Journal of Southeast Asian Orthopaedics
ISSN 2821-9848 (Print)
ISSN 2821-9864 (Online)
https://doi.org/10.56929/jseaortho-023-0177 https://jseaortho.org

Efficacy of Intra-Articular Ketorolac and Bupivacaine on Postoperative Pain Relief after Arthroscopic Anterior Cruciate Ligament Reconstruction: A Randomized Double-Blind Study

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Purpose: The purpose of our study was to determine whether there is any additional benefit to adding ketorolac, a non-steroidal anti-inflammatory drug (NSAID), to bupivacaine compared to bupivacaine alone in patients undergoing anterior cruciate ligament reconstruction (ACLR) surgery.
Methods: Fifty-two American Society of Anesthesiology I-II patients undergoing arthroscopic ACLR under spinal anesthesia were randomly assigned to one of two groups: group A (10 mL of bupivacaine 0.25% with ketorolac 60 mg) and group B (10 mL of bupivacaine 0.25%). At the end of the procedure, 10 mL of each drug was administered intra-articularly. The dose of intravenously administered analgesic medication (morphine) was calculated based on the patient's body weight and visual analog scale (VAS) score. The postoperative time to rescue analgesia, 24-hour analgesic requirement, VAS score at time of rescue (T-rescue), and findings at rest and during movement were observed.
Results: The VAS score at the time of rescue analgesic significantly lower in group A than in group B (33.85 ±19.61 ; 56.15±21.92) ($p < 0.001$). Group A had significantly lower 24-hour analgesic consumption than group B (0.28±0.07 ; 0.39±0.09) ($p < 0.001$).the mean duration of analgesia was longer in group A than in group B (320 minutes ; 235 minutes)($p = 0.194$) however, this difference was not statistically significant.
Conclusions: Intra-articular administration of a combination of ketorolac and bupivacaine resulted in a significantly longer duration of analgesia and reduced morphine use in the 24-hour postoperative period and is an effective option for reducing postoperative pain.

Keywords: intra-articular injection, ketorolac, anterior cruciate ligament reconstruction, postoperative pain, bupivacaine

Anterior cruciate ligament reconstruction (ACLR) is a common knee surgery that can cause intense pain at the sites of graft harvest and tibial and femoral tunnels, leading to a slower recovery and increased morbidity. Postoperative pain can negatively impact quality of life and work performance[1]. Numerous studies have been conducted on the use of various drugs and combinations of drugs administered intra-articularly to improve analgesic efficacy. However, many patients experience moderate-to-severe pain 24 hours after knee arthroscopy, which can disrupt sleep and affect activity levels[2].

Article history:
Received: October 14, 2022, Revised: April 26, 2023
Accepted: May 9, 2023
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Ketorolac, non-steroidal anti-inflammatory drug (NSAID), can be used locally as an analgesic or as an intra-articular injection. In its active form, ketorolac acts on synovial tissue. It has a high degree of protein and tissue binding, which slows drug transport across the synovium and out of the joints[3]. It may also prevent the release of proinflammatory cytokines such as interleukin-1, which is associated with excessive cartilage degradation under inflammatory conditions.

In an animal study[4], no differences were found between ketorolac (NSAID) and saline (SAL) injection groups for any parameter measured at any time point. This study evaluated knee kinematics, including measured forces (propulsion, vertical, medial, lateral, and braking), paw placement (stride width and length), and timing (speed, rate of loading, and stance time) of ambulation, for both the NSAID and SAL groups. Ge et al.[5] found that the use of NSAIDs after ACLR is relatively safe and could decrease the adverse side effects caused by opioid drugs. Constantinescu et al.[6] conducted a systematic review and found insufficient data to definitively state the effects of perioperative NSAIDs on soft tissue healing. The use of NSAIDs should be considered on a case-by-case basis and may not affect healing rates after meniscal, ACL, rotator cuff, or Bankart repair.

This study aimed to investigate whether the combination of ketorolac and bupivacaine has a synergistic effect in reducing pain and the use of opioids. The effects of both drugs on different pathways were evaluated.

METHODS

This study included a sample group of patients with ACL who underwent surgery between 2018 and 2020 performed by two experienced surgeons. The study was approved by the institute's ethics committee, and 52 American Society of Anesthesiology I-II patients were randomly assigned to one of two groups: group A received 10 mL of bupivacaine 0.25% with 60 mg of ketorolac, and group B received 10 mL of bupivacaine 0.25%. At the end of the procedure, 10 mL of each drug was administered intra-articularly. The postoperative time to rescue analgesia, 24-hour analgesic requirement, and visual analog scale (VAS) scores at rest and during movement were recorded. (Table 1)

Randomization was performed using computer-generated random numbers and the sealed-envelope technique. Patients were divided into two groups: group A received an intra-articular injection of 10 mL of bupivacaine 0.25% combined with ketorolac 60 mg, whereas group B received 10 mL of 0.25% bupivacaine only. The injections were administered through the anterolateral arthroscopy port immediately before skin closure. The patients were instructed to use the VAS for postoperative pain evaluation and were unaware of their group allocation. All patients received spinal anesthesia in accordance with standard protocols. After standard monitors (electrocardiogram, noninvasive blood pressure monitor, and pulse oximeter) were attached, patients were preloaded with 10 mL/kg of crystalloid and then given heavy spinal anesthesia (3 mL of bupivacaine 0.5%) using strict aseptic precautions while in the lateral position. A tourniquet was applied 10 minutes later at approximately T10 at a pressure of 100 mmHg above systolic blood pressure.

Smith & Nephew arthroscopic equipment was used for ACLR with an ipsilateral quadruple hamstring tendon graft (semitendinosus and gracilis double-folded) with an endobutton for femoral fixation and a bioabsorbable interference screw for tibial graft fixation via a two-portal technique. The treatment of patients with meniscal lesions involves using the all-inside technique for meniscal repair with the Fast-Fix 360 device from Smith & Nephew. At the end of the procedure, a blinded individual administered the drug combinations through the anterolateral port site using preloaded, unlabeled syringes prepared by another person. The tourniquet was gradually deflated after 10 minutes, and a compression bandage was applied along with an additional crepe bandage. The knees were immobilized using a knee brace.

After surgery, patients received postoperative care in the post-anesthetic care unit for approximately 1 hour. Pain was assessed using the 100 mm VAS (100 mm) every 4 hours for 24 hours after surgery. Pain relief medication (morphine)

was administered according to the level of pain reported by Aubrun et al.[7] Patients with a VAS score <30 were administered 0.075 mg/kg of morphine, those with a VAS score of 30-70 were given 0.1 mg/kg of morphine, and those with a VAS score >70 were given 0.15 mg/kg of morphine. The time to the first request for analgesics (T-rescue) and VAS findings (VAS T-rescue) were recorded. Tourniquet pressure and duration were also recorded along with demographic parameters, duration of surgery, and total dose of morphine administered within 24 hours. Pain intensity was monitored using a VAS (0 = no pain, 100 = worst possible pain). Any side effects such as nausea, vomiting, sedation, pruritus, or urinary retention were noted and treated as needed. Hemodynamic parameters (blood pressure, heart rate, pulse oximetry saturation, and respiratory rate) were recorded every 15 minutes for 2 hours postoperatively. Both groups received baseline pain medication in the form of paracetamol 500 mg orally every 6 hours to reduce pain.

RESULTS

Fifty-two randomized patients completed the study. The demographic data of the patients showed no significant differences between the two groups. The median age was 29.6 years and both groups were comparable in terms of age, weight, and height. There were more male (n = 46) than female (n = 6) patients. Two surgeons with 8 and 5 years of experience performed surgeries on 30 (57.7%) and 22 (42.3%) patients, respectively. There were no differences between the groups in terms of tourniquet or surgery duration (Table 1). The effect of meniscal repair surgery on postoperative pain has been observed in a patient population within the study. However, owing to the randomization, it can be concluded that the factors related to meniscal repair had equal effects in both groups. Group A had significantly lower 24-hour analgesic consumption than group B (0.28±0.07 ; 0.39±0.09) ($p < 0.001$) and the mean duration of analgesia was longer in group A than in group B (320 minutes ; 235 minutes) ($p = 0.194$), but this was not statistically significant. The VAS score at the time of rescue analgesic significantly lower in group A than in group B (33.85 ±19.61 ; 56.15±21.92) ($p < 0.001$). (Table 2). No adverse effects of ketorolac or bupivacaine were observed in any patient.

Table 1 Demographic data.

Variables	All	Ketorolac + bupivacaine	Bupivacaine	p-value
Age (years) mean ± SD	29.62 ± 8.58	29.62 ± 9.01	29.62 ± 8.30	1.00
BMI (kg/m²) mean ± SD	24.55 ± 4.45	24.20 ± 3.59	24.91 ± 5.22	0.570
Sex, n (%)				
Male	46 (88.46)	23 (88.46)	23 (88.46)	1.00
Female	6 (11.54)	3 (11.54)	3 (11.54)	
ACL side, n (%)				0.575
Right	22 (42.31)	10 (38.46)	12 (46.15)	
Left	30 (57.69)	16 (61.54)	14 (53.85)	
ACLR technique, n (%)				0.579
Tranportal	26 (50)	12 (46.15)	14 (53.85)	
Trantibial	26 (50)	14 (53.85)	12 (46.15)	
Meniscus lesion, n (%)				0.535
None	7 (13.46)	3 (11.54)	4 (15.38)	
Meniscus lesion	45 (86.54)	23 (88.46)	19 (84.62)	
Tourniquet duration (min)	61.31 ± 14.09	61.92 ± 17.66	60.69 ± 9.62	0.756
Duration of surgery (min)	56.73 ± 12.57	56.35 ± 14.48	57.12 ± 10.61	0.828

ACLR, anterior cruciate ligament reconstruction; BMI, body mass index.

Table 2 Results.

Variables	All (n = 52)	Ketorolac + bupivacaine (n = 26)	Bupivacaine (n = 26)	p-value
Time to first request for analgesic (min)	267.5 (90-655)	320 (120-645)	235 (90-655)	0.194
VAS score at T-rescue (scale of 100)	45 ± 23.47	33.85 ± 19.61	56.15 ± 21.92	<0.001
24-hour morphine requirement (mg/kg)	0.33 ± 0.10	0.28 ± 0.07	0.39 ± 0.09	<0.001

VAS, visual analog scale.
Results are shown as mean (range) or mean ± standard deviation.

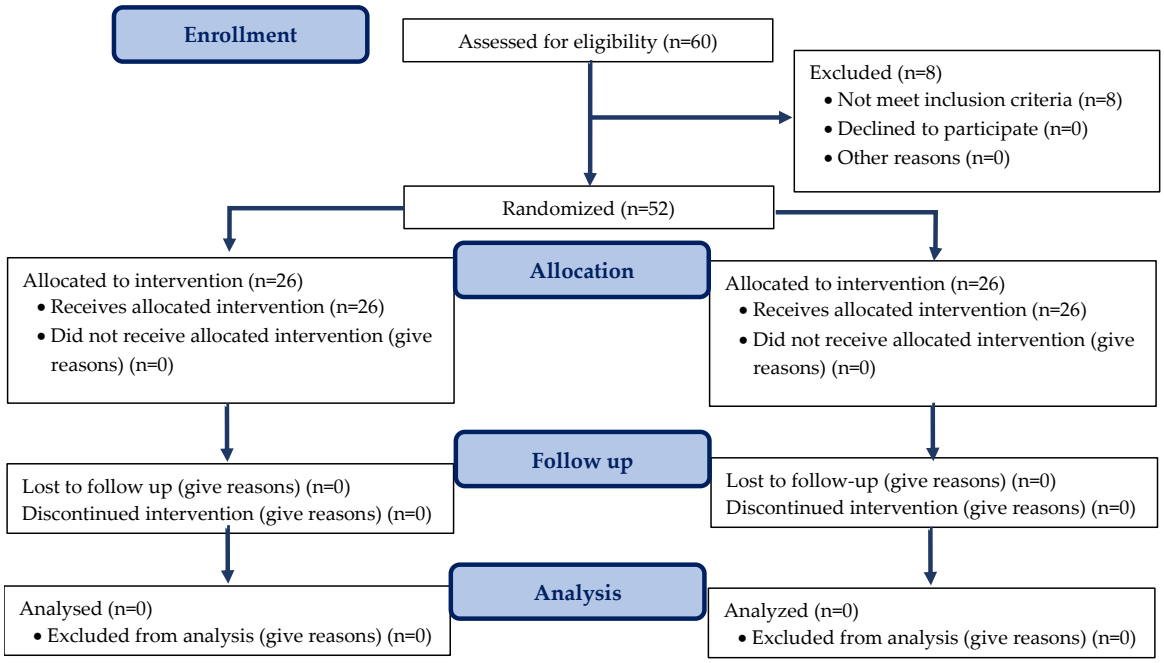

Fig. 1 CONSORT 2010 flow diagram.

DISCUSSION

The intra-articular administration of ketorolac and bupivacaine in patients undergoing ACLR helped reduce the use of morphine within 24 hours postoperatively.

Pain during arthroscopic surgeries is mainly due to surgical tissue handling and resection, causing irritation of the nerve endings in the synovial tissue, joint capsule, and anterior fat pad[8]. Bupivacaine, which has anesthetic effects and reduces pain, has been found to be effective in reducing pain and the use of opioids when used intra-articularly. Ketorolac has a high level of protein and tissue binding, which slows its transport across the synovium and out of the joints. NSAIDs act by inhibiting the production of COX-1 and COX-2, enzymes responsible for inflammation. It is used for the short-term management of moderate-to-severe pain in adults. Our study showed that the administration of a combination of ketorolac and bupivacaine resulted in a significantly longer duration of analgesia and reduced morphine use in the 24-hour postoperative period.

Guler et al.[9] compared intra-articular tenoxicam with morphine and saline and found that intra-articular tenoxicam injection significantly reduced pethidine use in patients after ACLR compared with morphine and saline.

Calmet et al.[10] compared the analgesic effects of intra-articular ketorolac, morphine, and

bupivacaine in patients undergoing arthroscopic knee surgery. Adding ketorolac to bupivacaine significantly reduced the dose of intravenous tramadol for postoperative pain relief. However, no studies have been conducted on intra-articular ketorolac in patients who underwent ACLR.

Vintar et al.[11] reported a significant difference in pain relief with an intra-articular mixture of ropivacaine, morphine, and ketorolac compared to placebo. However, there has never been a comparative study of formulations containing active NSAIDs such as ketorolac with other drugs. The purpose of this study was to determine whether analgesia combining ketorolac and bupivacaine compared to intra-articular bupivacaine alone could more effectively relieve pain in patients undergoing arthroscopic surgery.

In clinical practice, there are concerns regarding the effects of NSAIDs on ligament reconstruction healing. However, according to Ge et al.[5], the use of NSAIDs after ACLR is considered relatively safe and may decrease adverse side effects associated with opioid drugs. A systematic review by Constantinescu et al.[6] found that there are insufficient data available to determine the effect of perioperative NSAIDs on soft tissue healing. The use of NSAIDs should be evaluated on a case-by-case basis and may not affect healing rates following meniscal, ACL, rotator cuff, or Bankart repair.

This study has several limitations. First, short-term data were collected, with a period of 24 hours as the maximum time point. Second, a VAS was used as a subjective outcome measure, which may have introduced variability in the results. Third, although statistical differences were observed between the VAS scores at T-rescue and T-rescue, the clinical significance of these differences was not clearly defined. Patients with meniscal tears were enrolled in both randomized study groups and underwent repair using various techniques. However, data on the number of repairs performed in each group were not available, which could potentially affect postoperative pain outcomes.

CONCLUSIONS

The intra-articular administration of a combination of ketorolac and bupivacaine is an effective option for reducing postoperative pain.

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