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ORIGINAL INVESTIGATION

Minimum effective concentration of ropivacaine for ultrasound-guided transmuscular quadratus lumborum block in total hip arthroplasty: a randomized clinical trial☆

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Abstract

Objective: This trial aimed to identify the Minimum Effective Concentration (MEC_{90}, defined as the concentration which can provide successful block in 90% of patients) of 30 mL ropivacaine for single-shot ultrasound-guided transmuscular Quadratus Lumborum Block (QLB) in patients undergoing Total Hip Arthroplasty (THA).

Methods: A double-blind, randomized dose-finding study using the biased coin design up-and-down sequential method, where the concentration of local anesthetic administered to each patient depended on the response from the previous one. Block success was defined as a Numeric Rating Scale (NRS) score during motion ≤ 3 at 6 hours after arrival in the ward. If the block was successful, the next subject received either a 0.025% smaller dose (probability of 0.11) or the same dose (probability of 0.89); otherwise, the next subject received a 0.025% higher ropivacaine concentration. MEC_{90}, MEC_{95} and MEC_{99} were estimated by isotonic regression, and the corresponding 95% Confidence Intervals (95% CIs) were calculated by the bootstrapping method.

Results: Based on the analysis of 52 patients, MEC_{90}, MEC_{95}, and MEC_{99} of ropivacaine for QLB were estimated to be 0.352% (95% CI 0.334–0.372%), 0.363% (95% CI 0.351–0.383%), and 0.373% (95% CI 0.363–0.386%). The concentration of ropivacaine at 0.352% in a volume of 30 ml can provide a successful block in 90% of patients.

Conclusions: For ultrasound-guided transmuscular QLB in patients undergoing THA, 0.352% ropivacaine in a volume of 30 ml can provide a successful block in 90% of patients. Further dose-finding studies and large sample size are required to verify the concentration.

☆ Study conducted at the West China Hospital, Sichuan University.

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Introduction

Total Hip Arthroplasty (THA) is the most common type of hip replacement surgery. Most patients suffer moderate to severe pain after surgery, which can seriously affect diet, sleep and postoperative recovery.[1,2] Therefore, adequate postoperative pain management is essential for improving the comfort of THA patients.[3]

At present, pain management is conducted using numerous multimodal analgesia methods, such as intravenous opioids or non-steroidal anti-inflammatory drugs, epidural anesthesia, and peripheral nerve block.[4-7] However, several side effects and complications such as dizziness, nausea, vomiting, urinary retention, infection, local hematoma, hypotension, cardiovascular and renal complications are associated with these methods.[4-7] In recent years, ultrasound-guided regional anesthesia has been widely used for postoperative analgesia due to economy, efficiency, safety, and minimal adverse impact on patients' physiological functions.[8]

Ultrasound-guided Quadratus Lumborum Block (QLB) is a new type of nerve block in which local anesthetics are injected in the area surrounding the quadratus lumborum muscle, from where they spread along the Thoracolumbar Fascia (TLF) and block the sensory, motor, and sympathetic nerves, thereby providing postoperative analgesia.[9] Transmuscular QLB has the most widely affected dermatomes and can provide satisfactory postoperative analgesia for THA patients.[10]

Concentrations of ropivacaine from 0.2% to 0.75% have been reported for transmuscular QLB.[11-17] In one study, ultrasound-guided transmuscular QLB with 0.5% ropivacaine resulted in quadriceps muscle weakness, seriously limited postoperative exercise, and it did not aid recovery.[17] Furthermore, excessive use of local anesthetic may lead to local anesthetic poisoning or nerve damage.[18] The optimal concentration of ropivacaine for transmuscular QLB is still unclear, requiring a dose-finding study. Therefore, in the current prospective study, our objective was to determine the minimum concentration of ropivacaine that could provide transmuscular QLB block in 90% of THA patients (MEC_{90}).

Methods

This study was approved by the Clinical Trials and Biomedical Ethics Committee of our institution (2019-831) and written informed consent was obtained from all subjects participating in the trial. This study was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx). The clinical trial registration number was ChiCTR2100049654 (Date of registration: August 7, 2021). This manuscript was written following the CONSORT statement.

Patient recruitment

Between August 10 and October 1, 2021, we recruited patients at our institution who had previously been diagnosed with osteoarthritis of the hip, osteonecrosis of the femoral head (Ficat IIIB or IV), or developmental dysplasia of the hip. We included all patients between 18 and 80 years of age who opted for primary unilateral THA via a posterolateral approach. Patients also had to have a Body Mass Index (BMI) of 20−35 $kg.m^{-2}$ and an American Society of Anesthesiologists (ASA) physical status of I–III.

Patients were excluded if they presented any of the following: hip ankylosis, previous open hip surgeries, opioid addiction or dependence, alcohol addiction or dependence, cognitive impairment, psychiatric illnesses, recognized neuromuscular disorders, known allergies to the drugs used in this study, other neuropathic diseases of the relevant hip, or inability to communicate verbally.

Study design

This trial was a double-blind, randomized study to estimate the MEC_{90} for single-injection, ultrasound-guided, transmuscular QLB for patients undergoing THA. A Biased Coin Design (BCD) up-and-down sequential method to explore the MEC_{90} was used,[19] where the concentration of local anesthetic administered to each patient depended on the response from the previous one. Block efficacy was assessed using a patient-reported Numeric Rating Scale (NRS) (0−10/10), with successful block defined as an NRS score during motion ≤ 3, whereas block failure was defined as an NRS score during motion > 3 at 6 hours after arrival in the bed ward. Ultrasound-guided transmuscular QLB was performed in the preoperative room. The first patient received 30 ml of ropivacaine at 0.30%. This concentration and volume are usually used in clinical practice. If the block was successful in the first patient at 6 hours after arrival in the bed ward, the next patient received the same ropivacaine concentration (at a probability of 0.89) or a 0.025% lower concentration (at a probability of 0.11). If, however, a block failure occurred, the concentration of ropivacaine for the next patient was increased by 0.025%. In order to avoid weakening the quadriceps femoris muscle, 0.5% ropivacaine was set as the maximum concentration.[17] Therefore, if the block failed in a patient who received ropivacaine at 0.5%, the concentration administered to the next patient was not increased.

BCD sequential allocation was carried out based on randomization conducted by a statistician (PP) in Microsoft Excel. The concentration of local anesthetic had been obtained by dilution with normal saline, which was administered by an assistant (VV), and ultrasound-guided transmuscular QLB was performed by an experienced anesthesiologist (WW). Patients, anesthesiologists, surgeons, and the nursing staff were blinded to concentration allocation.

Perioperative analgesia and management

We collected data on age, sex, BMI, and ASA physical status of patients at admission. Patients were instructed to fast for eight hours before surgery and to drink 100 ml of a pure carbohydrate clear liquid two hours before surgery.[20] At 30 min

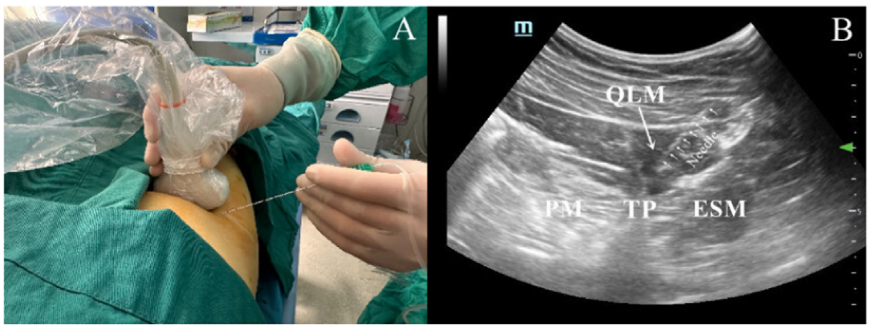

Figure 1 Ultrasound image of the transmuscular quadratus lumborum block. (A) Probe, needle, and patient set up for transmuscular QLB. (B) The trajectory of the needle is displayed on the ultrasound image. ESM, Erector Spinae mMuscle; PM, Psoas Muscle; QLM, Quadratus Lumborum Muscle; TP, Transverse Process.

before surgery, patients were admitted to the anesthesia preparation room, then their blood pressure, pulse oxygen saturation, electrocardiograph, and bi-spectral index were monitored noninvasively.

Patients received transmuscular QLB before general anesthesia. Each patient was placed in the lateral decubitus position with both legs flexed. After disinfection and placement of sterile towels, a low-frequency curvilinear ultrasound transducer (Mindray Anesus ME7, Mindray Bio-Medical Electronics, Nanshan, Shenzhen, China) was placed above the iliac crest, near the L4 vertebral body plane. After subcutaneous infiltration with 2% lidocaine (1 ml), a nerve block needle (21G*100 mm, UniPlex Nanoline) was introduced in-plane from the lateral to medial direction, the correct placement of the needle confirmed using 3 ml of isotonic saline, and then 30 ml of ropivacaine was injected between the quadratus lumborum and the psoas muscles (Fig. 1).

Motion block was assessed by comparing the changes in the muscle strength of the quadriceps femoris pre-QLB and 6 hours after arrival in the bed ward.[21] Patients were asked to flex their hip and knee, and their muscle strength was scored as follows: no muscle contraction, 0 points; muscle contraction but no joint movement, 1 point; joint movement but no gravity resistance, 2 points; gravity resistance, 3 points; gravity and partial counterforce resistance, 4 points; and normal joint function, 5 points. These scores were evaluated independently by another anesthesiologist. If strength was < 3, the patient was classified as having quadriceps muscle weakness.

On the day before surgery, celecoxib (200 mg) was administered twice as preemptive analgesic. All surgeries were conducted under general anesthesia by the same anesthesiologist. After pure oxygen inhalation, the following anesthetics were administered intravenously: midazolam, 2 mg; propofol, 2 $mg.kg^{-1}$; sufentanil, 0.3 $\mu g.kg^{-1}$; and cisatracurium, 0.2 $mg.kg^{-1}$. Patients were then intubated and given an inhaled anesthetic (sevoflurane, 1–1.5 MAC). At 20 min before the end of surgery, flurbiprofen (50 mg) was administered to prevent postoperative pain, along with tropisetron (5 mg) to prevent postoperative nausea and vomiting. All surgical procedures on patients in this study were performed by the same surgeon (QQ) at our institution.

After awakening from anesthesia, patients were transferred to the bed ward, and an ice compress was applied around the incision. Celecoxib (200 mg) and prolonged-release oxycodone hydrochloride tablets (10 mg) were administered twice a day for postoperative pain management. Within 6 hours after patients arrived in the bed ward, an investigator (ZZ) administered add-on opioid to the multimodal pain treatment in accordance with the standard protocol whenever the NRS exceeded a value of 3, along with administration of 10 mg of morphine hydrochloride when necessary. If patients were administered add-on opioid within 6 hours after arrival in the bed ward, the block was recorded as a failure.

Outcomes

The primary outcome was NRS pain score during motion at 6 hours after arrival to the bed ward. We also recorded block duration, quadriceps strength of the patients and adverse events associated with analgesia and surgery such as dizziness, nausea, vomiting, wound swelling, wound oozing, drowsiness, urinary retention, vascular puncture, falls after surgery and local anesthetic intoxication. Using the pinprick test with von Frey filaments and comparing to the opposite side of the block, the effective duration of the blockade was recorded and defined as the time from when the sensation decreased to when the sensation returned to normal.

Statistical analysis

Based on previous studies, we estimated that we would need to analyze at least 45 successful blocks in order to estimate the MEC_{90}.[22,23] Thus, we recruited patients until we reached this number.

Statistical analysis was performed using the R statistical software package, version 3.2.1 (2015 The R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0, URL http://www.r-project.org). The MEC_{90} was calculated using isotonic regression, and the corresponding 95% Confidence Interval (95% CI) was derived by bootstrapping.[24] Similar procedures were used to estimate the minimum effective concentrations to produce a successful block in 95% or 99% of patients (MEC_{95}, MEC_{99}).[25] Isotonic regression is a least squares problem under order restrictions, and an adjusted response probability was obtained by the Pooled Adjacent Violators Algorithm (PAVA). We used the dose estimator $\mu 3$, defined as the interpolated dose whose probability of effect was estimated to be 0.9.

The normality of data was analyzed using histograms and quantile-quantile plots. Continuous data were presented as mean and standard deviation. Categorical data were presented as numbers or percentages.

Results

A total of 55 patients were screened for eligibility to participate in this study, of whom 2 did not meet the inclusion criteria and another 1 declined to participate. Therefore, a total of 52 patients were finally enrolled in the study (Fig. 2). The clinical and demographic characteristics of patients in this study are shown in Table 1. The BCD up-and-down sequence is displayed in Figure 3. MEC_{90} was found to be 0.352% (95% CI 0.334–0.372%); MEC_{95}, 0.363% (95% CI 0.351–0.383%); and MEC_{99}, 0.373% (95% CI 0.363–0.386%).

The observed response rates for each concentration of ropivacaine are shown in Table 2. Also shown are the response rates adjusted by the PAVA to generate monotonically non-decreasing response rates for the isotonic regression method. Block duration and complications data are reported in Table 3. These patients showed no significant change in muscle strength of the quadriceps femoris between pre-QLB and 6 hours after arrival in the bed ward (4.71 ± 0.46 vs. 4.52 ± 0.51, p = 0.26), and none of the patients presented quadriceps muscle weakness.

The following adverse events occurred: nausea and vomiting (2 patients), wound swelling (5), wound oozing (2), urinary retention (2), and dizziness (1). There were no cases of drowsiness, vascular puncture, falls after surgery (motor block), or local anesthetic intoxication.

Table 1 Clinical and demographic characteristics of patients in this study (n = 52).

Age (years)	57.64 ± 11.07
Male	30 (57)
Female	22 (43)
Height (cm)	162.81 ± 7.83
Weight (kg)	62.49 ± 8.54
BMI (kg.m^{-2})	23.51 ± 2.08
ASA	
I	13 (25)
II	31 (59.6)
III	8 (15.4)
Surgery side	
Left	28 (53.8)
Right	34 (46.2)
Duration of surgery (min)	57.31 ± 15.19
Duration of anesthesia (min)	111.63 ± 22.86

Values are mean ± SD or n (%).
ASA, American Society of Anesthesiologists; BMI, Body Mass Index.

Discussion

This prospective study evaluated the MEC_{90} of ropivacaine for ultrasound-guided transmuscular QLB to improve postoperative pain relief in patients undergoing THA. We determined the MEC_{90}, MEC_{95} and MEC_{99} of ropivacaine to be 0.356%, 0.361% and 0.372%, respectively. These results may help clinicians achieve effective analgesia without undesired local side effects.

As an indicator of toxic reaction of local anesthetics, it was very important to find the optimal concentration. In our present study, no toxic reaction of local anesthetics was found, indicating that the concentration and dose of local anesthetics used were safe. The local anesthetic used in this study was ropivacaine hydrochloride, which is less toxic to the cardiovascular, central nervous systems, and presents greater separation of sensory and motor effects than bupivacaine, and more rapid recovery of motor function.[26] The

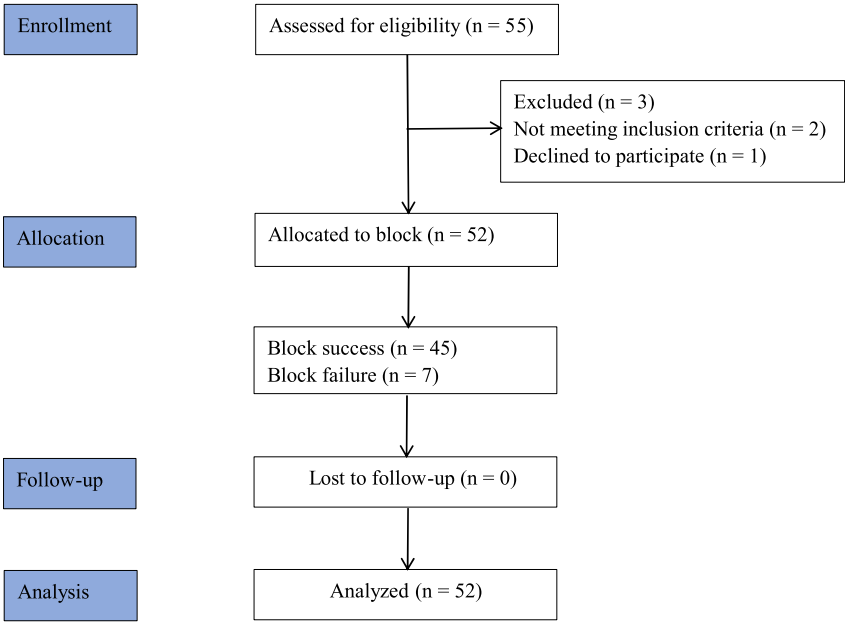

Figure 2 Flow diagram depicting patient selection.

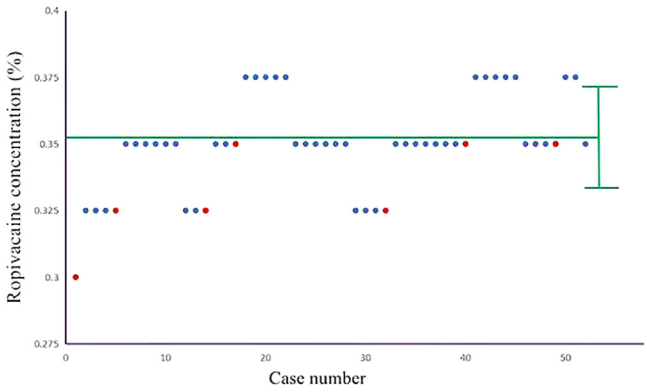

Figure 3 The biased coin design up-and-down sequence. Graph of successful (●) and failed (●) blocks at different ropivacaine concentrations. The horizontal line represents the calculated minimum effective concentration of ropivacaine providing successful transmuscular QLB in 90% of patients (MEC_{90}). Error bars represent the 95% Confidence Interval.

faster recovery and greater safety of ropivacaine make it the anesthetic of choice for patients undergoing orthopedic procedures, including THA.[27]

Several methods can be used to investigate the efficacy of a local anesthetic agent. The Dixon and Massy up-and-down design is the classic strategy to estimate the median effective dose (ED_{50}),[28] but this dose is less relevant to the clinical setting, where higher response rates are required. The BCD up-and-down method can directly determine higher quantiles (ED_{90} and ED_{95}), providing useful clinical knowledge. In the BCD design, the concentration assignment is carried out in a sequential and interactive way such that patients are randomized to doses more likely to be effective without incurring in higher toxicity risk. To the best of our knowledge, this is the first study investigating the MEC_{90} of ropivacaine for ultrasound-guided transmuscular QLB. Our analysis of MEC_{90}, MEC_{95} and MEC_{99} is likely to be more clinically relevant than studies that used Dixon's method to determine the MEC_{50} of local anesthetics on nerve blocks.[29,30] Indeed, the BCD design has been applied in anesthetic dose-finding studies for other peripheral nerve blocks.[22,31] Due to the only MEC_{50} of local anesthetics for Dixon and Massy methods, while the BCD up-and-down method could achieve MEC_{90}, MEC_{95}, or even MEC_{99}, those results are more accurate and reliable. Given the small sample size of our present study, further research and larger sample size to explore the differences will enrich our knowledge.

Table 3 Block duration and adverse events among all patients (n = 52).

Block duration, hours	12.6 ± 1.8
Nausea and vomiting	2 (3.8)
Dizziness	1 (1.9)
Wound swelling	5 (9.6)
Wound oozing	2 (3.8)
Urinary retention	2 (3.8)
Drowsiness	0
Vascular puncture	0
Falls after surgery (motor block)	0
Local anesthetic intoxication	0

Values are mean ± SD or n (%).

Transmuscular QLB was previously shown to provide satisfactory postoperative analgesia for abdominal and hip surgery.[11-17] Researchers originally thought that in transmuscular QLB, local anesthetics would diffuse directly into the paravertebral space along the TLF in order to achieve the effect of paravertebral block.[9,10] However, paravertebral spread has been observed only rarely in human study.[32] Further research should explore in detail how transmuscular QLB works. Whether QLB provides any benefit to patients after hip arthroscopy remains controversial. These disagreements may stem from dosing differences, highlighting the necessity of the current dose-finding study.

Given the promising results of our study, we believe that administering ropivacaine in a volume of 30 ml is appropriate, and the same volume of solution was used in previous studies to provide reliable surgical anesthesia.[33] According to the pooled-adjacent violators algorithm-adjusted responses in Table 2 and complications in Table 3, there were no patients with quadriceps muscle weakness, local anesthetic intoxication or any other complications, and a ropivacaine concentration of 0.375% was 100% effective in our patients and offered a good balance between block efficacy and safety.

The ideal dose of peripheral nerve block is a noble goal to guide anesthesiologists to improve the quality of patient care, although it is affected by many factors such as the surgical site, the degree of lesion and the patient's pain tolerance characteristics.

Several limitations of our study must be acknowledged. First, because all blocks were performed by one experienced anesthesiologist in our study, we could not assess potential effects of clinician experience on outcomes. The results of

Table 2 Observed and pooled-adjacent violators algorithm-adjusted response rates.

Assigned concentration	Successful blocks	Trials	Observed response rates	PAVA-adjusted response rates
0.3%	0	1	0	0
0.325%	8	11	0.727	0.727
0.35%	25	28	0.893	0.893
0.375%	12	12	1.000	1.000

PAVA, Pooled-Adjacent-Violators Algorithm.

this study are based on the multimodal analgesics combination (including two anti-inflammatories and oxycodone) routinely used in our hospital, although the optimal ropivacaine concentration for other multimodal analgesics combinations may vary. Second, we did not assess the effects of injection volume, since we fixed the volume at 30 ml based on the literature. Follow-up studies should determine the minimum effective volume. Third, the definition of a successful block was based on patient reported NRS scores, which increases the risk of individual bias and variability. Fourth, we did not analyze postoperative patient satisfaction or quality of life after discharge, which are ultimately important to consider when optimizing the use of ropivacaine. Given our small sample, larger studies are needed to verify the doses determined here. Fifth, in the present study, the primary outcome was NRS pain score during motion within 6 hours after arrival in the bed ward, and the patients suffered the heaviest pain during motion within 6 hours. The short follow-up of only 6 hours in the postoperative is a limitation of our study, and we will extend the observation time in further research. Sixth, morphine titration based on weight, age or treatment naive might be better to detect small pain differences and decrease consumption of morphine. We will adopt this method in further clinical and research work. Seventh, given our objective was to determine the minimum concentration of ropivacaine, perhaps it would be plausible to start with the lowest reported concentration of 0.2%. Eighth, although good postoperative analgesia in THA patients was provided by transmuscular QLB, the patients were placed in lateral decubitus position during the block, which reduced the comfort of patients. Almeida proposed the LALaT block,[34] DeFI block[35] and the PPIP.[36] These three blocks were performed on supine position, which could improve the comfort of patients. These three blocking methods were simple to operate and had good analgesic effects, which were promising and worthy of further exploration.

Conclusion

We found that ultrasound-guided transmuscular QLB using ropivacaine at 0.352% in a volume of 30 ml can provide successful block in 90% of patients undergoing THA. Additional dose-finding studies with larger samples are needed to verify these findings.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical review committee statement

This study was approved by the Clinical Trials and Biomedical Ethics Committee of West China Hospital, Sichuan University, and registered with the Chinese Clinical Trial Registry on August 7, 2021 (ChiCTR2100049654; http://www.chictr.org.cn/index.aspx). Patients were recruited for the study between August 10 and October 1, 2021. Written informed consent was obtained from all patients.

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