RBO REVISTA BRASILEIRA DE ORTOPEDIA
www.rbo.org.br

Original Article

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

Leandro Queiroz Pinheiro[a], *Edmundo Neri Junior*[a], *Reginaldo Mendonça Fernandes*[a], *Rodrigo Tavares Cardozo*[a,*], *Priscila Rodrigues Rezende*[b]

[a] *Serviço de Ortopedia e Traumatologia de Ribeirão Preto, Ribeirão Preto, SP, Brazil*
[b] *Cooperativa dos Anestesiologistas de Ribeirão Preto, Ribeirão Preto, SP, Brazil*

ARTICLE INFO

Article history:
Received 18 December 2013
Accepted 3 April 2014
Available online 16 June 2015

Keywords:
Morphine/administration and dosage
Arthroscopy
Anterior cruciate ligament/surgery
Anesthesia

ABSTRACT

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 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.

☆ Work developed at the Serviço de Ortopedia e Traumatologia de Ribeirão Preto and at Hospital São Francisco, Ribeirão Preto, SP, Brazil.

* *Corresponding author.*
E-mail: torradarodrigo@hotmail.com (R.T. Cardozo).

http://dx.doi.org/10.1016/j.rboe.2015.06.002

Reconstrução do ligamento cruzado anterior: comparação da analgesia com morfina intratecal, morfina intra-articular e levobupivacaína intra-articular

Palavras-chave:
Morfina/administração e dosagem
Artroscopia
Ligamento cruzado anterior/cirurgia
Anestesia

RESUMO

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

Métodos: Análise retrospectiva dos dados coletados nos prontuários de 60 pacientes entre 20 e 50 anos, submetidos à vídeoartroscopia 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% levobupivacaína em B, 10 mL de solução com 2.5 mg de morfina e 10 mL de solução a 0.5% de levobupivacaína 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.

Introduction

The anterior cruciate ligament (ACL) is the ligament most affected by knee injuries.[1] The majority of ACL injuries are related to practicing sports, especially those that demand rapid changes in direction in association with body contact.[2] Arthroscopic ACL reconstruction is a successful orthopedic procedure that is frequently performed. A considerable variety of techniques and materials are used in it.[3] In the United States, approximately 175,000 reconstructions involving this orthopedic operation are performed every year. ACL reconstruction has now become a worldwide practice[4] and is increasingly being performed as an outpatient procedure. In the service from which the present study originated, 204 ACL reconstruction operations were performed by two knee surgeons in 2012.

Adequate control over postoperative pain, particularly during its peak intensity on the first days after the operation, is a common concern shared by the surgeon, anesthetist, patient and physiotherapist. Good control over this pain enables early hospital discharge, comfort and the confidence to place weight on the operated limb early on and do physiotherapeutic exercises that have the objective of allowing gains in joint range of motion. It also prevents arthrofibrosis, improves tonus and muscle trophism and allows better motor control over the limb.[5,6] Among the benefits, greater independence in day-to-day activities and minimization of the duration of interruption of work activities can be highlighted.[5–7]

A variety of types of postoperative analgesia are frequently used: cryotherapy,[8,9] systemic analgesic and anti-inflammatory drugs (administered orally, intramuscularly or intravenously),[10] intra-articular injection of drugs,[11–18] anesthetic block of peripheral nerves[19,20] and intrathecal and peridural injection of analgesic drugs.[21]

The ideal treatment not only should provide adequate analgesia but also should be safe, with low incidence of complications and side effects. Intra-articular use of drugs has the advantage of diminishing the need for drugs with systemic action (intravenous or oral) and their side effects.[22] This is therefore an attractive method for clinical practice. Several drugs have been proposed and tested for intra-articular use, including non-steroidal anti-inflammatory drugs,[11,21] opioids[14,23] and local anesthetics.[17,23]

Although intra-articular analgesia after ACL reconstruction has already been analyzed in many studies, there are large numbers of variables relating to the surgical technique, type of anesthesia, drug dose, time for drug injection and postoperative protocol.

The expectation of the authors of the present study is that intra-articular drug application should be capable of replacing the use of intrathecal morphine and should diminish the need for intravenous administration of analgesics, in order to avoid their side effects. It can also be emphasized that, in investigating the pertinent literature, it was observed that in most of these studies, general anesthesia and autologous grafts from the flexor tendons were used. However, in the services where the present study was conducted, the anesthetic

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 dipyrone 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 dipyrone 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	t_{DA} 1.85 nst_{DB} 2.94 st_{DC} 4.35 s
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	

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.[24] 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.[25] Stein et al.[26] 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.[26,27] 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.[16] were able to perform a meta-analysis on 19 studies, among which 13 presented favorable results. These authors[16] 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.[15] 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.

REFERENCES

1. Camanho GL, Camanho LF, Viegas AC. Reconstrução do ligamento cruzado anterior com tendões dos músculos flexores do joelho fixos com Endobutton. Rev Bras Ortop. 2003;38(6):329–36.
2. Cohen M, Marcondes FB. Lesões ligamentares. In: Cohen M, coord., editors. Tratado de ortopedia. São Paulo, Roca: Comissão de Educação Continuada da Sociedade Brasileira de Ortopedia e Traumatologia; 2007. p. 401–11.
3. Astur DC, Aleluia V, Santos CV, Arliani GG, Badra R, Oliveira SG, et al. Riscos e consequências do uso da técnica transportal na reconstrução do ligamento cruzado anterior: relação entre o túnel femoral, a artéria genicular lateral superior e o epicôndilo lateral do côndilo femoral. Rev Bras Ortop. 2012;47(5):606–10.
4. Meuffels DE, Reijman M, Verhaar JAN. Computer-assisted surgery is not more accurate or precise than Conventional

Arthroscopic ACL Reconstruction: a prospective randomized clinical trial. J Bone Joint Surg Am. 2012;94(17):1438–45.
5. Wright RW, Preston E, Fleming BC, Amendola A, Andrish JT, Bergfeld JA, et al. A systematic review of anterior cruciate ligament reconstruction rehabilitation. Part I: continuous passive motion, early weight bearing, postoperative bracing, and home-based rehabilitation. J Knee Surg. 2008;21(3):217–24.
6. Wright RW, Preston E, Fleming BC, Amendola A, Andrish JT, Bergfeld JA, et al. ACL: a systematic review of anterior cruciate ligament reconstruction rehabilitation. Part II: open versus closed kinetic chain exercises, neuromuscular electrical stimulation, accelerated rehabilitation, and miscellaneous topics. J Knee Surg. 2008;21(3):225–34.
7. Shaw T, Williams MT, Chipchase LS. Do early quadriceps exercises affect the outcome of ACL reconstruction? A randomised controlled trial. Aust J Physiother. 2005;51(1): 9–17.
8. Daniel DM, Stone ML, Arendt DL. The effect of cold therapy on pain swelling and range of motion after anterior cruciate ligament reconstructive surgery. Arthroscopy. 1994;10(5):530–3.
9. Edwards DJ, Rimmer M, Keene G. The use of cold therapy in the postoperative management of patients undergoing arthoroscopic anterior cruciate ligament reconstruction. Am J Sports Med. 1996;24(2):193–5.
10. Practice guidelines for acute pain management in the perioperative setting. A report by the American Society of Anesthesiologists Task Force on Pain Management, Acute Pain Section. Anesthesiology. 1995;82(4):1071–81.
11. Reuben SS, Steinberg RB, Cohen MA, Kilaru PA, Gibson CS. Intrarticular morphine in the multimodal analgesic management of postoperative pain after ambulatory anterior cruciate ligament repair. Anesth Analg. 1998;86(2):374–8.
12. Tetzlaff JE, Dilger JA, Abate J, Parker RD. Preoperative intrarticular morphine and bupivacaine for pain control after outpatient arthroscopic anterior cruciate ligament reconstruction. Reg Anesth Pain Med. 1999;24(3):220–4.
13. Convery PN, Milligan KR, Quinn P, Scott K, Clarke RC. Low-dose intra-articular ketorolac for pain relief following arthroscopy of the knee joint. Anaesthesia. 1998;53(11):1125–9.
14. Gądek A, Wordliczek J, Zajaczkowska R. Evaluation of analgesic efficacy of intra-articular opioids (morphine, fentanyl) after arthroscopic knee surgery. Arthroscopy. 2012;28(7):897–8.
15. Koh IJ, Chang CB, Seo ES, Kim SJ, Seong SC, Kim TK. Pain management by periarticular multimodal drug injection after anterior cruciate ligament reconstruction: a randomized, controlled study. Arthroscopy. 2012;28(5):649–57.
16. Gupta A, Bodin L, Holmstrom B, Berggren L. A systematic review of the peripheral analgesic effects of intraarticular morphine. Anesth Analg. 2001;93(3):761–70.
17. Moiniche S, Mikkelsen S, Wetterslev J. A systematic review of intra-articular local anesthesia for postoperative pain relief after arthroscopic knee surgery. Reg Anesth Pain Med. 1999;24(5):430–7.
18. Shapiro MS, Safran MR, Crockett H, Finerman GA. Local anesthesia for knee arthroscopy. Efficacy and cost benefits. Am J Sports Med. 1995;23(1):50–3.
19. Edkin BS, Spindler KP, Flanagan JF. Femoral nerve block as an alternative to parenteral narcotics for pain control after anterior cruciate ligament reconstruction. Arthroscopy. 1995;11(4):404–9.
20. Tetzlaff JE, Andrish J, O'Hara J Jr, Dilger J, Yoon HJ. Effectiveness of bupivacaine administered via a femoral nerve catheter for pain control after anterior cruciate ligament repair. Clin Anesth. 1997;9(7):542–5.
21. Duthie DJR, Nimmo WS. Adverse effects of opioid analgesic drugs. Br J Anaesth. 1987;59(1):61–77.
22. Butterfield NN, Schwarz SK, Ries CR, Franciosi LG, Day B, MacLeod BA. Combined pre- and post-surgical bupivacaine wound infiltrations decrease opioid requirements after knee ligament reconstruction. Can J Anaesth. 2001;48(3):245–50.
23. Alagol A, Calpur OU, Usar PS, Turan N, Pamukcu Z. Intrarticular analgesia after arthroscopic knee surgery: comparison of neostigmine, clonidine, tenoxicam, morphine and bupivacaine. Knee Surg Sports Traumatol Arthrosc. 2005;13(8):658–63.
24. Loper KA, Ready LB. Epidural morphine after anterior cruciate ligament repair: a comparison with patient-controlled intravenous morphine. Anesth Analg. 1989;68(3):350–2.
25. Ho ST, Wang TJ, Tang JS, Liaw WJ, Ho CM. Pain relief after arthroscopic knee surgery: intravenous morphine, epidural morphine, and intra-articular morphine. Clin J Pain. 2000;16(2):105–9.
26. Stein C, Millan MJ, Shippenberg TS, Peter K, Herz A. Peripheral opioid receptors mediating antinociception in inflammation. Evidence for involvement of mu, delta, and kappa receptors. J Pharmacol Exp Ther. 1989;248(3):1269–75.
27. Stein C. Peripheral mechanisms of opioid analgesia. Anesth Analg. 1993;76(1):182–91.