BMJ Open

Comparison of ultrasound-guided anterior quadratus lumborum block at the lateral supra-arcuate ligament with posterior quadratus lumborum block for perioperative analgesia in laparoscopic nephrectomy: a protocol for a randomised, prospective, parallel group, non-inferior trial

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ABSTRACT

Objective Anterior quadratus lumborum block at the lateral supra-arcuate ligament (QLBA) is a new method for postoperative pain relief in patients undergoing abdominal surgery. Perioperative QLBA is effective, but it has not been compared with posterior quadratus lumborum block (QLB2). The present study aims to evaluate the postoperative pain of patients undergoing laparoscopic nephrectomy surgery with QLBA versus QLB2.

Methods/design This study is a randomised, prospective, parallel group, non-inferior trial. All patients undergoing laparoscopic nephrectomy surgery will be randomised 1:1 to the QLBA group or the QLB2 group with general anaesthesia. The objective of the trial is to evaluate the postoperative pain of patients undergoing laparoscopic nephrectomy surgery with QLBA (n=50) versus QLB2 (n=50). The primary outcome for this trial is the Visual Analogue Scale scores at rest and activity (dynamic pain scores are assessed with a cough or a trial to sit up in bed) 2 hours after surgery between patients who receive QLBA versus QLB2. The secondary objectives will be to compare (1) pain at rest and activity 0.5 hour, 2 hours, 24 hours, 48 hours after surgery; (2) the time spent on block operation; (3) the blocked dermatomal coverage 5 min and 15 min after block operation; (4) intraoperative opioid consumption; (5) types and doses of the rescue analgesic after surgery; (6) nausea and vomiting score within 24 hours after surgery; (7) time from the end of surgery to the first onset significant pain; (8) patient satisfaction score.

Discussion Clinical experience has supported that QLB is a very effective postoperative analgesic method, and we will answer the following questions in this trial: Will both approaches have the same analgesic effect and duration? Will the QLBA have a non-inferior postoperative analgesic effect compared with QLB2 or the QLBA be able to prolong the duration of analgesia after surgery? The results of this study could have actual clinical applications that could help to reduce postoperative pain and shorten hospital stays.

Ethics and dissemination The study design was approved by the ethical committee of Beijing Chao-Yang Hospital, Beijing, China (2020-ke-321). The trial results will be published in peer-reviewed journals and at conferences.

Trial registration number ChiCTR2000035354.

Strengths and limitations of this study

► This is the first parallel group, non-inferior trial designed to compare ultrasound-guided anterior quadratus lumborum block at the lateral supra-arcuate ligament (QLBA) with posterior quadratus lumborum block for perioperative analgesia in laparoscopic nephrectomy.

► In addition, this study investigates the safety and efficacy of QLBA in patients undergoing perioperative analgesia in laparoscopic nephrectomy.

► The limitation is that we only assessed Visual Analogue Scale within 2 days postoperatively, while long-term effects were not focused on.

INTRODUCTION

Reducing postoperative pain in patients undergoing laparoscopic nephrectomy has been a hot topic of research. Quadratus lumborum block (QLB) produces analgesia by blocking the abdominal wall nerves. Guidance with ultrasound can locate the nerve more clearly and accurately. Ultrasound-guided nerve block can reduce the amount
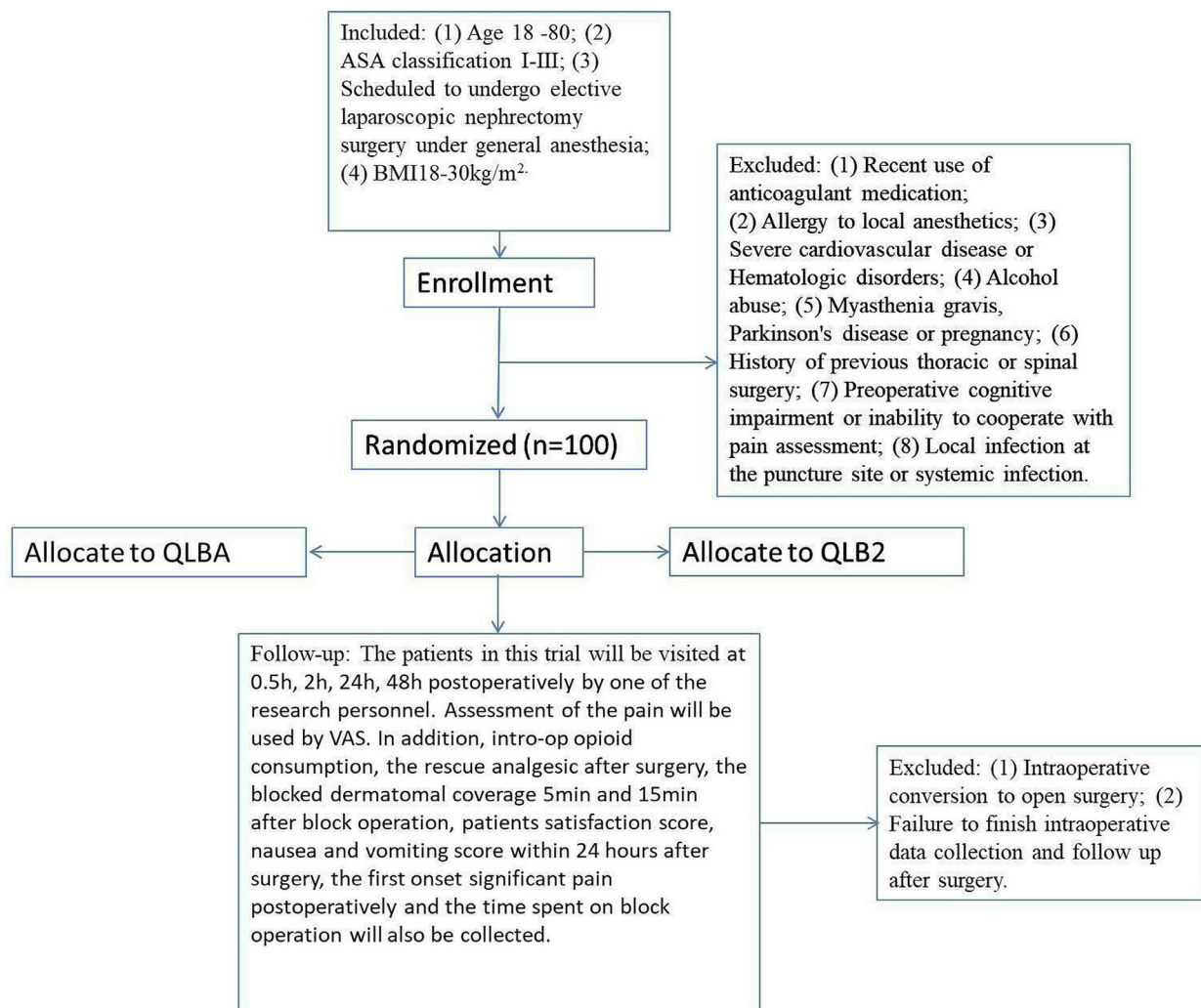
Figure 1 Patients' flow through the study. ASA, American Society of Anesthesiologists; BMI, body mass index; QLBA, quadratus lumborum block at the lateral supra-arcuate ligament; QLB2, posterior quadratus lumborum block; VAS, Visual Analogue Scale.

of intraoperative anaesthetics, reduce stress reaction induced by surgery and anaesthesia, smooth awakening, reduce postoperative pain and supplemental analgesics, and accelerate postoperative recovery. With the development of long-acting local anaesthetics such as ropivacaine and ultrasound techniques, QLB has become safer and more effective. It is a local anaesthetic technique by injecting local anaesthetics in the space. In recent years, it has been widely used for postoperative analgesia.[1–3]

QLB is usually administered before surgery in patients undergoing general anaesthesia with the effect of suppressing the reflexes of the skin incision, reducing the amount of intraoperative anaesthetic, and providing effective postoperative analgesia for patients undergoing abdominal surgery and laparoscopic surgery. But traditional QLB has disadvantages such as slow onset and inaccurate effects in our recent clinical observation. Each new technology must meet the growing demands for safety and efficacy.

Ultrasound-guided QLB is now often used for compound anaesthesia and postoperative analgesia for

caesarean section, hip surgery and abdominal surgery. Traditionally, there are four types of QLB. Injecting local anaesthesia into the anterolateral aspect of the quadratus lumborum (QLB1), between the quadratus lumborum and erector spinae (QLB2), between the quadratus lumborum and the psoas major muscle, and within the quadratus lumborum.

Administration of QLB2 after laparoscopic cholecystectomy is effective in relieving postoperative pain.[4] Preoperative QLB1 and QLB2 did not reduce opioid consumption, but improved postoperative analgesia 24 hours after surgery.[5] However, in our clinical experience, we have found that the traditional QLB has a slower onset of effect. Moreover, the vague fascial space and imprecise injection location can lead to unstable analgesic effect. Ultrasound-guided anterior QLB at the lateral supra-arcuate ligament (QLBA) is a novel pathway and was first proposed by Li *et al* in early 2020.[6] This method locates at the level of T12–L1. The quadratus lumborum, arcuate ligament and pleura are visible under ultrasound, and the drug was injected between the endothoracic fascia

Table 1 The schedule of planned investigation

Study component	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time	1 day before surgery	Before general anaesthesia	PACU	POD 1	POD 2	Hospital discharge
Eligibility screen	X	–	–	–	–	–
Informed consent	X	–	–	–	–	–
Demographic characteristics	X	–	–	–	–	–
Randomisation	X	–	–	–	–	–
Intervention	–	X	–	–	–	–
The time spent on block operation	–	X	–	–	–	–
The blocked dermatomal coverage	–	X	–	–	–	–
Intraop opioid consumption	–	–	X	–	–	–
VAS at rest	–	–	X	X	X	–
VAS during activity	–	–	X	X	X	–
The rescue analgesic	–	–	X	X	X	–
Nausea and vomiting score	–	–	X	X	X	–
The first onset significant pain	–	–	X	X	X	–
Patients' satisfaction score	–	–	–	–	–	X
Adverse events	–	–	–	–	–	X
Hospital stay	–	–	–	–	–	X

PACU, post-anaesthesia care unit; POD, postoperative day; VAS, Visual Analogue Scale.

and the quadratus lumborum at the level of lateral supra-arcuate ligament. In the pre-experiments, this method has relatively low operational difficulty, high recognition of tissue under ultrasound and clear analgesic effect.

There have been no randomised controlled trials comparing the differences between this method and the traditional way for perioperative analgesia. The purpose of this study was to explore the perioperative analgesic effect of QLBA and compare the differences between this method and QLB2 in laparoscopic nephrectomy surgery. Evidence suggested QLBA may become an important perioperative pain management method in multimodal analgesia management. The study is to provide a theoretical basis for future involvement in multimodal analgesia management. We hypothesised that performing the QLBA before surgery will have a rapid onset of action with no worse postoperative analgesia than the QLB2. The present report will follow the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

Trial objectives
The main objective of this study was to demonstrate that QLBA has no inferior perioperative analgesia to QLB2

and to demonstrate the safety, efficacy, and applicability of this new way in perioperative laparoscopic nephrectomy surgery.

METHODS
This protocol was written according to the SPIRIT guidelines.[7] The protocol is shown in figure 1 and table 1.

Design and setting
The study is a prospective, randomised, parallel group, non-inferior trial conducted at Beijing Chao-Yang Hospital, Beijing. All patients undergoing laparoscopic nephrectomy surgery will be randomised 1:1 to the QLBA group and the QLB2 group.

Ethics and dissemination
The study design was approved by the ethical committee of Beijing Chao-Yang Hospital, Beijing, China (2020-ke-321). The trial results will be published in peer-reviewed journals and at conferences.

Study site and period
This trial is being conducted at Beijing Chao-Yang Hospital, Capital Medical University. The study began in
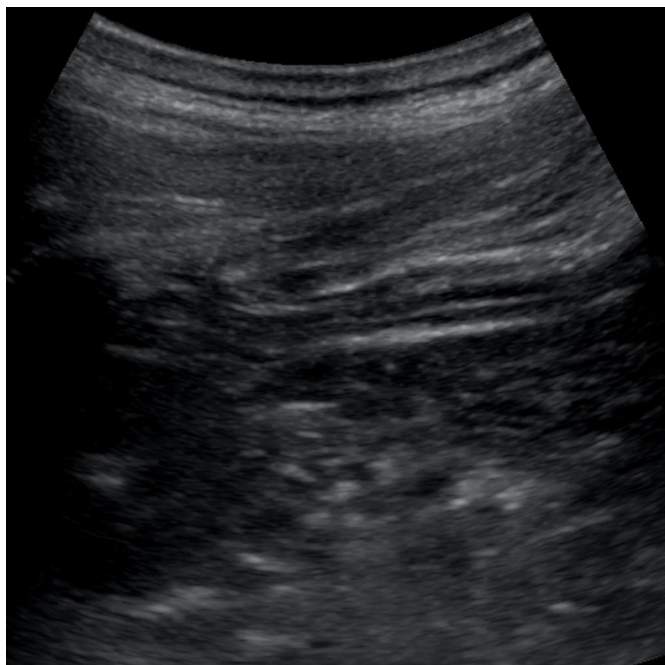
Figure 2 Ultrasound-guided quadratus lumborum block at the lateral supra-arcuate ligament.

October 2020 and will continue until useful data from 100 patients have been included in the trial. As of August 2020, all legislative and ethical approvals have been obtained.

Study participants

All patients planning to undergo laparoscopic nephrectomy surgery at Beijing Chao-Yang Hospital are invited
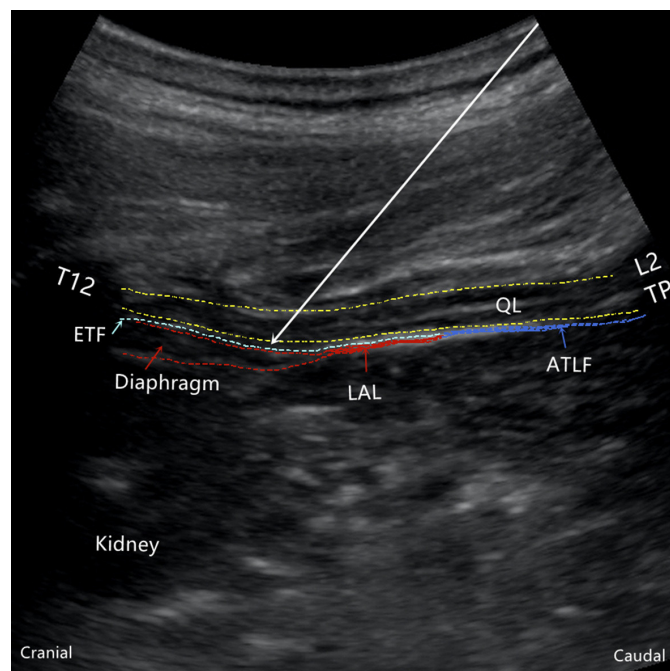

Figure 3 Ultrasound-guided quadratus lumborum (QL) block at the lateral supra-arcuate ligament. ATLF, anterior thoracolumbar fascia; ETF, endothoracic fascia; LAL, lateral arcuate ligament; TP, transverse process.

to participate in this study. Patients receive written and verbal information at the pre-anaesthesia evaluation. Subjects are not included until written consent has been obtained from the investigator. Participants are recruited 1 day before the procedure in the hospital ward. Team members visit patients who meet the eligibility criteria and invite them to join the study. All participants signed an informed consent form prior to enrolment in this trial.

Participants' inclusion criteria are as follows:
1. Age 18–80 years, American Society of Anesthesiologists (ASA) classification I–III.
2. Elective laparoscopic nephrectomy surgery under general anaesthesia.
3. Body mass index 18–30 kg/m^2.

Exclusion criteria are as follows:
1. Recent use of anticoagulant medication.
2. Allergy to local anaesthetics.
3. Severe cardiovascular disease and haematological disorders.
4. Alcohol abuse.
5. Myasthenia gravis, Parkinson's disease or pregnancy.
6. History of previous thoracic or spinal surgery.
7. Preoperative cognitive impairment and inability to cooperate with pain assessment.
8. Local infection at the puncture site or systemic infection.
9. Intraoperative conversion to open surgery.
10. Failure to finish intraoperative data collection and follow-up after surgery.

Risk and consent

As mentioned above, the two QLB ways are considered safe. First, ultrasound-guided QLB allows clear identification of the anatomy and location. Second, we have an experienced anaesthesia team that has been performing ultrasound-guided nerve blocks for many years. The QLBA is also considered to have no significant risk in our pilot study. The investigators assess the relationship between the event and the intervention and report it to the ethical committee and data and safety monitoring board. Benefits and potential risks are written in the informed consent document. Patients are informed of the purpose of the study, the intervention, the benefits and the possible risks.

Good Clinical Practice (GCP) standards are followed. This study protects the anonymity of participants as well as their data. All results are anonymised until they are shared and published. At any time, patients can withdraw their consent to participate in the trial. If patients decide to do so, this will not harm their relationship with the investigator and they will continue to receive the best treatment available from the department.

Randomisation, allocation concealment and blinding

The study will include 100 patients undergoing laparoscopic nephrectomy. Participants are randomly assigned to either the QLBA group or the QLB2 group in a 1:1 ratio with a group block size of 4 (SAS Software, V.9.4
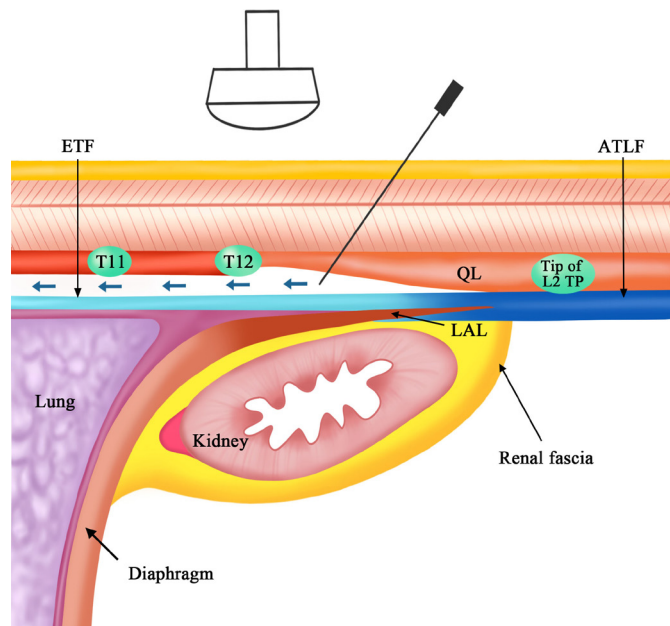
Figure 4 Diagrammatic description of the quadratus lumborum (QL) block at the lateral supra-arcuate ligament. ATLF, anterior thoracolumbar fascia; ETF, endothoracic fascia; LAL, lateral arcuate ligament; TP, transverse process.

(SAS Institute)). A statistician not involved in data collection or analysis generates a random list, which is then printed and sealed in an opaque envelope for assignment to each participant. A research nurse telephones the contact person at Beijing Chao-Yang Hospital to assign subjects to treatment. The contact person is not involved in the number generation or recruitment process. Participants are then randomly assigned to either the QLBA group or the QLB2 group.

Figure 5 Ultrasound-guided posterior quadratus lumborum block.

Data are collected by a person blinded to the study and patients are unaware of their grouping, and the final case report form (CRF) is collected into a database and managed by professional staff. A statistician who is not involved in data collection and analysis will generate randomised lists, which are then printed and sealed in an opaque envelope for each participant. The envelope is opened before anaesthesia. The contact person is not involved in the number generation or recruitment process.

Groupings are revealed via envelope on the morning of the surgery. The trial is monitored by an independent data and safety monitoring organisation. Group assignments will not be disclosed until the final statistical analysis is completed.

Study intervention
QLB is conducted under ultrasound guidance by an anaesthesiologist. After anaesthesia by local infiltration with 1% lidocaine, in-plane puncturing is operated with a long 22-gauge needle under direct vision. When the tip of the needle reaches the target area, 3 mL of saline is administered through the pump tube and puncture needle to confirm that the fluid is diffusing in the correct space, and then 0.5% ropivacaine with a dose of 0.4 mL/kg continued. All patients are transferred to the post-anaesthesia care unit after surgery.

Intervention group
In the QLBA group, a linear high-frequency (5–12 MHz) probe is placed at the paravertebral level obliquely towards the midline of the spine to identify a triangular compartment between the diaphragm endothoracic fascia and the quadratus lumborum at the lateral supra-arcuate ligament. Using an in-plane approach and an anterior to posterior direction, a 22-gauge needle is inserted until the tip is positioned between the triangular compartment (the description of the QLBA is shown in figures 2–4).

Control group
Patients assigned to QLB2 group are positioned in the lateral decubitus position with the operative side up. A 1.6–6.0 MHz curved array transducer is used to scan from the post-axillary line to identify the psoas, erector spinae and quadratus lumborum muscle. Using in-plane approach, a 9 cm, 22-gauge needle is inserted into the posterior side of the quadratus muscle (the description of the QLB2 is shown in figures 5–7).

General anaesthesia and standard postoperative pain treatment
In this study, patients receive routine general anaesthesia and surgery. Standard monitoring is performed while the patient is in the operating room, including blood pressure, ECG and oxygen saturation. Premedication is not administered. After applying standard monitoring devices, general anaesthesia is induced with midazolam 0.03 mg/kg, sufentanil 0.3–0.4 µg/kg, rocuronium 0.8 mg/kg, a target plasma concentration of 4 µg/mL and 4 ng/mL by propofol and remifentanil infusion, respectively. The
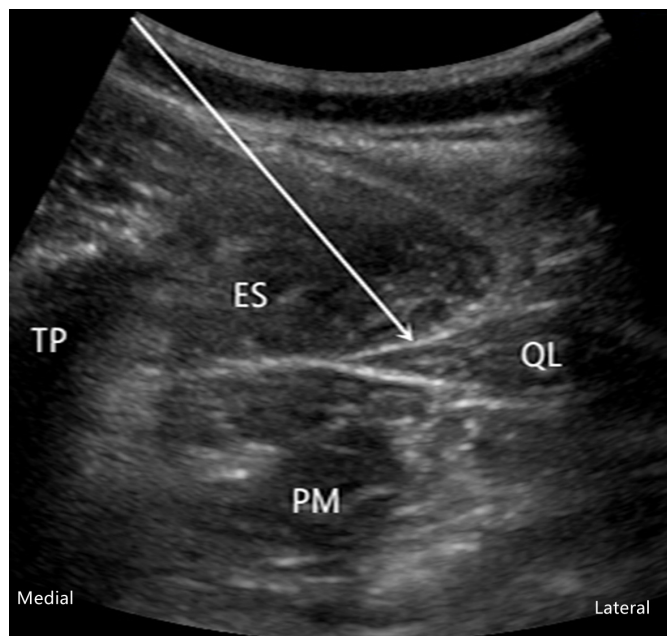
Figure 6 Ultrasound-guided posterior quadratus lumborum (QL) block. ES, erector spinae; PM, psoas major; TP, transverse process.

depth of anaesthesia is maintained using a bispectral index between 40 and 60. Sufentanil 5 µg is used 10 min before the end of the surgery, followed by continuous infusion of patient controlled analgesia (PCA).

PCA pump is used for postoperative analgesia, including sufentanil 2.0 µg/kg into 0.9% 100 mL saline at 2.0 mL/hour rate. The doctor will give an additional pain reliever if the patients needed (The rescue analgesic after surgery
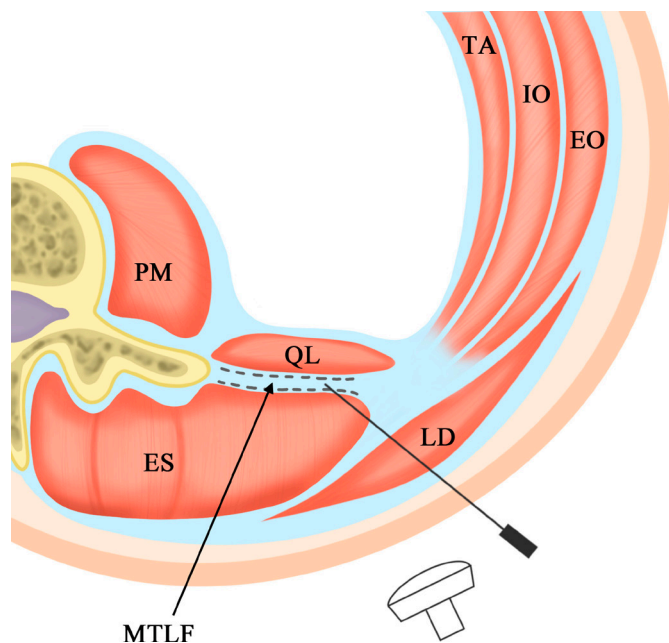

Figure 7 Diagrammatic description of the posterior quadratus lumborum (QL) block. EO, external oblique; ES, erector spinae; IO, internal oblique; LD, latissimus dorsi; MTLF, middle thoracolumbar fascia; PM, psoas major; TA, transversus abdominis .

is determined by the patient's Visual Analogue Scale (VAS) score and the patient's needs. Patients with VAS ≥7 or patients who strongly request the rescue analgesic will be given 50 mg keflex.), which will also be detailed in our CRF.

Data collection and management
Baseline data including demographic characteristics, diagnosis, preoperative comorbidities, ASA classification, history of smoking and alcohol use, etc are collected from patients who are included and signed an informed consent 1 day prior to surgery. Intraoperative and postoperative data including operative time, opioid use, intraoperative bleeding, urine output and length of stay are also collected postoperatively. All data are collected from the hospital's clinical information system and recorded in a CRF. Each participant is distinguished by study identifier and initials without a full name. An electronic file with passwords for statistical analysis will be set up by the statistical service. The analysis process will be performed by an experienced and designated team member. The CRF will be kept at the Department of Anesthesiology, Beijing Chao-Yang Hospital, Capital Medical University after the study is completed. The confidentiality and security of the participants' data are guaranteed. All data will be retained for 10 years for further analysis and investigation.

End of participation in the study
Patients will be terminated from the experiment if they meet any of the following criteria: (1) the patient refuses to participate, (2) difficulties during the intervention and the puncture cannot be completed successfully, and (3) the patient has a serious adverse event (SAE).

Criteria for removal from the study
Patients will be excluded from the study if they are found to have the following criteria: (1) the loss of over 1000 mL of blood during surgery, (2) an operation time of longer than 5 hours, (3) a violation of the trial protocol, (4) an unacceptable risk of a SAE or (5) desire to withdraw from the study.

Study outcomes
Primary outcome
The primary outcome for this trial is the VAS score at rest and activity 2 hours after surgery. The assessment time points include 0.5 hour, 24 hours and 48 hours postoperatively. Pain assessments are conducted one time per day by a researcher who is unaware of the grouping.

Secondary outcomes
Trial staff blinded to group assignments collect secondary outcomes during hospitalisation. These outcomes include:
1. The time spent on performance of block.
2. The blocked dermatomal coverage 5 min and 15 min after block operation.
3. Intraoperative opioid consumption.

4. Doses of the rescue analgesic after surgery. (The rescue analgesic after surgery is determined by the patient's VAS score and the patient's needs. Patients with VAS ≥7 or patients who strongly request the rescue analgesic will be given 50 mg keflex.)

5. Nausea and vomiting score within 24 hours after surgery (0=none, 1=nausea, 2=vomiting, 3=nausea and vomiting).

6. Time from the end of surgery to the first onset significant pain (VAS ≥7).

7. Patient satisfaction score (0=very unsatisfied, 1=unsatisfied, 2=satisfied, 3=very satisfied).

Sample size calculation

The study is currently recruiting patients. Recruitment began in October 2020. The primary outcome of this non-inferiority trial is the VAS score of 2 hours after surgery in both groups. Therefore, the sample size calculation was used for the difference between two groups using the non-inferiority test. A higher VAS score means that patients experienced worse pain. Power was 90% and two-sided α of 0.05. According to our pilot study, the VAS scores and the SD of the mean VAS score in the QLBA group and the QLB2 group were 3.34±0.5 and 3.02±0.4, respectively. The non-inferiority margin was set as 0.604 (20% of the VAS score in the QLB2 group). The target number of cases per group is 45. The total sample size for the final plan was 50 in each group with a dropout rate of 10%. Sample size calculations were performed on PASS software, V.14.0 (Digital Cruncher statistical software).

Statistical analysis

The trial will be terminated when 100 patients with useful data are all collected in the trial. All data will be used after blindness is revealed. Excluded patients, as well as missing, unused or poorly registered data, will be mentioned in the data description. The multiplex analysis will be calibrated using Bonferroni's test.

To compare baseline characteristics, normally distributed continuous variables are expressed as means (SD) and skewed data as medians (IQR). Categorical variables will be expressed as numbers (percentages). Clinical characteristics of the intervention and control groups will use two-tailed t-test or Mann-Whitney test for continuous variables, and X^2 test or Fisher's exact test for categorical variables. The primary outcome of our analysis is the postoperative VAS score in both groups. The comparison of VAS scores between the two groups will be assessed by a two-tailed t-test or Mann-Whitney test. All statistical tests will be two-sided and statistical significance will be defined as p<0.05. Statistical analysis will be performed using SPSS software, V.25.0 for Windows and the GraphPad Prism V.7.

Handling of missing data

To eliminate the impact of missing data on the final results, multiple imputation methods will be used, which included mean completer, median completer, regression, etc. Final data for both groups after conservative imputation will be analysed in the results.

Safety and adverse event reporting

This trial is monitored by an independent GCP team from Beijing Chao-Yang Hospital, Capital Medical University. Study oversight is being performed by an independent data safety monitoring committee consisting of two physicians and a statistician. An interim analysis will be performed after the inclusion of 20–50 participants. Any adverse events (AEs), adverse reactions (ARs), SAEs and serious ARs (SARs) that occur during the intervention will be collected. The investigator will foresee the necessary procedures and expertise to deal with any emergencies that may occur during the trial.

Patients are treated under standardised monitoring. Physicians and nurses participating in the trial can access the enrolled patients' electronic medical records at the hospital (electronic hospital information system) and report AEs to the principal investigator. Suspected unexpected SARs will be reported by the principal investigator to the health authorities.

Publication

All results, whether positive, negative or non-deterministic, will be published in an international peer-reviewed medical journal. Authorship will be granted according to the guidelines of the International Medical Journal Editorial Board.

DISCUSSION

Ultrasound-guided QLB is now widely used for perioperative analgesia. Previous studies and clinical experience have shown that QLB is a very effective technique for postoperative pain management.[8–11] However, the traditional methods have the disadvantage of slow onset and inexact effect. To the best of our knowledge, this is the first randomised clinical study investigating QLBA with QLB2 for patients undergoing laparoscopic nephrectomy surgery. Currently, ultrasound-guided nerve block is essential as an important modality to complement general anaesthesia. Finding the appropriate access is very crucial. However, the effectiveness of this new modality applied in the perioperative period is currently unclear. Therefore, we conducted this study.

The purpose of this study is to compare the feasibility of the QLBA compared with QLB2 for perioperative analgesia in patients undergoing laparoscopic nephrectomy. Besides, we will provide more experience and evidence for future clinical use of QLBA.

We will answer the following questions in this trial: Will both approaches have the same analgesic effect and duration? Will the QLBA have a non-inferior postoperative analgesic effect compared with QLB2 or the QLBA be able to prolong the duration of analgesia after surgery? To address this question, we will compare the analgesic effects of new way group with the traditional group.

The results of this study may have a practical and clinical advantage. It may allow a novel approach for QLB to be more widely used in the clinic and reduce postoperative pain.

Trial status

Patient recruitment started on 10 October 2020.

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