sup>(2,3)</sup>

Mechanism of peripheral analgesia provided by local injection of morphine has been related with activation of peripheral opioid receptors.<sup>(2,4)</sup> IT administration of morphine has been used to supply a prolonged analgesic effect after surgical procedures for about 30 years.<sup>(5)</sup> A dose of IT morphine between 0.1 mg and 0.5 mg usually provides a good analgesia and significantly reduces the need of additional analgesic agent.<sup>(1,6-8)</sup> Higher doses are associated with a significant increase in side effects such as nausea and vomiting, itching, urinary retention and even lethal respiratory depression.<sup>(9-13)</sup>

In the present study, we aimed to investigate whether IA administration of morphine provides a better pain management especially in regard to less additional

analgesic requirement compared to the IT or IM application of the drug.

## MATERIAL and METHODS

Following the approval of local ethics committee, a total of 76 patients of American Society of Anesthesiologists physical status I-II, undergoing arthroscopic knee surgery with spinal anesthesia were included in the study. The patients were between 18 and 65 years old. A written informed consent was obtained from all of the participants.

Patients were excluded if they had a contraindication to receive morphine or nonsteroidal anti-inflammatory drugs, if postoperative knee drainage was required, if the surgical procedure lasted more than 120 minutes or if bilateral arthroscopic knee surgery was necessary. Patients on long term analgesic therapy, cardiovascular disease, respiratory problem or liver dysfunction were excluded from the study.

A spinal anesthesia was applied to all patients with 12 mg of bupivacaine before the surgery. Each patient was randomly assigned via sealed envelope assignment, to one of four groups: Group IA (21 patients) received 10 mg of intraarticular morphine injection in 20 ml of saline at the end of the surgery. Group IT (21 patients) received 0.1 mg of intrathecal morphine injection in 0.5 ml of saline during the spinal anesthesia. Group IM (16 patients) received 10 mg of intramuscular (IM) morphine injection at the end of the surgery in 1 ml into the lateral compartment of the thigh on the operation side. Group C (18 patients) was control group and only spinal anesthesia was administered to this group. The tourniquet was deflated 10 minutes after intraarticular

morphine injection in Group IA. All solutions were prepared by an anesthesiologist who otherwise was not involved in the management of patient. At the end of the surgery, all patients received 8 mg of intravenous (IV) lornoxicam.

Postoperative pain was assessed with a 10-point verbal analog scale (VAS), with 0 corresponding to no pain and 10, the worst imaginable pain. The patients were trained preoperatively in the use of the VAS for pain evaluation. VAS pain scores were recorded at rest and at 15 min, 30 min, 45 min, 60 min, 6 hour, 12 hour, 24 and 48 hour after the completion of surgery. The anesthesiologist involved in assessment of VAS scores was blinded to which treatment the patients had received. In case of pain (a VAS score 3 or higher), patients received additional 8 mg of intravenous (IV) lornoxicam.

The rescue analgesia requirement and side effects of morphine (nausea, vomiting, itching, urinary retention, and sedation) were recorded. The hemodynamic parameters, blood pressure, heart rate and oxygen saturation, during the perioperative and postoperative period were also recorded.

The power of study was calculated as described by Dupont and Plummer<sup>(14)</sup> and was calculated as higher than 0.70 for the comparisons of different outcomes in

IA, IT and IM applications. The statistical analysis was performed with chi-square test for the comparisons of categorical variables. Kruskal Wallis and posthoc Bonferroni adjusted Mann Whitney U tests were used for the multiple comparisons of continuous variables. VAS scores among the groups were compared with variance analysis for the repeated measurements. Significance was determined at  $p < 0.05$ . Statistical evaluations were performed with SPSS for Windows 11.5 (Chi, Il., USA) program. Data was presented as median (min-max) and frequency.

## RESULTS

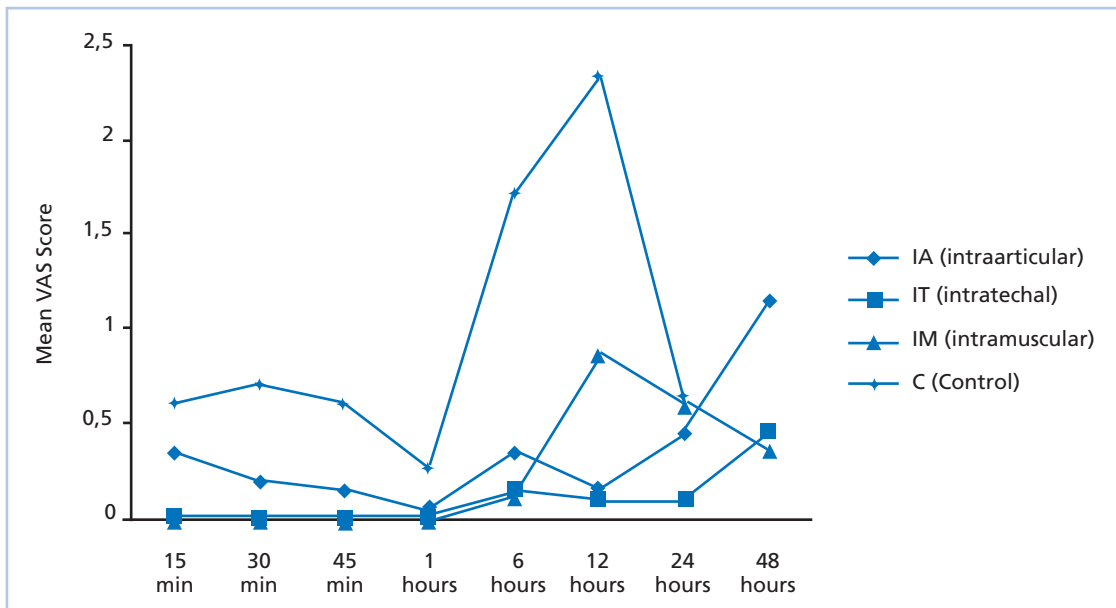
The groups were comparable with respect to age, gender and duration of operation time (Table I). Overall comparison of the groups revealed that the patients in the groups IA, IT and IM required significantly less additional analgesic (lornoxicam), in comparison to the control group (28.6 %, 4.8 %, 25.0 % vs. 77.8 %, respectively,  $p < 0.001$ ). Patients in the Group IT did not require any additional analgesic treatment in the first 24 hours, whereas in the groups IA, IM and C 86 %, 75 % and 28 % of the patients did not need additional analgesia, respectively (Table II,  $p < 0.001$ ). In the second 24 hour period, 61 % of the patients in the Group C did not require additional analgesic treatment, on the other hand 71 %, 95 % and 94 % of the pa-

**Table I. Operation time and some of the demographic data of the groups. Data was presented as median (min-max) and frequency. There was no difference between groups ( $p > 0.05$ ).**

	Control (n:18)	Intraarticular (n:21)	Intratechal (n:21)	Intramuscular (n:16)
Age	28.5 (23-46)	29 (20-65)	27 (18-59)	26.5 (19-40)
Gender				
Male	18	21	18	15
Female	0	0	3	1
Operation time	52 (21-112)	47 (22-108)	48 (26-71)	50 (25-117)

**Table II. Additional analgesic need (lornoxicaam 8 mg) of the groups at the first and second 24 hours.**

Rescue analgesic Requirement	Intraarticular (n=21)	Intratechal (n=21)	Intramuscular (n=16)	Control (n=18)	p value
1 <sup>st</sup> 24 hours					
1 time	2 (9.5%)	0 (0%)	4 (25.0%)	10 (55.6%)	<0.001
2 time	1 (4.8%)	0 (0%)	0 (0%)	3 (16.7%)	0.08
2 <sup>nd</sup> 24 hours					
1 time	6 (28.6%)	0 (0%)	1 (6.3%)	7 (38.9%)	0.02

**Figure 1. Mean visual analogue scale scores of the patients. The VAS scores were significantly different between the groups at the 6th, 12th, and 24th hour measurements  $p=0.008$ ,  $p=0.001$  and  $p=0.023$ , respectively.****Table III. Incidence of side effects observed in the patient groups.**

Rescue analgesic Requirement	Intraarticular (n=21)	Intratechal (n=21)	Intramuscular (n=16)	Control (n=18)	p value
Nausea or vomiting	0 (0%)	3 (14.3%)	3 (18.8%)	0 (0%)	0.07
Itching	3 (14.3%)	15 (71.4%)	0 (0%)	0 (0%)	<0.001
Sedation	0 (0%)	0 (0%)	2 (12.5%)	0 (0%)	0.05
Hypotension	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Urinary retention	0 (0%)	2 (9.6%)	0 (0%)	0 (0%)	0.15

tients in the groups IA, IT and IM did not need additional analgesic treatment, respectively (Table II,  $p=0.018$ ). One patient in the Group IA, and three patients in the Group C required second additional dose

of lornoxicaam in the first 24 hour postoperatively (Table II). Additional analgesic requirements were not significantly different among the morphine administered groups IA, IT and IM. Pain scores of the

patients are presented in Figure 1. A significantly lower mean VAS was observed in all of the morphine administered groups compared to the control group ( $p < 0.001$ , Figure 1). However, the mean VAS scores were not significantly different between the groups IA, IT and IM (between 0.73 and 0.99). The VAS scores were significantly different between groups at the 6<sup>th</sup>, 12<sup>th</sup> and 24<sup>th</sup> hour measurements ( $p = 0.008$ ,  $p = 0.001$  and  $p = 0.023$ , respectively). The number of patients suffering from nausea or vomiting was not significantly different among the groups (Table 3,  $p = 0.068$ ). On the other hand no patient reported nausea or vomiting in the Group IA receiving intraarticular morphine and in the control group. Three patients in the Group IA and 15 patients in Group IT experienced itching, whereas no patients suffered from itching in groups IM and C (Table III). Itching as a side effect was significantly higher in the Group IT compared to the other groups ( $p < 0.001$ ). Hypotension, oxygen saturation, sedation and urinary retention rates were not significantly different among the four groups (Table III). Two patients in the Group IM had sedation and two patients in the Group IT suffered from urinary retention.

## DISCUSSION

The local or systemic applications of opioids have been previously investigated for postoperative pain management to date.<sup>(1-7)</sup> Importance of the current investigation was the comparison of three different administration routes in the same study design. In this study, we found that 100 µg morphine intrathecal, 10 mg intraarticular and 10 mg intramuscular injections revealed an effective postoperative analgesia after arthroscopic knee surgery compared to the control group receiving no morphine.

Several reviews which have evaluated the literature data on IA administration of opioids revealed that the quality of most of the studies involving IA administration of morphine were weak.<sup>(1,6,15-17)</sup> Intraarticular use of morphine is controversial with some positive<sup>(1,16-18)</sup> and some negative results.<sup>(19-21)</sup> Thus the authors recommended further randomized controlled trials to clarify the contradictory results published in the literature.<sup>(15)</sup> The effect of intraarticular morphine has been attributed to the presence of peripheral opioid receptors, because the analgesic effect could be reversed by the injection of intraarticular naloxone.<sup>(2,4,22)</sup>

Evaluation of literature data on the effect of IA morphine injection and on the comparison of IA morphine with other routes seems to be complex due to the differences in study design, study medication, randomization and blinding.<sup>(23)</sup> Differences in evaluation of effects, time to and consumption of rescue analgesic drugs, statistics in these studies are also confounding factors during the evaluation of the data in the literature.<sup>(23)</sup> In our study, we only evaluated the resting pain with VAS. However, it could be more convenient to evaluate both resting and dynamic pain with VAS. We think that this is the major drawback of our study.

Gupta et al<sup>(2)</sup> revealed that morphine injected into the intraarticular space produces analgesia up to 24 hours after the injection, and this could be a dose-dependent effect. On the other hand some studies have failed to show a benefit from IA morphine with doses as high as 5 mg.<sup>(23-27)</sup> In our IA group with 10 mg morphine 86 % of the patients did not require additional analgesia.

The type of anesthesia has been reported to cause delay in onset of analgesic effect with the intraarticular morphine injection.<sup>(28)</sup> Presence of local anaesthetics may be a factor to inhibit neuronal mechanisms that are responsible for the effect of morphine. This may explain why some studies with regional or local anaesthesia have failed to show the effect of IA morphine,<sup>(29-31)</sup> whereas patients operated under general anaesthesia have demonstrated profound effect of IA morphine.<sup>(4,15,32,33)</sup> In the current study, spinal anesthesia with bupivacaine was applied. No use of local anaesthetics into the intraarticular space eliminates its possible negative effect on morphine analgesia in our study.

Raj et al<sup>(34)</sup> have compared the analgesic efficacy and plasma concentrations of morphine (10 mg) administered IA and IM. 10 mg of IA morphine has been reported to provide better analgesia than the same dose of IM morphine. Plasma concentrations of morphine after the injections of 10 mg IA and IM were similar at the first and 24th hours of the administration. Therefore the authors suggested the value of peripheral mechanisms for the drug action.<sup>(34)</sup> Contrarily, Cepeda et al<sup>(35)</sup> showed that IA and subcutaneous 10 mg doses of morphine had similar postoperative analgesia even in the patients followed up to 72 hours. In the present study, even though the additional analgesics requirement was higher in IM group compared to the IA group, this difference was not statistically significant.

Some studies showed that even IA injection of saline relieved moderate to severe pain after knee arthroscopy in randomized controlled trials.<sup>(28,36)</sup> This effect of saline has been attributed to a local analgesic effect by cooling or by diluting

IA algogenic substances.<sup>(28,36)</sup> However, a recent study has demonstrated that both IA injection of 10 ml and 1 ml saline produced equally good pain relief in the patients after knee arthroscopy.<sup>(37)</sup> A weak point in our study is that we did not include a group involving patients with only IA saline injection.

Intrathecal morphine administration has been reported to be effective in the control of postoperative pain. Rathmell et al<sup>(1)</sup> examined analgesia and side effects of intrathecal morphine in a dose range between 0.0 mg and 0.3 mg. The authors showed that patients receiving 0.2 and 0.3 mg of IT morphine were more satisfied with their pain control compared to those receiving 0.0 and 0.1 mg. after both hip and knee arthroplasty[1]. However, our findings suggested a similar postoperative analgesic effect of 0.1 mg IT administration compared to 10 mg IA and IM administration of the drug.

Itching, nausea and vomiting as side effects related to the administration of morphine have been reported due to the use of intrathecal 0.1 and 0.3 mg doses in a dose related manner.<sup>(1)</sup> On the other hand, Gürkan et al.<sup>(38)</sup> showed that even mini-dose intrathecal morphine usage is not acceptable because of these side effects. In the present study, we also observed increased rate of itching in the patients receiving 0.1 mg dose of IT morphine compared to the systemic and IA administration. We observed two patients suffering from urinary retention in the IT group. However, this side effect was not investigated by Rathmell et al.<sup>(1)</sup> because the patients were urinary catheterized before the operation.<sup>(1)</sup> Higher doses of IT morphine has also been used up to 1 mg. Bowrey et al.<sup>(3)</sup> has demonstrated that 0.5



mg use of IT morphine was more effective and as safe as injection of 0.2 mg.

As a conclusion, administration of morphine in any routes of IA, IT or IM provides similar analgesic effect but better analgesia compared to the control group in which morphine was not used. The overall incidence of side effects due to the administration of morphine was not significantly different between the study groups except itching which was significantly higher in the intrathecal group compared to the other groups. Therefore it seems safer and with no additional analgesic benefit to use either intramuscular or intraarticular routes compared to administration of morphine intrathecally in arthroscopic knee surgery.

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