

Randomized Trial

e Minimum Effective Concentration of Bupivacaine in Ultrasound-Guided Femoral Nerve Block after Arthroscopic Knee Meniscectomy: A Randomized, Double-Blind, Controlled Trial

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Background: Adequate analgesia is important for early hospital discharge after meniscectomy. A femoral nerve block may reduce the need for systemic analgesics, with fewer side effects; however, motor block can occur. Ultrasound-guided femoral nerve block may reduce the required local anesthetic concentration, preventing motor block.

Objective: The primary objective of this study was to determine the lowest effective analgesic concentration of bupivacaine in 50% (EC50) and in 90% (EC90) of patients for a successful ultrasound-guided femoral nerve block in arthroscopic knee meniscectomy.

Study Design: This was a prospective, randomized, double-blind, controlled trial.

Settings: This study was conducted at Hospital São Domingos.

Methods: A total of 52 patients undergoing arthroscopic knee meniscectomy were submitted to ultrasound-guided femoral nerve block using 22 mL bupivacaine. The bupivacaine concentration given to a study patient was determined by the response of the previous patient (a biased-coin design up-down sequential method). If the previous patient had a negative response, the bupivacaine concentration was increased by 0.05% for the next case. If the previous patient had a positive response, the next patient was randomized to receive the same bupivacaine concentration (with a probability of 0.89) or to have a decrease by 0.05% (with a probability of 0.11). A successful block was defined by a numerical pain intensity scale score < 4 (0 = no pain; 10 = worst imaginable pain) in 3 different evaluations. If the pain intensity score was ≥ 4 (moderate or severe pain) at any time, the block was considered failed. General anesthesia was induced with 30 µg/kg alfentanil and 2 mg/kg propofol, followed by propofol maintenance, plus remifentanyl if needed. Postoperative analgesia supplementation was performed with dipyrone; ketoprofen and tramadol were given if needed.

Data Measurements: The following parameters were evaluated: numerical pain intensity score, duration of analgesia, supplementary analgesic dose in 24 hours, and need for intraoperative remifentanyl.

Results: The EC50 was 0.160 (95% CI: 0.150 – 0.189), and EC90 was 0.271 (95% CI: 0.196 – 0.300). There was no difference in numerical pain intensity score for the different concentrations of bupivacaine. A successful block was achieved in 45 patients, with no difference according to bupivacaine concentration. Time to first analgesic supplementation dose was longer for bupivacaine concentrations ≥ 0.3% (543.8 ± 283.8 min.), compared to 0.25% (391.3 ± 177.8 min.) and < 0.25% (302.3 ± 210.1 min.). There were no differences in supplementary analgesic dose in 24 hours nor in the use of intraoperative remifentanyl according to bupivacaine concentration.

Limitations: The analgesic effect was measured only during the first 2 hours.

Conclusions: Bupivacaine EC50 for ultrasound-guided femoral nerve block was 0.160 (95% CI: 0.150 – 0.189), and EC90 was 0.271 (95% CI: 0.196 – 0.300).

Key words: Postoperative analgesia, femoral block, ultrasound-guided, bupivacaine minimum concentration, arthroscopic meniscectomy

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Postoperative pain relief is important for early rehabilitation after knee surgery (1). A peripheral nerve block may reduce the need for systemic medication with fewer adverse effects (2).

A combined sciatic and femoral nerve block has been practiced by some authors (3,4); however, there is a limitation related to the position of the patient and the need for large doses of local anesthetics, which may cause toxicity. Furthermore, an isolated femoral block provides adequate analgesia for surgeries such as ligament reconstruction (2).

For a suitable peripheral nerve block, the volume and concentration of the solution are important factors (5). The minimum effective concentration (EC) of the local anesthetic administered to each patient has been calculated by a biased-coin design up-down sequential method, which is conditional on the previous patient's response (6).

An ultrasound-guided block offers advantages, such as enabling a direct image of the nervous structures and guiding the movement of the needle in real time (7). Thus, the total dose of local anesthetic can be reduced, decreasing the possibility of toxic effects.

To date, there is no data assessing the minimum concentration of bupivacaine needed for effective analgesia in femoral nerve blocks for knee surgery. The primary objective of the current study was to determine the minimum effective analgesic concentration of bupivacaine in 50% (EC50) and in 90% (EC90) of patients undergoing ultrasound-guided femoral nerve block for arthroscopic meniscus surgery. Secondary objectives included numerical pain intensity score, duration of analgesia, supplementary analgesic dose in 24 hours, and need for intraoperative remifentanyl.

METHODS

Type of Study

This was a prospective, randomized, double-blind study. The study was registered in the ClinicalTrials database (record no. NCT02124005).

Randomization

Randomization of patients was performed using a biased-coin design up-down sequential method described by Dixon (6), as proposed by Durham et al (8). In case of a negative response by the previous patient, the concentration of bupivacaine was increased by 0.05% for the next patient (probability of 1). In case of a positive response by the previous patient, the next

case would randomly receive the same concentration of bupivacaine (0.89 probability) or a lower concentration by 0.05% (0.11 probability). Randomization was performed by number lottery using a guiding table. The solution was prepared by one of the researchers; the patient and the anesthesiologist who performed the block were blinded to the administered concentration.

Inclusion and Exclusion Criteria

This study was approved by the Ethics Committee of the Federal University of São Paulo (number 1020/10) and the Brazil Platform (approval no. 16819413.0.1001.5505), and signed informed consent was obtained from all study participants. Fifty-two men and women, aged 18 to 65, ASA (American Society of Anesthesiologists) Physical Status Classification I or II, and undergoing arthroscopic knee meniscectomy at Hospital São Domingos were included in the study.

Patients with coagulopathies, infection at the puncture site, chronic pain, pregnant, or on anticoagulants were excluded from the study.

Procedure

Patients received intravenous (IV) midazolam (0.01 mg/kg) 5 minutes before the block and were monitored using electrocardiogram (ECG), pulse oximeter, and non-invasive blood pressure measurements. An ultrasound-guided (SonoSite M-Turbo®) femoral nerve block with bupivacaine was performed before the induction of general anesthesia. A linear transducer with frequency ranging from 6 to 18 MHz (depending on the depth of the structures) was used with the patient in a dorsal decubitus position with lower limbs in a neutral position. After preparing the skin and the transducer, the probe was positioned parallel to the middle third of the inguinal ligament to visualize the pulse of the femoral artery, the femoral vein medial to the artery, the iliopsoas muscle posterior-lateral to the femoral vessels, the fascia lata (represented by a hyperechoic line superficial to the femoral nerve and vessels), the iliac fascia (superficial to the iliopsoas muscle and femoral nerve and deep to the femoral vessels), and, finally, the femoral nerve (visualized as a hyperechoic triangular region, lateral to the femoral artery, above the iliopsoas muscle). Local anesthetic was injected around the nerve.

A successful block was defined as a numerical pain intensity scale score < 4 (0 = no pain and 10 = worst imaginable pain) at 3 different times [after awakening (T0), and after one hour (T1) and 2 hours (T2)]. If the pain score was ≥ 4 , the blockade was characterized as a

failure. The first patient received 22 mL of 0.25% bupivacaine. The second patient would receive 0.30% bupivacaine if the pain score from the first patient was ≥ 4 ; if the pain score from the first patient was < 4 , the second patient would receive 0.25% or 0.20% bupivacaine, and so forth.

After femoral block, general anesthesia was induced with 30 $\mu\text{g/kg}$ of alfentanil, 2 mg/kg of propofol, and a laryngeal mask was placed; maintenance was performed with propofol target-controlled infusion at 3.5 ng/mL. If insufficient (defined as a heart rate that exceeded preinduction values by 15% and/or systolic arterial blood pressure exceeding baseline values by 20% for at least one minute), 0.5 $\mu\text{g/kg/min}$ remifentanyl would be administered.

At the end of the surgery, propofol was discontinued and the laryngeal mask was removed after awakening of the patient. After recovering consciousness (T0), defined as Ramsey 2 (cooperative, oriented, and calm patient), numerical pain intensity score was assessed at pre-specified time points.

Supplementary Analgesia

If the patient presented a pain score ≥ 4 , 2 g of intravenous (IV) dipyrone would immediately be given. In case of persistent pain score ≥ 4 after 10 minutes, 100 mg IV ketoprofen would be administered. In there was no pain relief after 10 minutes, 50 mg IV tramadol would be given.

After the 2 hours postoperative follow-up, patients would be discharged if pain intensity score was < 4 in the surgical wound and at mobilization. Outpatient rehabilitation and physical therapy were recommended to start as soon as possible. In case of persistent pain (score ≥ 4), immediate supplementary analgesia was administered until pain relief was sufficient for patient discharge.

All patients received verbal and written recommendations at discharge regarding possible side effects management, including pain control. They were instructed to note the time at which the pain intensity score was ≥ 4 , and received a medical prescription including the same supplementary analgesic protocol. Patients were contacted by phone call on the following day to inquire about post discharge symptoms and management.

Assessment

The following parameters were evaluated: block success (defined as a numerical pain intensity score < 4 at T0 (at awakening), T1 (after one hour), and T2 (after

2 hours); need for intraoperative remifentanyl; time to first analgesic supplementation; and total dose of supplementary analgesia during the immediate postoperative period (first 2 hours). Motor block was evaluated using the Bromage scale (9) at the times of numerical pain score assessment. Side effects and complications were noted.

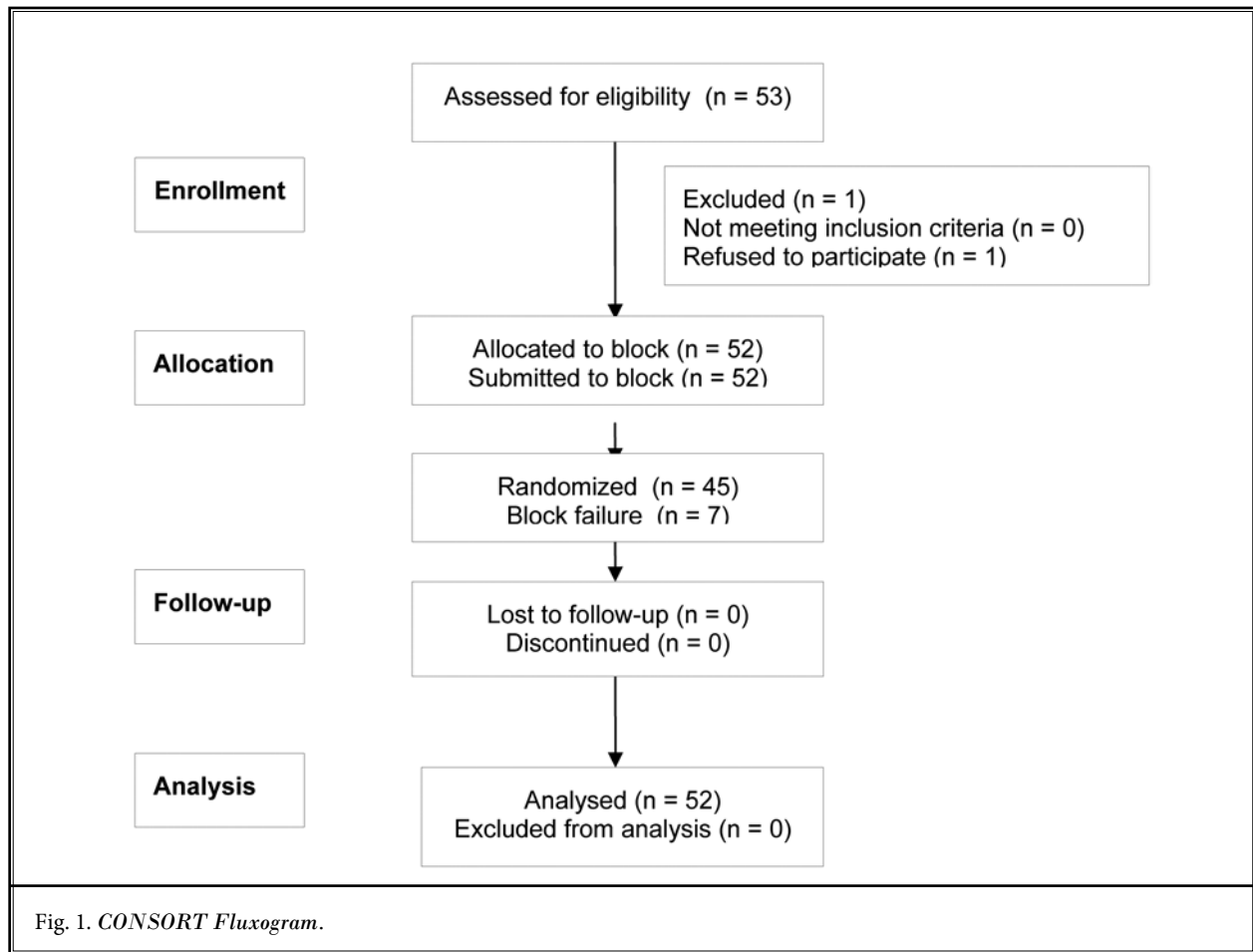
Statistical Analysis

Sample size calculation was based on the sample stabilization concept proposed by Pace and Stylianou (10) for a biased-coin design up-down sequential method. According to the authors, for EC50 calculation, the sample stabilizes at approximately 40 patients. EC90 calculation was based on a proposal by George et al (11) recommending that the smaller sample be greater than 40 and a multiple of 9, which for this study was 45 successful cases. From the success probabilities estimated with the 52 patients, 1000 bootstrap experiments were generated. Each of the 1000 experiments had its isotonic probability likely to succeed with the help of ISOREG function (R 3.1.2 software). Isotonic probability experiments with the doses EC90 and EC50 were estimated by the regression estimator isotonic μ_3 proposed by Pace and Stylianou (10), which showed favorable properties in comparison with other estimators. After calculating the EC90 and EC50, 95% confidence intervals were estimated. This process was repeated with the generation of 2,500, 5,000, and 10,000 bootstrap samples.

The likelihood ratio was used to compare the rate of blockade success and supplementary analgesic requirements according to different concentrations of bupivacaine. Analysis of variance (ANOVA) test was used to evaluate differences in time to first analgesic supplementation according to different bupivacaine concentrations. T test was used to compare postoperative pain intensity scores for the different bupivacaine concentrations and Spearman correlation was used to evaluate correlation between the duration of surgery and time to first analgesic supplementation dose); *P* value was considered ≤ 0.05 . Statistical analysis was performed using R 3.1.2 program for Windows and SPSS 15 for Windows.

RESULTS

All 52 patients included completed the study protocol (CONSORT flow chart; Fig. 1). Patient characteristics are shown in Table 1. Mean surgery duration was 58.2 min (20 to 120 minutes). There was no difference

Table 1. *Patient characteristics.*

Gender M:F (%)	43(82.7) : 9(17.3)
Age (years) – mean ± SD	40.9 ± 10.2
Weight (Kg) – mean ± SD	79.9 ± 13
Height (cm) – mean ± SD	172.3 ± 7.9
BMI (kg.m-2) – mean ± SD	26.9 ± 3.6
ASA I:II (%)	35(67.3) : 17(32.7)
Duration of surgery (min) – mean ± SD	58.2 ± 20.1
Total	52

in time to the first dose of analgesic supplementation according to the duration of surgery (Spearman correlation coefficient; P : 0.513).

The bupivacaine concentrations used were 0.15% (in 3.8% of patients), 0.2% (21.2%), 0.25% (30.8%), 0.3% (28.8%), and 0.35% (15.4%). There was no difference in pain intensity scores according to different

concentrations of bupivacaine (Table 2). The EC50 was 0.160 (95% CI, 0.150 – 0.189) and the EC90 was 0.271 (95% CI, 0.196 – 0.300) (Fig. 2).

The peripheral femoral block was considered successful in 45 patients. Among the 7 failed cases, 2 patients experienced pain relief ($EN < 4$) after dipyrone, one needed nonsteroidal anti-inflammatory drugs (NSAID), and 4 needed tramadol (Table 3). Time until need for analgesic supplementation was significantly longer for concentrations of bupivacaine $> 0.30\%$ compared to $< 0.20\%$; there was no significant difference when comparing $< 0.20\%$ to 0.25% and 0.25% to $> 0.30\%$ (Table 3). Intraoperative remifentanyl was not needed for any patient.

There were no reported side effects or complications related to the local anesthetic or to the femoral block. Two patients experienced a motor blockade after the procedure, with a Bromage score ≥ 1 and duration of 240 and 600 minutes.

Minimum Concentration of Bupivacaine in Femoral Nerve Block

Table 2. Correlation between bupivacaine concentration and pain intensity.

Concentration	≤ 0.20%	0.25%	≥ 0.30%	P
T0	0.6 ± 1.5	0	0.52 ± 1.47	0.327
T1	0.9 ± 1.6	0.7 ± 1.2	0.26 ± 0.69	0.207
T2	0.6 ± 1.0	0.6 ± 0.9	0.35 ± 1.11	0.696

T test

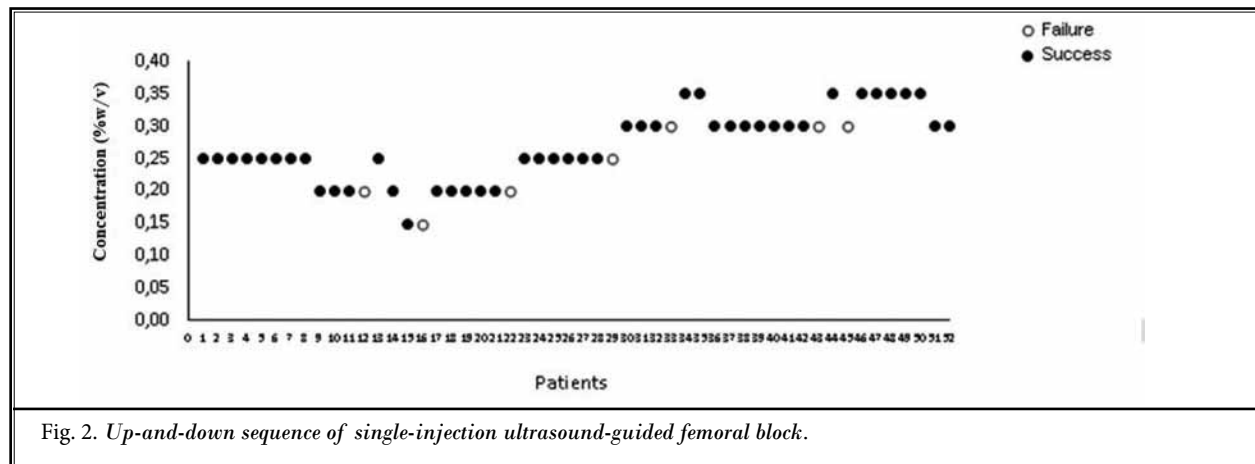


Table 3. Correlation between bupivacaine concentration with block success, first supplementation, supplementation dose, and motor block.

Concentration	≤ 0.20%	0.25%	≥ 0.30%	P
Block success	10/13 (76.9%)	15/16 (93.8%)	20/23 (87%)	0.417*
First supplementation (min)	302.3 ± 210.1	391.3 ± 177.8	604.3 ± 255.2	0.001**
Supplementation				
Dipyrone T0	2 (15.4%)	0	2 (8.7%)	0.417*
T1	1 (7.7%)	1 (6.3%)	0	
T2	0	0	1 (4.3%)	
Ketoprophen T0	1 (7.7%)	0	2 (8.7%)	0.749*
T1	0	1 (6.3%)	0	
T2	0	0	1 (4.3%)	
Tramadol T0	1 (7.7%)	0	1 (4.3%)	NC
T1	1 (7.7%)	0	0	
T2	0	0	1 (4.3%)	
Motor block	1 (7.7%)	1/16 (6.3%)	0 (0)	NC

* Likelihood ratio test; **ANOVA test; NC: Not calculated

Discussion

The use of large doses and high concentrations of local anesthetics are directly related to higher rates of nerve damage and systemic toxicity (12). Limiting the dose and concentration of local anesthetic would reduce this risk. This study intended to assess

the minimum analgesic dose of bupivacaine needed for a femoral nerve block for knee meniscectomy, a procedure that would theoretically result in adequate postoperative analgesia, with fewer associated side effects compared to neuroaxial anesthesia. The EC90 of bupivacaine for the femoral nerve block with adequate postoperative analgesia after knee surgery was found to be 0.271%.

The duration of postoperative analgesia was longer for the higher bupivacaine concentrations tested; however, there was no difference in the rate of block success for different concentrations of local anesthetics according to pain intensity score assessment, the primary study endpoint.

Patients were followed for 2 hours after awakening from anesthesia to evaluate the success of postoperative analgesia. Two hours was considered the minimum required follow-up time prior to discharge after the knee surgery. At the 2-hour time, patients would be discharged if there was no pain in the surgical wound and no pain at mobilization. Outpatient rehabilitation and physical therapy were recommended to start as soon as possible. If there was persistent pain (pain score ≥ 4), immediate supplementary analgesia was administered according to study protocol until pain relief and patient discharge could be achieved. To obtain 45 successful events as per protocol definition, a total of 52 patients were included to account for the 7 failed procedures.

Spinal blocks are often used for knee surgery. However, in a previous study comparing peripheral femoral nerve block to intrathecal morphine for knee arthroplasty, there was no difference in postoperative morphine consumption, but there were fewer side effects associated with the peripheral block (13).

The duration of postoperative analgesia has been reported to be 10 to 15 hours with the use of different doses of intrathecal morphine (14). In the current study, time until need for the first analgesic supplementation was 419.8 minutes, similar to that observed by Davarci et al (3). For bupivacaine concentrations greater than 0.3%, the duration of postoperative analgesia was 543.8 minutes, which is similar to the results obtained with morphine spinal blocks.

There was no direct correlation between higher bupivacaine concentrations and rate of block success, characterized per protocol definition according to postoperative pain intensity score. Although not statistically significant, there was a numerically greater success rate for the 0.25% bupivacaine concentration compared to 0.3%. There is no clear explanation for this lack of correlation and the numerically better outcomes for the 0.25% concentration, but individual patient pain perception and poor understanding of the analgesic scale system might have played a role (15).

There was no increase in the occurrence of motor block with the use of higher bupivacaine concentrations. In a previous study using peripheral nerve block

with 0.25% and 0.125% bupivacaine infusion for knee arthroplasty, all patients ambulated on the first postoperative day with no reported fall events (16). Additionally, the analgesic effect of the femoral block has been found to be better than that of intravenous or epidural patient-controlled analgesia (PCA) in another study, with no increase in motor block events (17).

The femoral block used in the current study followed a method previously described in the literature (4). The peripheral block was performed with a previously drawn concentration of local anesthetic according to protocol, which was followed by general anesthesia, and supplementary rescue analgesia for postoperative pain with anti-inflammatories as needed.

Gupta et al (18) found an effective volume of local anesthetics for ultrasound-guided femoral nerve block of 17 mL, with fewer failed procedures (3/40 patients) compared to this study (7/45). However, a different local anesthetic was used (1% prilocaine) (18).

No previous studies of ultrasound-guided femoral nerve block using bupivacaine and a similar methodology were found. However, the minimum effective concentration of 0.5% bupivacaine has been shown to be equivalent to 0.5% ropivacaine for femoral nerve blocks performed for a different purpose, which also intended to achieve quadriceps muscle block (19). A volume of 22 mL of 0.5% ropivacaine has been described for ultrasound-guided femoral nerve blocks (20), and in view of their similar pharmacological profile, the same volume was adopted for this study.

The biased-coin up-down sequential method design is useful to assess the minimum necessary dose of a drug to obtain a pharmacological response, requiring a smaller sample size than studies with multiple comparison arms using fixed predefined concentrations of the drug. Other advantages of this method include the reduced number of patients exposed to inadequate analgesia and to adverse effects, and increased cost-effectiveness (21).

In this method, the concentration of the drug is determined by the response of the previous patient. This strategy is particularly powerful to determine the dose/amount of a drug that will be effective in 50% (EC50) and in 90% (EC90) of the exposed patients. The EC50 of a drug, however, is of little clinical use despite its theoretical value; on the contrary, the EC90 is of important clinical relevance. A probit regression method has also been used to obtain the EC90 (4,20,22); however, this strategy has received much criticism.

A different methodology proposed the randomiza-

tion of each study patient following a successful event to receive either the same dose or a reduced dose of the study drug, using an isotonic regression with bootstrapping resampling (23). This method achieved more accurate results and was adopted here.

To ensure a similar pain stimulus in all studied patients, only patients undergoing meniscectomy were included. A similar study by Tantry et al (2) also obtained adequate postoperative analgesia after ligament reconstruction with the use of a femoral nerve block. Additionally, an ultrasound-guided block facilitates the injection of local anesthetics closer to the nerve, further reducing the chance of analgesic failure.

To promote adequate intraoperative analgesia, a supplementary analgesic procedure is necessary in addition to the peripheral femoral nerve block. Taha et al (24) have described effective analgesia in 90% of patients undergoing ultrasound-guided femoral nerve blocks using 0.167% ropivacaine; however, sciatic, obturator, and lateral femoral cutaneous nerve blocks with 0.5% ropivacaine were added to the femoral block to obtain intraoperative analgesia, which would delay patient discharge.

In the current study, general anesthesia was used to ensure adequate intraoperative analgesia. Remifentanyl would be administered if needed; however, it was not necessary for any patient, suggesting that the peripheral block contributed to the intraoperative anesthesia.

CONCLUSION

Ultrasound-guided femoral nerve block is a good analgesic option for patients undergoing knee surgery, with prolonged postoperative analgesia directly correlated to the bupivacaine concentration used. It is associated with a low risk of motor block and a favorable side effect profile, enabling early patient discharge.

Limitation

The analgesic effect was measured only during the first 2 hours.

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