The median effective analgesic concentration (MEAC) of ropivacaine in ultrasound-guided sciatic nerve block for postoperative analgesia after ACL-R

Cheng Xu[1], Jie Lu[2], Chengyu Wang[1], Fei Gu[1], Yang Liu[1], Rui Chen[1], and Quanhong Zhou[1]

[1]Shanghai Jiaotong University Affiliated Sixth People's Hospital
[2]Affiliation not available

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Abstract

Background: The median effective concentration of ropivacaine of ultrasound guided sciatic nerve block required for effective postoperative analgesia after arthroscopic anterior cruciate ligament reconstruction has not yet been determined. This study was to explore the median effective analgesic concentration of ropivacaine required to produce a successful sciatic nerve block for postoperative anesthesia. Method: A total of 29 patients underwent elective arthroscopic anterior cruciate ligament reconstruction were enrolled in study. A concentration of 20mL ropivacaine administered for the sciatic nerve was determined using the up-and-down sequential. The starting concentration was 0.2% in the first patient, the next patient would receive decremented 0.025% of ropivacaine if the prior patient's postoperative visual analog pain score was less than 4 in the initial 8h. Otherwise, the following patient would received an incremental of 0.025% of ropivacaine. The analytic techniques of linear, linear-logarithmic, exponential regressions and centered isotonic regression were used to determine the EC50 of ropivacaine. Results: The concentration of ropivacaine administered ranged from 0.1% to 0.2%. The ED50 (95% confidence interval) from 4 different statistical approaches (linear, linear-logarithmic, exponential regressions and centred isotonic regression) were 0.129% (0.103%, 0.359%), 0.142% (0.112%, 0.347%), 0.113% (0.108%, 0.343%), and 0.115%, respectively. Among all of the 4 models, the exponential regression had the least residual standard error (0.2243). Conclusion: The EC50 derived from four statistical models for 20ml ropivacaine in ultrasound-guided sciatic nerve block for postoperative analgesia was distributed in a narrow range of 0.113%–0.142%, and the exponential regression was the model to best match the study data

Introduction

Anterior cruciate ligament (ACL) reconstruction can cause considerable postoperative discomfort. After ACL reconstruction, femoral nerve blockade was reported to provide analgesia effect[1-3]. However, many patients with femoral nerve blockade still complained of knee pain after ACL reconstruction. The articular branches of the tibial nerve provide sensory afferents to the posterior knee, while the articular branches of the common peroneal nerves contribute sensory afferents to the anterior knee. Therefore, even in the case of a femoral nerve block (FNB), blockade of the tibial and common peroneal nerves through a sciatic nerve block could reduce the severity of pain in both anterior and posterior knees[4, 5].

The analgesic benefits of adding sciatic nerve blockade to femoral nerve blockade to knee surgeries is controversial [6-9]. Retrospective data showed that compared with FNB alone, combined femoral-sciatic nerve blockade (CFSNB) performed before complex knee surgery may improve analgesia and decreases opioid consumption[10, 11]. Several recent randomized controlled studies of total knee arthroplasty have shown that CFSNB provides superior pain control[12, 13], and a recent randomized controlled trial by Abdallah et al.[4]demonstrated that CFSNB specifically reduces posterior knee pain after total knee arthroplasty.

Currently, limited data, with only 1 randomized study, on the analgesic role of sciatic blockade in ACL reconstruction can be found[14].

Ropivacaine, a long-acting local anesthetic, has also been used for administering sciatic nerve blockade. Ropivacaine offers two advantages over bupivacaine: in low doses it provides similar sensory blockade to bupivacaine with less motor block, and its systemic toxicity will be less[15], which can provide better conditions for knee joint functional reconstruction after ACL surgery.

This study aims to evaluate the median effective analgesic concentration (MEAC, EC50= effective concentration in 50% of patients) of ropivacaine required for successful postoperatively analgesia with sciatic blockade.

Method

Study design and population

This single-armed prospective study was approved by the Ethics Committee of the Sixth People's Hospital of Shanghai (reference No. 2021-095-(1)) and registered with the Clinical TrialRegistry of china (http://www.chictr.org.cn/; registration No. ChiCTR2100045439; date of registration, April 15, 2021; date of patient enrollment, April 16, 2021). All patients who underwent anterior cruciate ligament reconstruction were assessed for eligibility. All eligible patients obtained written informed consent. American Society of Anesthesiologists physical status I or II patients, in the age group of 18 to 60 yr, with a body mass index between 18 and 30kg/m^2. We set exclusion criteria including local infection at the block site, preexisting neuropathy or coagulopathy, allergy to local anesthetics and opioids, dementia, known history of intravenous (IV) drug abuse, preoperative chronic opioid requirements, chronic pain, psychiatric illness, patients who failed to understand the scoring systems used in the study, uncontrolled hypertension or ischemic heart disease, renal or hepatic dysfunction, pre-existing neurologic deficits.

Blinding Method

Experienced anesthesiologists who had performed at least 100 ultrasound-guided femoral nerve block combined with sciatic nerve block using a high-frequency (6 to 13 MHz) ultrasound probe (Sonosite, Inc., USA) were responsible for performing all blocks. The procedural data was recorded by an independent investigator. The performers and the investigator did not further participate in the study. An independent observer evaluating the sensory and motor block was absent in the operating room during block placement and was blinded to the concentration of local anesthetic injected. The same observer followed up the patients postoperatively within the first 24hs.

Technique of Block Administration

All peripheral nerve blocks were performed under the guidance of ultrasound and the patient was under the monitor of HR, BP and SpO2. Local anesthetics toxicity rescue kit was at handside. Sciatic nerve block was performed after femoral nerve block (0.2% ropivacaine 20ml). Patients was in lateral decubitus postion with the operative leg on top. The injection site was located in the subgluteal or upper to-middle thigh region. Disinfection of the puncture site and local anesthesia were performed as described above. A 10-cm 21-gauge insulated needle (UniPlex Nanoline; Pajunk, Geisingen, Germany) was used to inject a total of 20 mL of ropivacaine 0.2% around the sciatic nerve using real-time ultrasonography guidance and an in-plane approach. Using the small-sample up-and-down sequential allocation study design, the concentration of local anesthetic (20mL ropivacaine) administered through the block needle was determined. A concentration of 0.2% of 20mL ropivacaine was injected to the first patient. After a successful block (in the initial 8 hours after operation, the VAS score was less than 4), the concentration of local anesthetic in the next patient was decreased by 0.025%. However, if the block was unsuccessful, then the local anesthetic concentration was increased by 0.025% in the next patient. All patients received less than 3 mg/kg of ropivacaine in order to avoid local anesthetic toxicity

Clinical procedures

Propofol 2-3mg/kg and 0.1-0.15 μ g / kg sufentanil were used for general anesthesia induction, and a laryngeal mask airway was placed at proper position. Volatile anesthetics sevoflurane was used to maintain anesthesia, with end expiratory sevoflurane concentration above 0.7MAC(minimum alveolar concentration) and ETCO2 between 35 and 45mmHg. During the operation, the anesthesiologist would use 0.1ug/kg sufentanil intravenously if any sign showing the insufficient anesthesia. All patients received PONV prophylaxis droperidol IV before emergence. Patients reached discharge criteria when (1) pain was controlled with a score less than 5, (2) airway remained patent with oxygen saturation greater than 95% on room air, (3) heart rate and systolic and diastolic blood pressures were within 20% of preanesthetic levels, and (4) minimal levels of nausea occurs when taking clear liquids. 1 g paracetamol was given every 6 h in postoperative analgesia and droperidol was used to prevent systematic postoperative nausea and vomiting (PONV). An independent observer who knew nothing about the study concentration of ropivacaine recorded the VRS (Visual Analogue Score) in the post-anaesthesia care unit (PACU), then once upon arrival in the ward, and finally at the end of the study 24 hours after the surgery.

Sensory and motor blockade in the operated foot was evaluated every 5min after local anesthetic injection by an observer blinded to the concentration of local anesthetic injected. Sensory block was evaluated as an absence of sensation to pinprick in the common femoral and sciatic nerve nerve distributions, and classified as follows: 1= normal sensation within the nerve distribution (no block); 2 = blunted sensation (analgesia); 3 = absence of sensation (anesthesia). Motor block was assessed for voluntary motor response by asking the patient to plantar-flex or dorsi-flex the foot, and was classified as follows: 1 = normal movement; 2 = decreased movement; 3 = absence of movement (complete motor block). The time between local anesthetic injection and successful complete block was considered the onset, and thereby registered

UDM

A concentration of 0.2% of 20mL ropivacaine was injected to the first patient. After a successful block (in the initial 8 hours after operation, the VAS score was less than 4), the concentration of local anesthetic in the next patient was decreased by 0.025%. However, if the block was unsuccessful, then the local anesthetic concentration was increased by 0.025% in the next patient. All patients received less than 3 mg/kg of ropivacaine in order to avoid local anesthetic toxicity.

Adverse effect

Soght and noted the known adverse effects of ropivacaine (visual and hearing disturbances, dysguesia, dizziness, muscular twitching, arrhythmia, QRS modification) and of sufentanil (vomiting, nausea, pruritus, sedation, urinary retention, respiratory depression) in the PACU and on the ward.

Statistical Analysis

In most cases, the exact sample size for Dixon's UDM could not be determined in advance. When 6 crossovers (conversion from successful block to unsuccessful block or vice versa) had occurred, we ceased to recruit patient[16, 17]. We can see that at least 20–40 patients will be required to provide reliable estimates of the target dose in our simulation studies in anesthesia trials using the Dixon's UDM[18]. Our study recruited 29 patients and achieved this goal.

To explore the target dose ED50, four statistical approaches were used, including 3 parametric estimates of dose responsive curve[18]: linear, linear-logarithmic and exponential regressions, and one nonparametric model: the centered isotonic regression, which was only for assuming a nondecreasing dose and response relationship[19].

Residual standard errors, a statistical tool to determine the goodness of fit, which analyses how well a set of data points fit with the actual model, were calculated for all four statistical approaches.

Results

This study screened and included a total of 40 patients. Thirty-two patients met the inclusion criteria, of which 3 patients suspended surgery due to high fever on the day of operation. Finally, a total of 29 patients

were selected with ten independent up-down deflections(see Figure 1). Patient characteristics are presented in Table 1.

Median Effective Analgesic Concentration of Local Anesthetic

The illustration of sequence of successful and failed blocks is in figure 2. The linear model estimator led to an EC50 of 0.129 %, the linear-logarithmic model resulted in an EC50 value of 0.142 %, the exponential regression gave an EC50 of 0.113%, and the centred isotonic regression (a nonparametric method) yielded an EC50 of 0.115%(see Figure 2). The 95% confidence intervals for the 3 parametric models (linear, linear-logarithmic and exponential) were 0.103%, 0.359%; 0.112%, 0.347%; and 0.108%, 0.343%, respectively(Table 2) and they showed similar fitted probabilities within the range of the ED50, and the 95% confidence intervals from these models successfully covered all observed data. Table 2 also showed the results of residual standard deviations for goodness of fit of each model. The exponential regression has the least residual standard error (0.2243) among the all models.

Block performance Characteristics

The mean onset time of sensory block and motor block were 3.8±0.93 and 11.4±2.65min, respectively. The onset time of sensory block and motor block was not significantly different between patients having successful and failed blocks (P = 0.1303, P =0.2633, respectively). The average duration of motor block was 8.6±1.57 h. No difference occurred in duration of motor block between successful and unsuccessful blocks(P =0.7494).

Postoperative pain and rescue Analgesia required

Out of the total patients included in the study, 16 patients had a successful block. All patients with a successful block had a postoperative visual analogue scale score less than 4 in the initial 8h (see Figure 3A and Figure 3B). The average intraoperation sufentanil consumption was 10.8±3.33μg. Intraoperation sufentanil consumption between successful and unsuccessful blocks(P =0.2579) showed no difference. However, the mean time to 1st rescue analgesic was 9.2±2.71 h. The time to 1st rescue analgesic between successful and unsuccessful blocks(P =0.0024) was significantly different. The time to 1st analgesic request was moderately positively correlated with administered local anesthetic concentration, with the Spearman rank correlation r being 0.4865. This value of r was found to be statistically significant(P =0.0074)(see Figure 3C and D).

Postoperative adverse events

In all patients, the femoral nerve combined with sciatic nerve and the spread of ropivacaine were visualised, and the uncomplicated block was performed. No adverse effects of either ropivacaine or sufentanil were observed. No PONV was recorded.

Discussion

As we all know, the success of peripheral nerve blocks depends on the accuracy with which the nerves are localized and impregnated. However, it has reported that other relevant factors can affect the success rate and quality of nerve blocks, including the concentration and volume of local anesthetic injected in proximity of the nerves[20, 21]. In this concentration-finding study, we found that the median EC50 was 0.113%(95%CI, 0.108% to 0.343%).

There are various approaches for sciatic nerve blocks, including popliteal, subgluteal or mid-femoral approaches performed under US guidance[22, 23]. Among these approaches, the subgluteal approach showed following advantages. First of all, the depth of the puncture needle through the subgluteal approach is shallow, and ultrasound can more clearly show the course and structural characteristics of the sciatic nerve. Secondly, it was shorter that the onset time of subgluteal sciatic nerve block compared with that of popliteal sciatic nerve block, but the effect of block was basically comparable among the three groups[24].

Circumferential injection is beneficial for US-guided sciatic nerve block[25]. Compared with the multiple injections of LA used to achieve circumferential spreading[26], a single-injection technique was used in our study. It was found that, after injection of 20mL of LA, all patients could achieve circumferential spreading

around the sciatic nerve. This is one of the reasons why the EC50 of ropivacaine concentration is so low. Meanwhile, multiple injections for circumferential spreading of LA should be used with caution, since it might cause patient discomfort.

A previous study by Frost et al.[27] found that femoral nerve blockade did not reduce postoperative analgesic requirements in patients undergoing ACL reconstruction when a hamstring graft was harvested. This is anatomically meaningful because femoral blockade only covers the anterior thigh and knee, while hamstring graft harvesting would likely lead to posterior thigh and knee pain, which is the sciatic nerve sensory distribution. A retrospective study demonstrated that the pain scores of patients with hamstring autograft was higher than those patients who received allograft[11]. However, in the study of Jansen et al.[14], it showed no association between hamstring autograft and higher PACU pain scores or increased opioid consumption. In our study, the patients who were conducted femoral nerve block combined with sciatic nerve block had low PACU pain scores and low opioid consumption perioperatively. The posterior knee pain during ACL reconstruction surgery is possibly unrelated to graft harvest site but rather may be due to surgical factors (manipulation, drilling a hole in the tibia), posterior knee edema, tourniquet pain, or a combination of factors.

This study used a relatively high volume of local anesthetic (20mL of ropivacaine) for the nerve blocks. Although lower amounts of local anesthetic can be used, these volumes are used in our practice for prolonging duration. There may be some adverse effects on motor function and early mobilization due to the dose of local anesthetic used; however, our surgeons do not want any knee mobilization on the day of surgery. Despite the amount of local anesthetic used and use of FNB over a more motor-sparing adductor canal block, we saw no decline in our study. This is in accordance with a previous study by Memtsoudis et al[28], which suggests that peripheral nerve blocks are not the major culprit of falls after knee surgery.

This study has limitations. UDM allows determination of an EC50 for a clinical variable with a binary outcome[29], while in a smaller sample size. As we all know that the UDM is unreliable when calculating small or large percentage points, such as the EC95[30], which is a more relevant indicator for clinical application. Although the EC95 level may be more clinically useful, our simulation calculations results in 29 small samples were significantly less accurate.

When calculating EC50 with UDM, the premise is that the concentration-effect relationship is the traditional s-shaped curve, which may be incorrect. It is not accurate to speculate the EC95.

Thus, we conclude that the median EC50 is 0.113%. Further concentration-comparative studies are needed for other volume of ropivacaine and multiple-injection techniques as well as to strengthen the validity of the results of our study.

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None

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

All authors agree to submit. Cheng Xu and Cheng-Yu Wang wrote the manuscript; Jie Lu and Quanhong Zhou designed the research; Cheng Xu, Fei Gu, Rui Chen and Yang Liu performed the research; Cheng Xu, Cheng-Yu Wang and Qanhong Zhou analyzed the data; Fei Gu and Rui Chen contributed new reagents/analytical tools.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analysed in this study. These data can be found here:*http://www.chictr.org.cn(ChiCTR2100045439)*.

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Legend

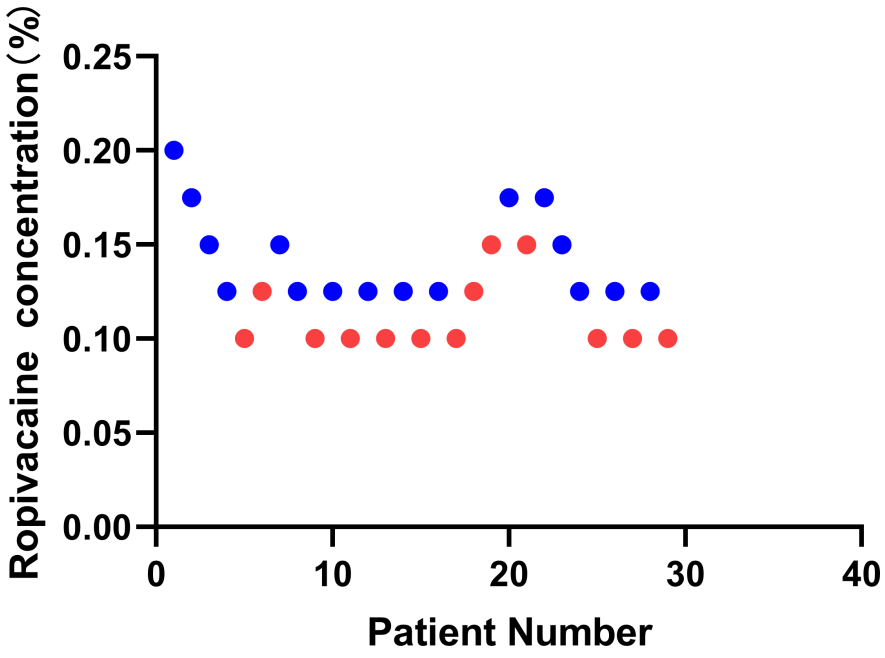
Table 1. patient characteristic

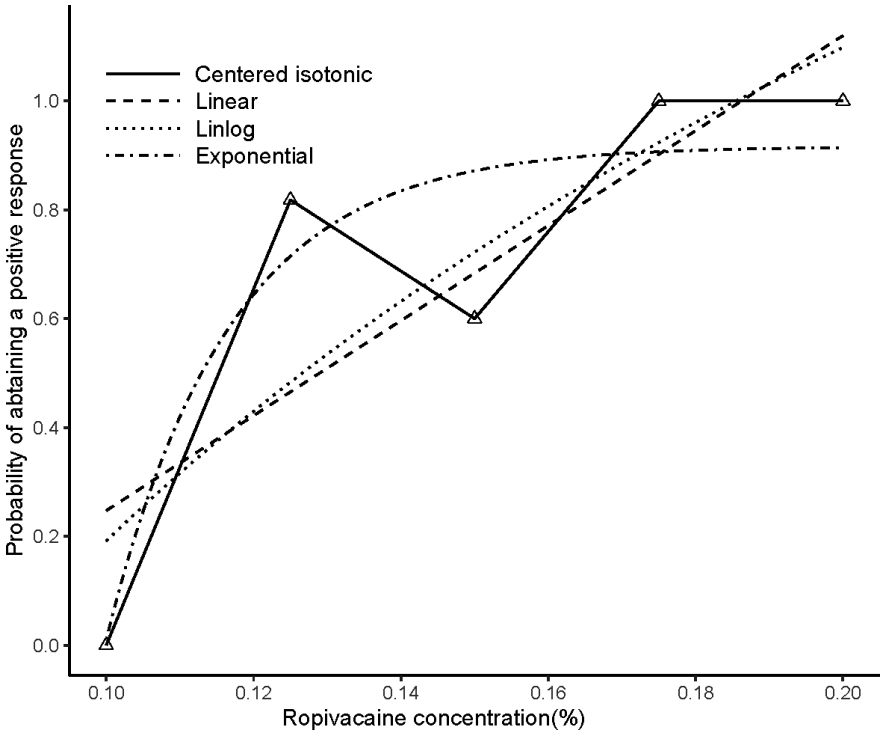
Table 2. The ED50 and 95% confidence interval (CI) of different models

Figure 1. Sequential block results of ultrasound-guided sciatic nerve block using ropivacaine 20mL according to the Dixon and Massey up-and-down method.

Figure 2. Estimated ropivacaine–sciatic nerve block relationship for a given dose level and probability of successful block. Median estimators for each model are plotted. The numbers of measurements at each ropivacaine concentration are represented by numbered triangles.

Figure 3. postoperative pain scores. A: Rest pain score 24 hours after surgery. B: motor pain score 24 hours after surgery. C: Duration of sciatic nerve block with different concentrations of ropivacaine. D: Correlation between ropivacaine concentration and time to 1st rescue analgesic in sciatic nerve block





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