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Original Article

Analgesic efficacy of a single-dose, intraoperative, intra-articular morphine application in ACL reconstruction

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ABSTRACT

Background: Anterior cruciate ligament (ACL) reconstruction is the mainstay treatment for the symptomatic anterior cruciate ligament insufficiency. Postoperative rehabilitation is the key main factor in successful surgical outcome but, the postoperative pain is a major obstacle to achieve good postoperative rehabilitation. The purpose of this study is to compare the effects of intra-articular morphine (IAMO) with normal saline [control group (C)] for postoperative pain control in the ACL reconstruction knees. **Methods:** Patients who underwent ACL reconstruction during 2017–2019 were included, prospectively, from Khon Kaen hospital and randomized into 2 groups: IAMO group and the control group (C). After surgery, all patients received the same rehabilitation protocols. The results were assessed using the visual analogue scale (VAS), following the spinal block anesthesia at 6, 12, 18 and 24 hours. Time to first analgesic request, range of motion and adverse effects were recorded.

Results: Forty patients were included and twenty were designated to the IAMO group. The mean age was 25.3 ± 7.6 years and 80 percent of the patients were males. The IAMO group had lower VAS scores at the 12 and 24 hour postoperative periods [greatest variance at 12 hours (4.7 ± 1.7 vs 5.8 ± 1.6)]. In the IAMO group, time to first analgesic request was longer and morphine consumption was less, but these were not statistically significant. No complications were observed in both groups.

Conclusions: The trend of VAS in the IAMO group was lower than in the control group, especially at 12 hours after surgery with no statistically significant differences. From this study and with the advantages of IAMO after ACL reconstruction, IAMO is useful in ACL reconstruction patients without complications.

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Introduction

Anterior cruciate ligament (ACL) injury is one of the most common injuries among athletes. From chronic instability of the knee due to an ACL injury, the patient may have the chance of repeated episodes of instability and this may injure the meniscus, cartilages and other ligaments. Long term consequences of an ACL injury can result in knee osteoarthritis, create pain and functional disability.¹ In the majority of cases, the surgery is necessary to constitute stability and prevent further injury. Currently, ACL reconstruction remains the mainstay treatment.

In addition to surgery, the essential factor that determines the

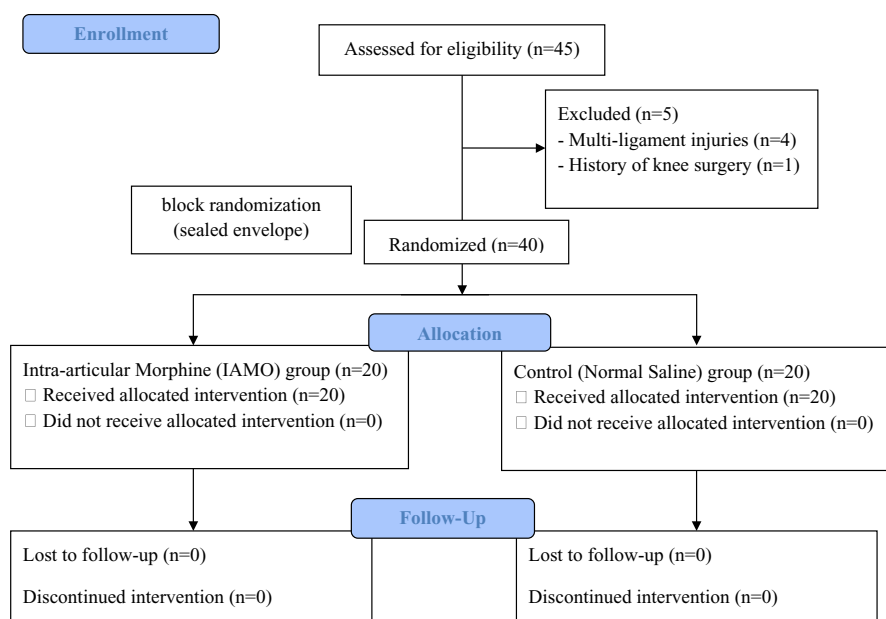
success rate of treatment is postoperative rehabilitation. This constitutes early restoration of range of motion, proprioception training and muscle strengthening.^{2,3} However, early postoperative rehabilitation can be a struggle because of postoperative pain leading to a less than satisfactory outcome. Therefore, adequate pain control would aid the patient to efficiently achieve postoperative rehabilitation goals, decrease the length of stay and reduce complications such as; stiffness and range of motion deficits that have an impact on pain, gait, and function.⁴

Intraarticular analgesia has been recommended to alleviate the pain. Recent studies suggest that apart from rehabilitation, intra-articular injections also help reduce opioid use.⁵ According to the (American Society of Anesthesiologist) ASA Task Force on Acute Pain Management, a multimodal analgesic approach is effective for pain control and reduces the adverse effects of each analgesic.^{6,7}

However, Intraarticular analgesia should be used with caution

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because there are reports that Bupivacaine or Lidocaine may cause chondrolysis in joints with compromised cartilages^{8,9} while exposure to morphine or fentanyl has not shown increased chondrotoxic effects.^{10,11}

Morphine is an opioid and generally used in postoperative pain management. Thus, this study's aim is to evaluate the analgesic effect of intraarticular morphine injection for postoperative pain control. There are studies which indicate that peripheral inflammation can be effectively controlled by opioid peptides with opioid receptors on peripheral sensory nerve terminals that can produce significant analgesic and anti-inflammatory effects without the central opioid-mediated side effects (e.g., respiratory depression, pruritus, sedation, etc.).¹¹ This is a great benefit to the patients. The purpose of this study is to compare the effect of intra-articular morphine (IAMO) with normal saline (control) in postoperative ACL reconstruction.

Material and methods

Inclusion and exclusion criteria

After formal approval by the institutional review board in human ethical committee research of Khon Kaen hospital No.KE60094, this study was registered with the Thai Clinical Trials Registry (www.clinicaltrials.in.th) TCTR No.TCTR20190903004. The inclusion criteria in this study consisted of patients between 18 and 40 years of age who were scheduled to undergo ACL reconstruction. Exclusion included; patients who refused to participate in the study, patients with injuries to other knee ligaments, patients with a history of knee surgery, patients with a history of opioid allergy, patients with a history of drug addiction, and patients who received any anesthesia or postoperative analgesia different from stated protocol.

Consecutive series of patients who met the inclusion criteria were recruited between June of 2017 to June of 2019. Forty patients were included in this prospective study. No patients were excluded. All patients signed the consent form and gave assent for participation in this study.

Study design

The anesthesia was always performed by the same group of anesthetists and consisted of a spinal block with 15 mg of bupivacaine without a spinal opioid. All the patients who have undergone arthroscopic ACL reconstruction had the surgery performed by the same surgeon (ST). Associated meniscal and chondral lesions were also treated and recorded.

Forty patients who met the eligible criteria were enrolled in the study and were randomized into 2 groups; intra-articular morphine (IAMO group) and Normal saline [control group (C)], without the recognition of the surgeon or of the patient by using a block randomization technique and drawing a sealed envelope just prior to the surgery by the operating room technician. After performing ACL surgery and before arthroscope removal and closure: (1) In the IAMO group, 15 mg of morphine (10 mg/ml) with 20 ml normal saline were injected into the knee joint. (2) In the Control group, 20 ml of normal saline was injected into the knee joint. The patient's drain was clamped for an hour after the injection. The postoperative medication protocols were established to reduce pain for all postoperative patients; patients received Acetaminophen (500 mg) 2 tablets every 6 h and Naproxen (250 mg) 1 tablet every 12 h. If the patient had pain scores from a visual analog scale (VAS) greater than 5, 0.05 mg/kg intravenous morphine was prescribed to reduced pain every 2 h, depending on the patient's need. All patients received the same analgesic protocol.

Study outcomes

We recorded four parameters for comparisons of the outcomes between both groups. These include: (1) Time to first analgesic request; (2) The postoperative pain which was assessed by using the visual analogue scale (VAS) and recorded at 6, 12, 18 and 24 h after the spinal block; (3) Postoperative consumption of intravenous opioids; (4) Postoperative complications such as nausea, vomiting, sedation, pruritus, and urinary retention.

Table 1
Baseline characteristics.

Baseline characteristics	Control group (n = 20)	IAMO Group (n = 20)	p-value
Age (years) – Mean (SD)	27.8 (9.3)	22.9 (4.6)	0.041
Sex – Male/Female	16/4	16/4	–
Height (cm) – Mean (SD)	170.5 (5.3)	171.5 (8.7)	0.663
Weight (kg) – Mean (SD)	67.9 (12.5)	68.6 (14.5)	0.871
BMI – Mean (SD)	23.3 (3.5)	23.2 (3.8)	0.974
ACL injury – n	20 (100%)	20 (100%)	–
Medial meniscus injury – n	8 (40%)	6 (30.0%)	0.507
Lateral meniscus injury – n	9 (45%)	3 (15%)	0.038
PF joint arthrosis – n	0	0	–
Medial compartment arthrosis – n	0	0	–
Lateral compartment arthrosis – n (%)	0	0	–
Operative time (minutes) – Mean (SD)	84.1 (18.5)	78.1 (22.8)	0.367

Statistical analysis

The sample size was calculated for a paired design to determine that at least 20 surgical knees per group were required to detect a difference in the accuracy of >10% with 80% power. Quantitative data were expressed as the means \pm SD and qualitative data as numbers and percentages. The time to the first rescue medication, pain visual analog scale scores, consumption of postoperative morphine of both groups were compared by using the paired Student's t-test. A value of $p < 0.05$ was considered as indicating a statistical significance. Statistical analysis of the results was conducted using SPSS for Windows, version 10.0.

Results

Forty patients were enrolled in the study, 20 patients were in the IAMO group with an equal number in the control group. Demographic data of both groups are shown in Table 1. All data had been collected and documented. Time to first analgesic request was longer ($P = 0.069$) in the IAMO group. Total morphine consumption was lower ($P = 0.562$) in the IAMO group. The postoperative pain, which was assessed by using the visual analog scale (VAS), was recorded at 6, 12, 18 and 24 h after the spinal block and was lower in every period. This was especially evident at 12 h (4.7 ± 1.7 vs 5.8 ± 1.6 , $P = 0.0518$). No adverse events occurred in either group. The summary of the data is shown in Tables 2 and 3.

Discussion

Multimodal analgesia is generally used and is widely accepted for the treatment of postoperative pain⁶. One of the approaches is intra-articular analgesia that can control the pain and help to avoid

supplementary medications. Morphine is one of the most common drugs that can be used, safely. However, the optimal dose and safety for intraarticular analgesia with high dose morphine has yet to be determined. We used in intra-articular morphine comparing to normal saline because of the safety and analgesic effect proven of the intra-articular morphine administration.¹¹ Intra-articular injection used the same volume of morphine and normal saline should reduce the bias of study due to intra-articular extension of joint fluid. We did not compare to the other analgesic drugs such as bupivacaine or lidocaine that might induce chondrolysis of the joint.^{8,9}

The result of this study demonstrates that intra-articular analgesia with 15 mg morphine can reduce the pain in every period of data collection after spinal anesthesia, especially at 12 h post-operatively. This is a critical factor for postoperative rehabilitation in ACL reconstruction. Moreover, the time to the first analgesic request was longer, and total morphine consumption (did not include the 15 mg IAMO) was slightly lower than in the control group (no significant difference between the 2 groups, $P = 0.562$). Despite the relatively high dose of Morphine, intra-articular injections are apparently safe. As a result, no complications were observed. IAMO patients had less pain during mobilization especially in the first 12 h post-operative and all achieved expect range of motion. Some of the control patients did not achieved range of motion as expectation.

We came to corresponding results when comparing our study with others. Yari et al.⁵ has shown that adding 15 mg Morphine to Bupivacaine after arthroscopic knee surgery can reduce systemic narcotic use and prolong analgesic duration without any complications. However, our study did not use Bupivacaine as its effects may be confounding.

Drosos et al.¹² reported the postoperative analgesic effect of

Table 2
Summary of Time to first analgesic request and total morphine consumption.

Outcome	Control group (n = 20)	IAMO Group (n = 20)	p-value
Time to first analgesic request (Hours) – Mean (SD)	6.2 (1.7)	7.3 (1.8)	0.069
Total morphine consumption (mg/kg) – Mean (SD)	0.12 (0.07)	0.11 (0.05)	0.562

Table 3
Summary of Visual analogue scale.

Outcome	Control group (n = 20)	IAMO Group (n = 20)	Mean difference (95%CI)	p-value
6 h – Mean (SD)	4.4 (3.0)	4.6 (2.7)	0.3 (–0.9 to 1.6)	0.824
12 h – Mean (SD)	5.8 (1.6)	4.7 (1.7)	–0.9 (–2.2 to 0.4)	0.052
18 h – Mean (SD)	5.1 (2.0)	4.6 (2.1)	–0.4 (–1.7 to 0.9)	0.449
24 h – Mean (SD)	4.2 (1.8)	3.8 (1.7)	–0.2 (–1.5 to 1.1)	0.533

intra-articular administration of a low- and a high-dose morphine solution after knee arthroscopy (diagnostic arthroscopy or arthroscopic meniscectomy). They found that the pain scores in the group of low-dose morphine were lower than in the control group. Also, there was evidence that higher doses can cause hyperalgesia. However, our study indicates an opposing conclusion. Our study revealed only 12 h post-operative time point showed statistically significant difference, the intra-articular morphine may have efficacy about 6–12 h after administration. The intra-articular route might not have initially effect when first administer due to low lipid solubility, morphine penetrates the blood–brain barrier slowly, causing it to have a relatively slow onset of effect if administered via a route beyond this anatomical route.¹³

Our study has several strengths. First, morphine is an opioid and is generally used for postoperative pain management. Second, the postoperative pain evaluator was blinded and that can reduce or eliminate experimental biases. Third, from our information, this study is the fundamental investigation using high-dose intra-articular morphine in patients who underwent ACL reconstruction. Fourth, all patients were treated by the same surgeon, the same group of anesthetists and received the same postoperative rehabilitation program to reduce performance bias.

This study has weaknesses. First, the relatively low number of participants. Second, pain control was assessed by the patients' requests of opioid injections, not by patient-controlled analgesia.

In this study, we use 15 mg of morphine, which is relatively high. However, there's still inconclusive information regarding the optimal dose of intra-articular morphine. Further studies could be done with higher doses that may, significantly improve pain control.

Conclusion

Intraarticular morphine provides improved pain control, notably at 12 h post-operative and has shown beneficial effects on decreasing systemic narcotic use. The IAMO is useful in ACL reconstruction patients without complications. Further studies addressing the optimal dosage of intra-articular morphine are needed to verify our results and to determine benefits and pitfalls with higher doses.

Ethics approval

This study was conducted with the formal approval of the institutional review board in human ethical committee research of

Khon Kaen hospital No.KE60094. Informed, signed consent forms were obtained from all of participants prior to injections.

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No funding was obtained for this study.

Declaration of competing interest

None of the authors have relevant conflicts of interest to declare.

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