Epidural administration of ropivacaine and midazolam is superior to intra-articular administration as postoperative analgesia after isolated arthroscopic anterior cruciate ligament reconstruction with hamstrings autograft: a randomized controlled clinical trial

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ABSTRACT

Objective: Reconstructive surgery of the anterior cruciate ligament (ACL) is quite common, previous studies have documented that adequate pain control in the early phases of the postoperative period translates into early mobility and a rapid start of rehabilitation. Therefore, the search for new strategies for postoperative pain control is justified. The aim of this study was to compare intra-articular to the epidural administration of ropivacaine and midazolam as postoperative analgesia after arthroscopic ACL reconstruction with hamstring autograft (HA).

Material and methods: Double-blinded, prospective randomized clinical trial included 108 consecutive patients aged from 18 to 50 years that had undergone arthroscopic ACL reconstruction with HA. The patients were randomly assigned to 2 groups. The first group received intraarticular ropivacaine and midazolam. The second group received epidural ropivacaine and midazolam. The need for rescue analgesia, the postoperative pain experienced, side effects and complications of the analgesic drugs were evaluated.

Results: The intra-articular group received statistically significantly higher mean doses of rescue analgesia on the first two days (2.8 ± 1.0 vs. 1.3 ± 0.6 in the epidural group; p = 0.001). Visual Analogue Scale scores at flexion were statistically significantly higher in the intra-articular group over the entire study period. The intra-articular group also reported a statistically significantly lower range-of-motion 87 ± 15 vs. 102 ± 11 in the epidural group (p = 0.001).

Conclusions: Epidural administration of ropivacaine combined with midazolam in patients undergoing primary ACL reconstruction with HA was clinically and significantly better relative to rescue analgesia and the intensity of pain in the first 48 postoperative hours when compared to intraarticular administration. There was no difference in terms of adverse effects and complications.

Level of evidence: 2.
What are the new findings?

- Pain, opioid consumption, and range-of-motion results were significantly better in the group with epidural administration of midazolam and ropivacaine when compared to the intra-articularly administered group.
- In patients undergoing isolated reconstructive surgery of the anterior cruciate ligament with a hamstring autograft, the use of midazolam and ropivacaine epidurally is effective for the treatment of immediate postoperative pain and is proposed as a new analgesia option for orthopedists and anesthesiologists.

INTRODUCTION

Anterior cruciate ligament (ACL) reconstruction is a common surgical procedure that presents moderate to severe postoperative pain in the knee [1–3]. Therefore, adequate pain control is required to start early mobilization and rehabilitation. Furthermore, pain relief has been associated with improved outcomes, early hospital discharge, and reduced oral and intravenous anesthetic drug administration [4–7].

ACL injuries have an incidence of 68.6 per 100,000 inhabitants in the United States, with them being the most common surgery for ligament injuries [4]. This lesion has also seen increased incidence over the last twenty years [8]. Similarly, the rate of ACL reconstructions increased 12-fold in the United Kingdom over the last 20 years [9].

Several analgesic strategies such as systemic medication, central or peripheral blocks, and intraarticular drug administration have been used to control pain [10–15]. Combined spinal-epidural anesthesia is a better option for knee surgery because it has advantages over general anesthesia and spinal or epidural anesthesia alone [16–20]. The combination reduces hospital stay and extends analgesia into the postoperative period without increasing morbidity. It also offers speed of onset, efficacy, and the minimal toxicity of spinal anesthesia and extends the analgesia into the postoperative period [16–18].

Intraarticular administration of single-dose local anesthetic solutions is an alternative to provide postoperative analgesia in patients undergoing ACL reconstruction. It reduces consumption and the possible side effects of oral and intravenous anesthetics [10,14,21]. Ropivacaine is the local anesthetic agent most administered in the knee. It provides effective pain relief in the ACL reconstruction postoperative period and has fewer chondotoxic effects than bupivacaine or mepivacaine [14,22–24].

Intra-articular midazolam has been widely studied in combination with dexmedetomidine, fentanyl, and bupivacaine [21,25–27] and have demonstrated effective control of postoperative pain in arthroscopic knee surgery [26,28]. Midazolam is the only fat-soluble benzodiazepine, which makes it the drug of choice for epidural administration. A similar mechanism occurs for the intra-articular route since human joints also have receptors that interact with the neurotransmitter GABA [21,24,26,29]. A few studies have reported that the addition of midazolam to epidural analgesia enhances the effect of local anesthetics without having adverse effects. It also provides better postoperative analgesia in arthroscopic surgeries [30,31].

The primary outcome of this study was the postoperative need for rescue analgesia (intravenous tramadol 0–48 h postoperatively) in addition to a standard non-opioid analgesic regimen in adults after primary ACL reconstruction with a hamstring autograft (HA). Secondary outcomes included pain after surgery assessed with the Visual Analogue Scale (VAS), the side effects of the analgesic drugs, the need for extra days of hospitalization due to pain, and the range-of-motion at 48 h postoperatively. We hypothesized differences in the need for rescue analgesia and postoperative pain when midazolam plus ropivacaine is administered epidurally when it is compared to intra-articular ropivacaine and midazolam.

METHODS

The protocol was registered in ClinicalTrials.gov with registration number NCT05078372 and approved by our institution’s Internal Review Board and Research Ethics Committee with registration number AN19-00003. All patients provided written informed consent for study participation before surgery. The study was conducted in accordance with the Declaration of Helsinki [32] and followed the established guidelines of the Consolidated Standards of Reporting Trials (CONSORT) [33].

Study group

Patients between 18 and 50 years who had undergone arthroscopic single-bundle ACL anatomic reconstruction with hamstring tendon autograft were candidates to participate in the study. Patients who had undergone another ligament surgery (posterior cruciate ligament, medial collateral ligament, posterolateral corner reconstruction), revision surgery, ACL reconstruction with an allograft, bone to bone or quadriceps autograft, double-bundle technique, patients with previous knee surgeries, open ACL reconstruction, partial reconstruction, augmentation or reparation of the ACL, use of the over-the-top technique or patients who underwent a corrective knee osteotomy, articular cartilage repair surgery, meniscal transplantation or a lateral extra-articular tenodesis at the time of the ACL reconstruction were excluded. Pregnant or lactating patients, patients consuming oral contraceptives, patients who presented with any contraindication for neuraxial blockade (e.g., coagulation defects, infection at the puncture site, or pre-existing neurological deficits in the lower extremities), anticoagulant or antiplatelet therapy that has not been suspended 48 h before the surgery, systemic infection, fever above 38.5 °C, preoperative assessment with ASA III-IV, previously known hypersensitivity to the study drugs, patients with intellectual impairment or psychiatric conditions that limit adequate communication or rehabilitation, patients with a diagnosis of fibromyalgia, polymyalgia rheumatica, reflex sympathetic dystrophy syndrome, complex painful syndromes or sciatic neuropathy (to avoid confounding biases), patients with chronic use of pain medications, and patients who refused to participate were also excluded.

Habitual treatment before hospital admittance with morphine, oxycodeone, tramadol, gabapentinoids, or selective serotonin reuptake inhibitors was continued. The VAS pain assessment, which consists of 11 points from 0 no pain to 10 maximum pain, was explained to the patients before treatment [34].

This study proposed a 1 on 1 randomization of ropivacaine plus intra-articular midazolam (intra-articular group) and ropivacaine plus midazolam via epidural block (epidural group) using a computer-generated randomized sequence (randomization.com) with varying block sizes (either 3, 6, or 9) unknown to the researchers. In strict accordance with the order of entry, each patient was assigned an identification number when they agreed to participate. The recruited patients were randomly assigned to two experimental groups: Intra-articular group: ropivacaine plus midazolam by intra-articular administration, and Epidural group: ropivacaine plus midazolam by epidural administration.
Anesthesia protocol

All patients received intravenous Ringer's lactate solution at 10 ml/kg. In the operating room, continuous electrocardiogram output, heart rate (HR), mean arterial blood pressure (MAP), and arterial oxygen saturation (SpO2) were monitored.

The surgeries were performed under combined spinal-epidural anesthesia by two anesthesiologists. Both anesthesiologists homogenized the protocol of the combined spinal-epidural block, which is described further on, before the start of the study. The patient was placed in the lateral decubitus position. Using an aseptic technique, the intervertebral space between L2-L3 or L3-L4 was superficially infiltrated with 2% lidocaine. The lumbar spinal level was identified with an 18-gauge Tuohy needle in the combined spinal-epidural kit (Espocan®, B Braun, Germany). The loss of resistance to a saline solution was used to confirm correct needle placement. Then, a Whitacre 25 spinal needle was placed, and the anesthesiologist confirmed the correct position by the free flow of cerebrospinal fluid. Then, 7.5 mg (1.5 ml) of 0.5% hyperbaric bupivacaine was administered. Afterward, an epidural catheter was introduced about 4 cm into the epidural space through the Tuohy needle for anesthesia maintenance, and 60 mg (3 ml) of lidocaine with 2% epinephrine was administered to ensure correct positioning outside a blood vessel. In case of a prolonged surgical time (>120 min), the anesthetic effect was extended through the epidural catheter. A third of the total dose calculated on the Bromage scale was administered according to the patient's age, lidocaine with 2% epinephrine [35]. Once the surgical procedure was completed and depending on the patient's group, postoperative analgesia was administered.

Intra-articular group: Intra-articular ropivacaine plus midazolam. Ropivacaine 0.75% at 1.5 mg/kg (Ropiconest®, PISA) was used with midazolam 50 mcg/kg (Relacum®, PISA) and saline solution to come to the 20 ml solution that was administered in the knee joint 10 min before tourniquet release. An elastomeric pump (Home Pump®, 5 ml/h for 24 h) was prepared for epidural infusion with 150 ml of physiological solution.

Epidural group: Epidural ropivacaine plus midazolam.

An elastomeric pump (Home Pump®, 5 ml/h for 24 h) was prepared for epidural infusion. The solution contained 150 mg (20 ml) of 0.75% ropivacaine plus midazolam 50 mcg/kg/12 h in 125 ml of physiological solution. Moreover, 20 ml of physiological solution was administered intrarticularly as a placebo in the ropivacaine plus epidural midazolam group. In both cases, the surgeon received a prefilled syringe for the intrarticular infiltration. The content was blinded for the team.

At the end of the surgery and before placing the patient in a supine position, liquid adhesive (Mastisol, Ferndale Pharmaceutics Ltd, UK) was placed on the back and then Tegaderm film (3 M, Neuss, Germany) and tape was put in place to achieve a correct fixation to the patient's skin. The patient and medical staff were asked to carefully move the patient away from the bed or surfaces when moving or transferring to avoid accidental loss of the catheter.

Only one person not related to the study knew which drugs were administrated. The drugs were prepared in unlabeled syringes with the same volume and were recorded separately by a nurse who was not involved in the study analysis. A blinded investigator, who was not involved in the patients' anesthetic care or surgery, collected all study data. The surgeon, anesthesiologist, and rehabilitator were blinded to group allocation.

Surgery protocol

Two knee surgeons were involved in the present study (RMA and SDC). All patients received an arthroscopic ACL reconstruction with an ipsilateral HA. A tourniquet inflated to 300 mm Hg was used in all the procedures with the patient in supine position with lateral and distal positioners. The semitendinosus and gracilis tendons were harvested through a 2 cm anteromedial incision [36]. Two different suspension systems were used: TightRope® system (Arthrex, U.S.A.) and Endobutton® (Smith and Nephew, UK). Tibial fixation was performed with an interference screw in all cases. In neither case was a second fixation used on the tibia.

After the surgery, an anti-edema bandage was placed with a knee immobilizer. Regional anesthetic blocks, tranexamic acid, or intra-articular drainage were not used.

Postoperative protocol

All patients were hospitalized for 48 h after surgery. The epidural catheter was removed at the end of that time, and the patient was discharged. The instances in which patients were not discharged due to pain were recorded.

One gram of acetaminophen (Salpífar®, PISA or Efferralgan®, Bristol-Myers Squibb) and 30 mg IV of ketorolac (Dolac®, PISA) were initially administered in each group every 8 h. For pain greater than 4 points on the VAS, 50 mg IV of Tramadol (Tradol®, Grünenthal, Germany) was indicated. This dose could be repeated every 6 h if needed. The total number of doses of tramadol administered in 48 h and the time in postoperative hours in which the first dose was administered were documented. The performance of equianalgesic conversion of opioids for the dose used for rescue analgesia, considering that 200 mg IV/day of tramadol is equal to 20 mg IV/day of morphine and 120 mg IV/day of oral tramadol is equal to 16.6 IV/day of morphine, was taken the main reference for opioid analgesics. Tramadol 400 mg/day should not be exceeded [37–39].

All patients who presented nausea received ondansetron 4 mg per oroperatively. Supplemental doses of ondansetron 8 mg (Antivon®, PISA, Mexico) were administered at the first indication of moderate to severe nausea. These side effects were collected for the study. Additionally, omeprazole 40 mg IV (Pentren®, PISA, Mexico) was administered every 24 h, and heparin 5000 IU (Inhepar®, PISA, Mexico) was administered subcutaneously 6 h after the surgical procedure.

Twenty-four hours after surgery, the patient began rehabilitation supervised by a rehabilitation physician. The focus was on the recovery of complete range-of-motion with a combination of active and passive mobility of the knee and isometric quadriceps muscle exercises. In the case of meniscal sutures, it was limited to 90° for the first week. The range-of-motion for the purposes of this study was that was achieved 48 h postoperatively. A knee brace with proprioceptive weight-bearing was used for the first two weeks. The patients were discharged with oral medication: 1 g of acetaminophen every 8 h, 10 mg of ketorolac every 8 h for 7 days, and tramadol 50 mg every 8 h (only in case of pain greater than 4 points in the VAS). The use of a prophylactic dose of 100 mg of acetylsalicylic acid was indicated for three weeks and the use of ice on the knee for 25 min every 4–6 h in the first week after surgery were also prescribed. All patients attended a follow-up consultation one week after being discharged.

The primary outcome of our study was total opioid consumption in milligrams of intravenous morphine equivalents 0–48 h after surgery and the time to the first rescue analgesic request. We also measured the 0–10 Visual Analogue Scale (VAS) for pain at 2, 6, 12, 24, and 48 h and at 7 days after surgery [40] during a 45° flexion of the knee and at rest (full extension). Each patient was given a logbook and asked to self-evaluate pain on the 10-point VAS and record it before analgesic administration. They also recorded the number of times it was necessary to take tramadol at home. Additionally, they registered the side effects of analgesic drugs, including the levels of nausea, sedation, and dizziness at 24 and 48 h and the number of vomiting episodes and use of additional antiemetics (ondansetron and/or droperidol) in the periods 0–24 and 24–48 h. That information was evaluated by another anesthesiologist not related to the study during [41]. At home, the patient selected the side effects they had during the first postoperative week from a list. Patient satisfaction regarding anesthetic care was assessed on a five-point Likert scale as follows [1]; very dissatisfied [2]; slightly dissatisfied [3]; neither satisfied nor dissatisfied [4]; satisfied; and [5] highly satisfied. For this study, scales 1, 2, and 3 were categorized as non-satisfied, while scales 4 and 5 were categorized as satisfied.
were categorized as satisfied [42]. After 7 days, this scale was evaluated by telephone call.

**Statistical analysis**

All the analyses were performed with the SPSS software package ver. 19 (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean and standard deviations (SD). Categorical variables are presented as percentages and frequencies. A p value less than 0.05 was considered significant.

Based on previous studies that estimated that after arthroscopy, the mean time for rescue analgesia administration was less than 60 min. A group of at least 15 patients is necessary to detect a 50% prolongation in this delay (α = 0.05; β = 0.20 and power = 80%) [43]. The Shapiro–Wilk test was used to confirm the normality of the variables. The inference in continuous variables was calculated with the unpaired t-test. The inference for categorical variables was studied with the chi-squared test or Fisher's exact test, depending on what corresponded.

The minimal clinically important difference (MCID) was used to identify true clinically meaningful changes in the measures that were not the result of measurement error. We predefined 10 mg of intravenous morphine as a minimal clinically important difference (MCID), corresponding to a 22% reduction in morphine consumption based on unpublished clinical data from a sample of 46 patients at Næstved Hospital [44]. An MCID of 1.4 was predefined for VAS pain intensity levels [45].

**RESULTS**

Between January 2019 and August 2021, 119 patients were candidates to participate in the study. Of those, 11 patients were excluded: two due to accidentally pulling out the epidural catheter within the first 24 h after surgery, six because of a lack of collaboration in the postoperative period, one due to analgesic therapy required for the occurrence of hemarthrosis, and the last two because they requested their voluntary discharge before completing the 48 h of hospital admission. Finally, 108 patients were enrolled and completed the study, 50 for the intra-articular group and 58 for the epidural group (Fig. 1).

The two groups were homogenous in terms of demographic data and the duration of the surgical procedure (Table 1). A statistically significantly higher number of doses of rescue analgesia were administered in the first two days in the intra-articular group in comparison with the epidural group (2.8 ± 1.0 vs. 1.3 ± 0.6 respectively) (p = 0.001).

**Table 1**
Demographic and surgical-anesthetic description of the population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intraarticular group (n = 50)</th>
<th>Epidural group (n = 58)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>29 ± 7.1</td>
<td>32 ± 6.1</td>
<td>0.67</td>
</tr>
<tr>
<td>Gender (male: female)</td>
<td>30:20 (60%/40%)</td>
<td>34:24 (59%/41%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Weight (kg ± SD)</td>
<td>77 ± 22</td>
<td>81 ± 19</td>
<td>0.56</td>
</tr>
<tr>
<td>Duration of surgery (minutes ± SD)</td>
<td>64 ± 12</td>
<td>58 ± 14</td>
<td>0.34</td>
</tr>
<tr>
<td>Meniscal suture, n (%)</td>
<td>22 (44%)</td>
<td>25 (43.10%)</td>
<td>0.23</td>
</tr>
<tr>
<td>ASA physical status classification, I/II, n (%)</td>
<td>33:17 (66%/34%)</td>
<td>35:23 (60%/40%)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

SD, standard deviation; ASA, American Society of Anesthesiologists; kg, s kilogram.
The number of rescue medication doses administered at home, the time elapsed to requiring the first dose of rescue medication, the number of patients who did not require the administration of rescue medication, the consumption of tramadol as well as the need for extra days of hospitalization showed statistically significant differences between both groups, with favorable results for the epidural group (Table 2). VAS scores on flexion (45°) were statistically significantly higher in the intra-articular group over the entire study period (2, 6, 12, 24 and 48 h postoperatively) (Table 2). All of them reached the MCID and all of them were statistically significant. In addition, the epidural group presented statistically significantly lower tramadol consumption, and it reached the MCID after 48 h. There were no statistically significant differences in VAS scores at rest between the groups (Table 2).

Additionally, the epidural group reported a statistically significantly greater range-of-motion in comparison to the intra-articular group (102° ± 11 vs 87° ± 15) (p = 0.001) (Table 2). The epidural group reported more side effects, but this finding was not statistically significant. There was one complication in the epidural group that was a case of seizures. That patient had a history of this condition. Therefore, its appearance cannot be totally related to the surgery or the administration of the medications. The result of the rest of the parameters studied such as the requirement for antiemetic medications and patient satisfaction are shown in Table 2.

**DISCUSSION**

The main finding of this study was that there were differences between the postoperative need for rescue analgesia and a standard non-opioid analgesic regimen in adults after a primary ACL reconstruction with a HA using ropivacaine in combination with midazolam via epidural and intra-articular administration, with superior results for epidural administration.

### Table 2
Clinical Results after surgical-anesthetic procedures.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intraarticular group (n = 50)</th>
<th>Epidural group (n = 58)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of administered doses of rescue analgesia (0–48 h)</td>
<td>2.8 ± 1.0</td>
<td>1.3 ± 0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean number of administered doses of rescue analgesia (Home)</td>
<td>7.1 ± 2.7</td>
<td>4.3 ± 1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Elapsed time to first rescue analgesia dose (minutes ± SD)</td>
<td>183 ± 109</td>
<td>285 ± 121</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of patients who did not require any dose of rescue analgesia</td>
<td>8</td>
<td>22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intravenous tramadol consumption (0–48 h), (mg ± SD)</td>
<td>138 ± 42 (13.8 mg of IV morphine equivalent)</td>
<td>80 ± 29 (8 mg of IV morphine equivalent)</td>
<td>0.01</td>
</tr>
<tr>
<td>Oral tramadol consumption (48 h–7 days) (mg ± SD)</td>
<td>314 ± 49 (26.1 mg of IV morphine equivalent)</td>
<td>198 ± 37 (16.5 mg of IV morphine equivalent)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average pain at 2 h postoperatively (45° flexion/rest)</td>
<td>3.8 ± 1.0/1.1 ± 0.2</td>
<td>2.1 ± 0.9/1.3 ± 0.2</td>
<td>0.02/0.56</td>
</tr>
<tr>
<td>Average pain at 6 h postoperatively (45° flexion/rest)</td>
<td>4.9 ± 1.1/2.1 ± 0.7</td>
<td>3.1 ± 0.8/2.0 ± 0.4</td>
<td>0.03/0.85</td>
</tr>
<tr>
<td>Average pain at 12 h postoperatively (45° flexion/rest)</td>
<td>4.7 ± 1.3/2.5 ± 0.9</td>
<td>3.0 ± 0.7/2.4 ± 0.5</td>
<td>0.02/0.74</td>
</tr>
<tr>
<td>Average pain at 24 h postoperatively (45° flexion/rest)</td>
<td>5.9 ± 1.7/2.5 ± 0.6</td>
<td>4.0 ± 1.0/2.7 ± 0.6</td>
<td>0.03/0.78</td>
</tr>
<tr>
<td>Average pain at 48 h postoperatively (45° flexion/rest)</td>
<td>3.7 ± 0.9/1.1 ± 0.2</td>
<td>2.0 ± 0.4/1.1 ± 0.1</td>
<td>0.01/0.36</td>
</tr>
<tr>
<td>Average pain at 2–7 days postoperatively (45° flexion/rest)</td>
<td>2.9 ± 0.3/1.0 ± 0.1</td>
<td>1.5 ± 1.0 ± 0.1</td>
<td>0.04/0.94</td>
</tr>
<tr>
<td>Average pain at 7 days postoperatively (45° flexion/rest)</td>
<td>2.8 ± 0.5/1.6 ± 0.4</td>
<td>2.0 ± 0.3/1.6 ± 0.3</td>
<td>0.04/0.99</td>
</tr>
<tr>
<td>Range of motion at 48 h (grades)</td>
<td>87 ± 15</td>
<td>102 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>Need for extra days of hospitalization (cases) n (%)</td>
<td>6 (12)</td>
<td>2 (3.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Side effects (cases), n (%)</td>
<td>1 (2%) (dizziness)</td>
<td>2 (3.4%) (nausea and dizziness)</td>
<td>0.67</td>
</tr>
<tr>
<td>Antiemetics requirement (cases), n (%)</td>
<td>1 (2%)</td>
<td>1 (1.7%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Complications</td>
<td>0</td>
<td>1 (1.7%) (seizure episode)</td>
<td>0.67</td>
</tr>
<tr>
<td>Satisfaction score (points ± SD)</td>
<td>4.2 ± 0.4</td>
<td>4.4 ± 0.3</td>
<td>0.78</td>
</tr>
</tbody>
</table>

SD, standard deviation; mg, milligrams.
Combined spinal–epidural analgesia is widely believed to provide adequate pain control after knee surgery and is at least as effective as the intravenous administration of opioids [16–20,25,26,46]. There has been controversy around the administration of intra-articular analgesic drugs in ACL reconstruction. Wang et al. reported that the combined intra-articular injection of opioids and a local anesthetic provided a better analgesic effect than sufentanil or ropivacaine alone following ACL reconstruction [24]. That finding is similar to that reported by Sentthilkumar et al. with intra-articular morphine and bupivacaine administration [47]. Moreover, Guler et al. reported better pain relief with analgesic intra-articular injection after tourniquet release in ACL reconstruction than before tourniquet release [48]. In contrast, a relatively small improvement in patient comfort was found in some trials [12,49]. On the other hand, the intra-articular administration of bupivacaine, ropivacaine, and mepivacaine has been reported to be chondrotoxic in a time-dependent, concentration-dependent, and drug-dependent manner. Cell death rates were higher in osteoarthritic cells in comparison to intact cartilage after local anesthetic treatment [23].

Krishna et al. reported prolonged analgesia and fewer hemodynamic fluctuations with a low dose of midazolam and ketamine with bupivacaine intrathecal in orthopedic surgery [31], similar to our patients who reported lower administered doses of rescue analgesia. Furthermore, longer effective analgesia in the midazolam group was reported without prolonging recovery and any adverse effects [27,50,51]. Some studies report large opioid rescue administration after an ACL reconstruction. We found a lower administration of analgesic tramadol doses after an ACL reconstruction in the group with epidural infusion than the intraarticular analgesia administration at 48 h. Dauri et al. reported lowerVAS scores in the group with epidural infusion than in patients with intraarticular postoperative opioid administration [11]. These outcomes are like our results with lower VAS scores in the second group. What is more, there was a longer time duration of the epidural blockade in patients with midazolam and ropivacaine when compared to ropivacaine alone and there were no significant side effects. Midazolam used in an epidural block has been shown to have analgesic properties and enhance the effect of intrathecal local anesthetics [31]. The intrathecal analgesic action of the midazolam may be associated with the lower release of the C-fiber transmitters and a hyperpolarization of dorsal horn neurons. In addition, midazolam is known to cause arterial desaturation and apnea [25]. Nevertheless, no serious side effects were reported in our study and both groups reported high satisfaction scores.

There are several limitations to this study. The procedures were performed by different surgeons, as it was carried out in two centers. The indication of supplementary opioid consumption was based on the patient’s request. No VAS score was assessed after rehabilitation.

CONCLUSIONS

The use of ropivacaine in combination with midazolam administered via the epidural route as an analgesic agent in patients undergoing primary ACL reconstruction with autograft hamstrings demonstrated clinical and superior and statistically significant efficacy in terms of the consumption of rescue analgesia and a level of pain in the first 48 postoperative hours compared to its intra-articular use with no differences relative to adverse effects and complications. Therefore, we propose this technique as a new therapeutic option for pain management. Nevertheless, we recognize that more studies are necessary to support our observations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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