Original Article

Reconstruction of the anterior cruciate ligament: comparison of analgesia using intrathecal morphine, intra-articular morphine and intra-articular levobupivacaine

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Objective: To compare the analgesic effect of intra-articular administration of morphine and levobupivacaine (separately or in combination) with intrathecal administration of morphine in patients undergoing anterior cruciate ligament (ACL) reconstruction using autologous grafts from the patellar tendon.

Methods: This was a retrospective analysis on data gathered from the medical files of 60 patients aged 20 to 50 years who underwent knee video arthroscopy for ACL reconstruction. The patients were divided into four groups of 15 individuals (A, B, C and D) according to the agent administered into the joint and around the incision: 20 mL of saline solution with 5 mg of morphine in A; 20 mL of 0.5% levobupivacaine solution in B; 10 mL of solution with 2.5 mg of morphine plus 10 mL of 0.5% levobupivacaine solution in C; and morphine administered intrathecally in D.

Results: All the groups presented low pain scores during the first 12 h after the surgery. Groups B and C presented significantly greater pain scores than those shown by group D (control), 24 h after the surgery. There was no statistical difference in pain scores between group A and group D.

Conclusion: The patients in group A presented analgesia comparable to that of the patients in group D, whereas the procedure of group C was no capable of reproducing the analgesic effect observed in group D, as observed 24 h after the surgery. Further studies are needed in order to show the exact mechanism of action, along with the ideal dose and concentration for applying opioids to joints.

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### Resumo

**Objetivo:** Comparar o efeito analgésico da administração intra-articular de morfina e levobupivacaina (isoladas ou associadas) com a administração intratecal de morfina em pacientes submetidos à reconstrução do LCA com exerto autólogo de tendão patelar.

**Métodos:** Análise retrospectiva dos dados coletados nos prontuários de 60 pacientes entre 20 e 50 anos, submetidos à videoartroscopia de joelho para reconstrução do LCA. Os pacientes encontravam-se separados em quatro grupos de 15 pessoas (A, B, C e D) de acordo com a administração intra-articular e peri-incisional de 20 mL de solução salina com 5 mg de morfina em A, 20 mL de solução a 0,5% levobupivacaina em B, 10 mL de solução com 2,5 mg de morfina e 10 mL de solução a 0,5% de levobupivacaina em C e morfina intratecalmente em D.

**Resultados:** Todos os grupos apresentaram baixos escores de dor nas primeiras 12 horas após a cirurgia. Os grupos B e C apresentaram escores de dor significativamente maiores do que o grupo D (controle) 24 horas após a cirurgia. Não houve diferença estatística entre os escores de dor do grupo A e do grupo D.

**Conclusão:** Nos pacientes do grupo A houve analgesia comparável à dos pacientes do D, ao passo que o procedimento em C não foi capaz de reproduzir o efeito analgésico observado em D quando os indivíduos foram estudados após 24 horas da cirurgia. Novos estudos são necessários para evidenciar o exato mecanismo de ação, bem como a dose e concentração ideais para aplicação articular de opioides.

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### A Introdução

O ligamento cruçado anterior (ACL) é um dos ligamentos mais afetados por lesões de joelho.1 O número de lesões de ACL é aumentando rapidamente devido ao aumento nas atividades físicas e esportivas.2 Arthroscópica ACL reconstrução é um procedimento cirúrgico de sucesso no campo ortopédico.3 A preponderância de técnicas e materiais são usados em todo o mundo.4 O hipertônico tornam-se cada vez mais comuns como uma opção de cirurgia de tratamento de joelho.5 A compreensão da técnica ortopédica para desempenho adequado após a reconstrução torna-se extremamente importante.6 A condução da dor pós-operatória é uma questão importante para os cuidadores do paciente e os próprios pacientes.7 A dor pós-operatória está associada com o tempo de recuperação e os custos de hospitalização.8 As técnicas anestésicas são usadas durante a cirurgia e após a cirurgia para diminuir a dor.9 As técnicas de anestesia incluem o uso de analgésicos, sedação e técnicas de bloqueio neuromuscular.10,11 As técnicas anestésicas utilizadas incluem a analgesia intratecal, peridural, regional e local.12,13

A variedade de métodos de analgesia pós-operatória é frequentemente usada: cryo-, systemic analgesics e anti-inflammatory drugs (administered orally, intramuscularly or intravenously),10 intra-articular injection of drugs,11-18 anesthetic block of peripheral nerves19,20 and intrathecal and peridural injection of analgesic drugs.21

O tratamento ideal não deve fornecer apenas analgesia adequada, mas também deve ser seguro, com um baixo risco de complicações e efeitos colaterais. A analgesia intra-articular de uso de drogas há a vantagem de diminuir o uso de drogas com ação sistêmica (intravenosa ou oral) e seus efeitos colaterais.22 Isso pode ser uma técnica atraente para uso clínico. Seis diferentes foram propostos e testados para a analgesia intra-articular, que incluem opioides11,21 não-esteroidais anti-inflamatórios11,21 e anestésicas locais.17,23

A analgesia intra-articular após a reconstrução é um assunto que já foi analisado em vários estudos. No entanto, são necessárias mais variações relacionadas à técnica cirúrgica, tipo de anestesia, dose de analgésico, tempo de administração e protocolo pós-operatório.

A expectativa dos autores deste estudo é que a analgesia intra-articular depois da reconstrução de joelho deve ser capaz de substituir o uso de analgésicos intratecal e evitando-se o uso de anestésicos sistêmicos, com uso de drogas que evitem os efeitos colaterais. Isso pode ser uma questão importante que deve ser investigado no futuro.22 A dor pós-operatória após a reconstrução de joelho é um assunto que precisa ser abordado adequadamente.24-26
and surgical techniques most often used are spinal anesthesia and arthroscopic reconstruction using autologous grafts from the patellar tendon.

This study had the objective of comparing the analgesic effects from intra-articular administration of morphine and levobupivacaine (separately or in association) with intrathecal administration of morphine, in patients who underwent ACL reconstruction with an autologous graft from the patellar tendon.

**Material and methods**

A retrospective analysis was conducted on data gathered from the medical files of 60 male patients aged 20 to 50 years, whose physical state graded in accordance with the standard of the American Society of Anesthesiology (ASA) was I to II. These patients underwent videoarthroscopy on a knee for ACL reconstruction by means of the same surgical technique in 2012, consisting of use of a graft from the patellar tendon and interference screws for its fixation to the femur and tibia.

This study was conducted in the Orthopedics and Traumatology Service of Hospital São Francisco de Ribeirão Preto, São Paulo, after obtaining approval from the Ethics Committee of Hospital das Clínicas, Ribeirão Preto Medical School, University of São Paulo (USP).

Among all the medical files analyzed, 15 patients received intra-articular application (15 mL) and peri-incisional application (5 mL) of 5 mg of morphine in 20 mL of physiological solution at the end of the operation. These patients were identified as Group A. Fifteen patients received intra-articular application (15 mL) and peri-incisional application (5 mL) of 20 mL of 0.5% levobupivacaine without vasoconstrictor and were identified as Group B. Fifteen patients received intra-articular application (15 mL) and peri-incisional application (5 mL) of a solution containing 2.5 mg of morphine in 10 mL of physiological solution plus 10 mL of 0.5% levobupivacaine without vasoconstrictor and were identified as Group C. Fifteen patients received 75 mcg of intrathecal morphine alone, added to a spinal anesthesia solution, and were identified as Group D (Table 1).

The analgesia method used for each patient was chosen only as a function of the protocol that was in force at the time of the surgery. There was no draw or random selection of the protocol for each individual. The other patients operated over the period of this study were not included because either they did not fit within the inclusion criteria described above or no data relating to the numerical pain scale was available for them.

| Table 1 – Distribution in groups. |
|-----------------------------------|
| Group | No. of individuals | Interventions |
|-------|--------------------|---------------|
| A | 15 | Intra-articular and peri-incisional administration of 20 mL of saline solution with 5 mg of morphine |
| B | 15 | Intra-articular and peri-incisional administration of 20 mL of 0.5% levobupivacaine without vasoconstrictor |
| C | 15 | Intra-articular and peri-incisional administration of 10 mL of saline solution with 2.5 mg of morphine plus 10 mL of 0.5% levobupivacaine without vasoconstrictor |
| D | 15 | Administration of 75 mcg of intrathecal morphine |

All the patients underwent spinal anesthesia consisting of 3 mL of 0.5% hyperbaric bupivacaine and postoperative analgesics were only prescribed if necessary, at the patient’s request. The following were used preferentially and progressively: 1 g of dipyrene intravenously, 100 mg of ketoprofen intravenously and 100 mg of tramadol intravenously. All of the patients received a prophylactic dose of between 50 mg/kg and a maximum of 2 g of cefalotin, along with 1 g of dipyrene and 30 mg of ketorolac tromethamine, intravenously, immediately before the start of the anesthesia. Furthermore, all the patients underwent the same surgical technique for ligament reconstruction, with or without associated meniscectomy, depending on the needs of each case, by two orthopedists who were knee surgeons with experience of this type of surgery.

Assessments of pain and postoperative side effects were recorded after six, 12 and 24 h by means of a numerical pain scale and values from 1 to 5 were attributed: 1 = absence of pain, without administration of analgesics; 2 = mild pain, without any need to use analgesics; 3 = moderate pain, alleviated using a single dose of analgesic; 4 = moderate pain, resolved using two or more doses of analgesics; and 5 = intense pain without any response to ordinary analgesics.

The results were analyzed using Student’s t test (p < 0.05) in comparison with Group D.

**Results**

All the groups presented similar distribution regarding weight and age. The results are presented in Table 2. The last column shows the values obtained from Student’s t test at the 5% significance level for comparing Group D with the other groups.

| Table 2 – Analgesic effect of different doses administered in patients who underwent ACL reconstruction. |
|---------------------------------------------------------------|
| Group | n | Weight (kg) | Age (years) | ASA | Pain index (1-5) | t |
|-------|---|-------------|-------------|-----|-----------------|---|
|       |   |             |             |     | 8 h             | 12 h | 24 h |
| A     | 15| 88 ± 14     | 29 ± 9      | I to II | 1.30 ± 0.21     | 1.40 ± 0.26 | 2.00 ± 0.23 |
| B     | 15| 80 ± 2.17   | 29 ± 1.98   | I to II | 1.13 ± 0.09     | 1.69 ± 0.15 | 2.42 ± 0.25 |
| C     | 15| 82 ± 2.40   | 31 ± 2.82   | I to II | 1.05 ± 0.05     | 1.20 ± 0.09 | 2.58 ± 0.18 |
| D     | 15| 97 ± 13     | 26 ± 6      | I to II | 1.10 ± 0.10     | 1.50 ± 0.26 | 1.40 ± 0.22 |

| t | \( t_{150.85} \) | n t | \( t_{0.05} \) |
|---|----------------|-----|----------------|
| 8 h | 1.85 | 2.94 | 4.35 s |

levobupivacaine.
Regarding the pain evaluation, all the groups presented low scores over the first 12 h after the surgery. Groups B and C presented significantly greater scores than Group D (control), 24 h after the surgery. There was no statistical difference between the scores of groups A and D.

There were no records of any allergic reactions or side effects.

**Discussion**

Opioid analgesics are widely used for achieving postoperative analgesia, either orally or intravenously, with well-known side effects: hypotension, respiratory depression, urinary retention, pruritus, nausea, constipation and mental alterations. Addition of morphine to the solution used for spinal anesthesia produced a good analgesic effect and reduced the need for systemic drugs, but this presented greater incidence of side effects than did the other administration routes. Stein et al. showed the presence of opioid receptors in peripheral tissues, which enabled local use of these drugs. The literature suggests that these receptors are preferentially present in inflamed tissues. Consequently, several authors have studied ways of using these drugs with different forms or associations, doses and application methods. Other variables involve the surgical procedure itself, the anesthesia techniques and the patients’ individual characteristics (gender, age, time with the injury and preoperative condition of the joint, etc.).

The pertinent literature presents contradictory results regarding the efficacy of intra-articular analgesia with opioids. In a systematic review of 27 articles on the efficacy of intra-articular application of morphine, Gupta et al. were able to perform a meta-analysis on 19 studies, among which 13 presented favorable results. These authors concluded that morphine injection in the joint space seemed to produce dose-dependent analgesia for up to 24 h. However, it was not possible to determine whether the effect was mediated by peripheral receptors or by systemic action. In this light, it is believed that variables such as preoperative joint morbidity, drug dose, volume of solution used and different anesthesia protocols may have contributed toward the heterogeneity of the results in the literature.

The type of graft used for ligament reconstruction also has an influence on the postoperative pain. Harvesting grafts from the patellar tendon involves greater surgical trauma than in relation to grafts from the flexor tendons and increases the pain generated by extra-articular structures. Koh et al. did not achieve pain reduction through intra-articular use of drugs among patients who underwent reconstruction with grafts from the patellar tendon. However, through an association of intra and periarticular applications, there was a significant decrease in the pain scores.

In the present study, intra-articular and peri-incisional application of 5 mg of morphine diluted in 20 mL of saline solution resulted in pain scores and use of systemic analgesics that were comparable with use of intrathecal morphine. The groups that only received 20 mL of levobupivacaine or 10 mL of levobupivacaine plus 2.5 mg of morphine obtained pain scores and use of systemic analgesics that were significantly greater than those of Group D (intrathecal morphine), especially 24 h after the procedure. None of the patients in Groups A, B, C or D presented any allergic reactions or side effects, but comparison between the side effects of different types of analgesia would require a greater number of patients and was not an objective of the present study.

This study presents some possible limitations. Standardization of the groups in relation to associated lesions and procedures such as meniscectomy, synovectomy, notch plasty and chondral lesions was not taken into consideration. Because the plasma levels of the drugs were not assayed, it cannot be stated whether the result obtained from Group A was due only to the effect of morphine on local receptors or also to the systemic distribution of the drug. Although there were statistically significant differences between Groups B and D and between Groups C and D, the pain scores and use of analgesics were very low among all the individuals. This indicates that adequate postoperative analgesia and comfort can be achieved efficiently with any of the approaches used.

**Conclusion**

Intra-articular and peri-incisional application of 5 mg of morphine in 20 mL of saline solution resulted in analgesia that was comparable with application of 75 mcg of intrathecal morphine in patients who underwent ACL reconstruction with grafts from the patellar tendon. Local administration of 20 mL of levobupivacaine or a solution of 10 mL of levobupivacaine plus 10 mL of saline solution containing 2.5 mg of morphine was not capable of reproducing the analgesic effect of intrathecal morphine in the individuals studied, 24 h after the surgery. New studies are needed in order to show the exact mechanism of action, along with the ideal dose and concentration for applying opioids to joints. Comparative studies on the incidence of side effects and complications from the different types of analgesia are also necessary.

**Conflicts of interest**

The authors declare no conflicts of interest.

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