Study Protocol

Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial

Principal Investigator

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Background

Although increasing attention has been given to analgesia after surgical procedures, some patients still experience severe postoperative pain [1]. More seriously, previous studies reported that approximately 10% of patients have severe acute pain after all surgeries, indicating vast potential for chronic postsurgical pain (CPSP) [2]. Overall, severe postoperative pain seriously impacts the physical and mental health of patients and leads to secondary complications and delayed recovery after surgery. Clinical guidelines strongly recommend that nerve block, which has favorable analgesic effects, should be performed as an essential component of multimodal analgesia to alleviate pain after thoracoabdominal surgeries [3]. Recently, advantages offered by different fascial blocks, including the ease of performing them, analgesic efficacy, and low risk of complications, have been reported and increasingly applied in clinical practice.

Since it was successfully performed for the first time to manage severe thoracic neuropathic pain in 2 cases with metastatic disease of the ribs and malunion of multiple rib fractures in 2016, erector spinae plane block (ESPB) has become a popular emerging regional anesthetic technique [4]. ESPB, either using a single-injection technique or via catheterization for continuous infusion, has been widely applied in a variety of surgical procedures, such as cervical, thoracic, cardiac, breast, chest, abdominal, and lumbar surgery, for providing postoperative analgesia [5-11]. More recently, clinical evidence has demonstrated that continuous bilateral ESPB might be a promising alternative to epidural catheters and continuous paravertebral blocks (PVBs) for pain management after thoracic and abdominal surgeries [12-13]. Previously published case reports have roughly clarified the analgesic efficacy of ESPB for certain surgeries, such as cervical, thoracic, and abdominal surgery, and reported its success when performed for acute and chronic pain. However, because the majority of case reports include a non-detailed description and publication bias (since studies with unsuccessful blockades might not be published), there is still a lack of prospective studies.

Rational and Specific Aims (eAppendices 1, 2, and 3)

Convincing clinical evidence regarding opioid-sparing analgesia and enhanced recovery with ESPB is limited; the lack of more well-designed prospective studies makes recommending its use in postoperative analgesia challenging. Thus, we designed the current randomized controlled study to compare the postoperative analgesic efficacy and recovery outcomes between ESPB and conventional opioid-based pain management. We aims to develop a completely opioid-free postoperative pain management for open major hepatectomy.

Outcome Assessment

Primary outcome

The primary outcome was to compare the overall postoperative analgesic efficacy, as indicated by the cumulative area under the curve (AUC) of pain rating according to the visual analog scale (VAS) scores and the postoperative time within the first postoperative 48 hours, between the ESPB and conventional groups. The trapezoidal area calculation method was used to obtain the AUC of the Time-VAS curve.

$$AUC = \sum (VAS_i + VAS_j) \times (t_j - t_i) \div 2$$

$$\text{The cumulative } AUC_{PACU\text{-}48h} = [(VAS_{0h} + VAS_{12h}) \times 12 \div 2] + [(VAS_{12h} + VAS_{24h}) \times 12 \div 2] + [(VAS_{24h} + VAS_{48h}) \times 24 \div 2]$$

$\mathbf{VAS_i}$ and $\mathbf{VAS_j}$ are the VAS scores corresponding to two adjacent observation postoperative time points $\mathbf{t_j}$ and $\mathbf{t_i}$ ($\mathbf{j > i}$), respectively. VAS_{0h} is the VAS at PACU. 0 to 10 score VAS rating was used, Higher scores mean more severe pain. The postoperative VAS score [PACU(0h), 12 h, 24 h, 48 h, 72 h, 96 h] at rest and at movement were follow-up and collected by a third-part staff. The co-primary outcomes were both the cumulative $AUC_{PACU\text{-}48h\ at\ rest}$ and the cumulative $AUC_{PACU\text{-}48h}$ at movement. Noninferiority margin is satisfied for the cumulative $AUC_{PACU\text{-}48h}$ at rest and the cumulative $AUC_{PACU\text{-}48h}$ at movement.

Secondary outcomes

The secondary outcomes included:

(1) Anesthesia events: postoperative VAS score (PACU, 12 h, 24 h, 48 h, 72 h, 96 h) at rest and movement, the number of postoperative rescue analgesia administrations of NSAIDs and pethidine within the first postoperative 48 hours and beyond the first postoperative 48 hours, flushing, nausea, vomiting, dizziness, bradycardia, respiratory depression, delirium, and spasticity.

(2) Recovery outcomes: postoperative length of hospital stay (from the operative day to discharge), time to off-bed (the time to walking or other out-of-bed activities after surgery), time to bowel movement (time to first bowel movement after surgery), and time to oral intake (the time to first semiliquid intake).

(3) Complications: bile leakage, hemorrhage, abscess, ileus, wound infection, liver failure, pneumonia, pleural effusion, arrhythmia, renal insufficiency, sepsis, major complications (Clavien-Dindo grading of grade III or higher), 30-d reoperation or readmission, and 30-d death

(4) ESPB events: All adverse events related to the ESPB and catheterization procedures were recorded, including the VAS after catheterization (both the VAS before catheterization and preoperative abdominal pain complaints should be considered and evaluated), preoperative decannulation, suspected allergy, local site paresthesia, local site hemorrhage, local site infection, pneumothorax, rash, cardiopalmus, dyspnea, nausea, vomiting, fever, shock, and death.

(5) Local anesthetic diffusion: After ESPB catheterization procedures and the first injection, fast enhanced T1-sequence MRI scanning of the thoracic spine was used to identify the specific diffusion in the bilateral paravertebral space and injection space. Diffusion was evaluated by a professional radiologist (blind to this trial treatment), and the result was recorded (blind to the anesthesia team, surgical team, and follow-up team). Considering the symmetric diffusion of the injected liquid and the distribution of nerves innervating the liver and incision, once contrast was observed in the paravertebral space of any single segment of T5-T10, we defined it as MRI-positive.

Study Duration/Enrollment

The study was carried out from October 2019 at Fujian Provincial Hospital and conducted in compliance with the Declaration of Helsinki. This study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Written informed consent was obtained from all the patients.

Inclusion/Exclusion Criteria

Patients were eligible for participation if they were aged 18–80 years old, had an Eastern Cooperative Oncology Group performance status of 0 to 1, had an American Society of Anesthesiologists (ASA) physical status I – III and were diagnosed with hepatocellular carcinoma and planned to undergo open extended hepatectomy (≥3 segments) including extended left hepatectomy (left hemihepatectomy, left trisectionectomy), extended right hepatectomy (right hemihepatectomy, right trisectionectomy) and

central hepatectomy (S4\5\8) (**eAppendix 1, eAppendix 4**).

The exclusion criteria included:

(1) Patients who clearly asked for laparoscopic surgery;
(2) Patients with a body mass index ≥30 kg/m^2 or <18.5 kg/m^2;
(3) Patients with an allergic history to any local anesthetics (ropivacaine, lidocaine, bupivacaine, procaine, tetracaine, benzocaine, dacronin etc.);
(4) Patients with an allergic history to any anesthetics (propofol, remifentanil, sufentanil etc.);
(5) Patients with an allergic history to any CT or MRI contrast medium (iodinated contrast, gadolinium-containing contrast, etc.)
(6) Patients with an allergic history to any ultrasonic couplant;
(7) Patients with obvious renal insufficiency (serum creatinine >2 times the normal upper limit);
(8) Patients with severe spinal deformities;
(9) Patients with distant tumor metastases;
(10) Patients who had undergone minor hepatectomy;
(11) Patients who required emergency surgery, such as spontaneous tumor rupture and massive hemorrhage;
(12) Patients with a skin infection, furuncle, abscess, or paraspinal tuberculosis close to the punctuation site;
(13) Patients with a history of a cerebrovascular accident within the past 6 months before inclusion;
(14) Patients with a history of unstable angina pectoris, myocardial infarction, or heart failure within the past 6 months before inclusion;
(15) Patients with severe lung diseases (e.g., pulmonary fibrosis, severe emphysema, pulmonary heart disease); or a forced expiratory volume in 1 second (FEV1) < 50% of predicted values, arterial O_2 ≤ 60 mmHg, or arterial CO_2 > 50 mmHg;
(16) Patients with poorly controlled acute or active infections (infection-induced fever >38°C);
(17) Patients with poorly controlled hypertension or diabetes;
(18) Patients with severe mental diseases or disorders;
(19) Patients with suspicious systemic or regional nervous system diseases;
(20) Patients with receiving systematic administration of corticosteroids;
(21) Patients requiring concomitant surgical treatment for other diseases;
(22) patients with chronic pain or opioid use histories;
(23) Women who were pregnant or breastfeeding;
(24) Patients with other underlying serious diseases;
(25) Patients who were unable or refused to comply with the treatment and monitoring required by the study;
(26) Patients participating in other clinical trials;
(27) Patients who refused to provide informed consent.
(28) Patients whose data was missing.

Study design

This is a single-center, prospective, parallel randomized controlled noninferiority comparative trial.

Patients grouping

Patients were randomly assigned in a 1:1 ratio to the VC-ESPB group or the conventional group.

Expected sample size

(1) The postoperative analgesic efficacy based on previous studies and attempts in hepatectomy was used to estimate the sample size [14-16];

(2) No direct and appropriate previous reference resources about the postoperative cumulative AUC of continuous ESPB were found, and after a discussion with all the investigators, the noninferiority of ESPB was set according to previous studies and previous attempts (1/5 to 1/10 of the previous mean cumulative AUC at rest and at movement of the mean in conventional group). According to the 10 attempts of VC-ESPB procedures [at rest: mean 170.40 SD 38.59; at movement: mean 216.60 SD 32.05] and 10 attempts of conventional procedures [at rest: 166.80 SD 34.15; at movement: 211.80 SD 34.76], the noninferiority margin was was finally set as 26.5 [14-16], which is met the range of 1/5 to 1/10 for both at rest and at movement.

(3) Calculation software for sample size: PASS (version 11.0, NCSS, LLC, 329 North 1000 East Kaysville, Utah 84037);

(4) The alpha error was set at 0.05, and the power was 0.90;

(5) The number of patients in the ESPB and conventional groups was assigned in a 1:1 ratio;

(7) Based on the above calculations, 90 patients were required for analysis, of 45 for the ESPB and 45 for conventional groups at rest. 84 patients were required for analysis, of 42 for the ESPB and 42 for conventional groups at rest. 90 was used for sample size according to the larger sample size required for the two main outcomes calculated separately;

(8) Considering a 5% dropout rate after randomization and 5% inadequate data collection, 50 patients per study group were needed, with a total of at least 100 patients required in the trial.

Blinding

The randomization process was performed by third-party professional medical staff not involved in this study. An internal randomization group generated the random sequences, and the list was loaded onto a computer interactive response system (IRS). Before the VC-ESPB procedure, the third-party staff generated a random number for each patient and then entered it into the IRS to obtain the randomization number for allocation of the grouping and corresponding treatment (active intervention drugs for the VC-ESPB group, control drugs for the conventional group). The third-party staff completed the preparation of the drug packages, and both the active intervention drugs and control drugs were packed in packaging of the same size and appearance. The corresponding drugs were prepared by the third-party staff and brought to the anesthesia team for VC-ESPB and postoperative pain management. The third-party staff evaluated the whole randomization process and recorded the patient allocation of the grouping and corresponding treatment.

Staff arrangement

Surgeon team (Shi Chen, Yifeng Tian, Yaodong Wang, Long Huang, Tiansheng Lin, Chengyu Liao)

Anesthesia team (ESPB: Danfeng Wang, General anesthesia team: Xiaochun Zheng, Ting Zheng, Chaoqun Li)

Third-party staff for blinding (Zenggui Yu)

MRI check staff (Jiawei Su)

Follow-up team (primary outcome and anesthesia events: Huazhen Ye; secondary outcome: corresponding surgeons in charge)

Study Procedure

Interventions, Dosage and Administration

Intervention drugs package: 60 ml 0.25% Ropivacaine compounded with 1.5 ml MRI-contrast for the first injection of ESPB; 5 bottles (60 ml each bottle) of 0.25% ropivacaine for the postoperative injections of ESPB; postoperative intravenous pump (10 mg tropisetron diluted to 100 ml with 0.9% NS) [17-22].

Control drugs package: postoperative intravenous pump (2.5 μg/kg sufentanil and 10 mg tropisetron diluted to 100 ml with 0.9% NS).

VC-ESPB procedure

The patient was admitted to the anesthesia preparation room before ESPB catheterization, and preoperative VAS was evaluated. With the establishment of venous access and the measurement of vital signs (electrocardiogram, noninvasive blood pressure, and oxygen saturation), ESPB was performed in the prone position by an experienced anesthesiologist. Under the aseptic ultrasound-guided technique, a high-frequency (12–15 MHz) linear array probe was placed 3 cm from the spine to identify the bilateral transverse process of T8 and the erector spinae and trapezius attached above the transverse process of T8; the trapezius and erector spinae were marked. Then, the local skin was anesthetized with 3 ml 2% lidocaine. A 20 G trocar (Braun nerve block kit) was inserted into the posterior space of the erector spinae muscle in front of the transverse process of T8 from the caudal side to the cephalic side, which is based on the distribution of the nerves innervating the liver, the incision and symmetric diffusion of the injected liquid. Next, 5 ml 0.9% NS was injected to separate and enlarge the space consisting of the deep surface of the erector spinae and the transverse process space. After confirming the space, the catheter (Braun nerve block kit) was inserted through the sheath tube at a depth of approximately 4–5 cm to reach the separated space, keeping the tip of the catheter between the transverse processes of T7 and T8, and the depth of the catheter (length of the subcutaneous segment of the catheter) was recorded. After the proper position of the catheter was confirmed and fixed via the subcutaneous tunnel, the given drug (30 ml 0.25% Ropivacaine compounded with MRI contrast) was injected. The diffusion of the liquid into the injection space was first observed using ultrasound. The same procedure was performed on the contralateral side. Then, the catheters were fixed with sterile dressing, and the VAS was evaluated again 30 minutes after catheterization. In the prone position, the patient's vital signs were monitored for additional 15 minutes when ESPB was done, and any adverse events or complaints, including allergies, were recorded. If life-threatening adverse events occurred, the trial intervention and corresponding treatment was immediately terminated.

Visible MRI check for ESPB

Local anesthetic diffusion: After the ESPB catheterization procedure and the first injection, fast enhanced T1-sequence MRI scanning of the thoracic spine was used to identify the specific diffusion of the drug in the bilateral paravertebral space and injection space. Diffusion was evaluated by a professional radiologist (blind to this trial treatment), and the result was recorded. Considering the symmetric diffusion of the injected liquid and the distribution of nerves innervating the liver and incision, once contrast was observed in the paravertebral space of any single segment of T5-T10, we defined it as

successful drug diffusion/MRI-positive.

Surgery

All operations were performed by experienced chief surgeons who had specialized in hepatobiliary surgery for more than 20 years; the chief surgeons were assisted by two well-trained attending surgeons, a senior resident, and skilled nurses. All patients received a reverse L-shaped incision, which was sutured with skin staples.

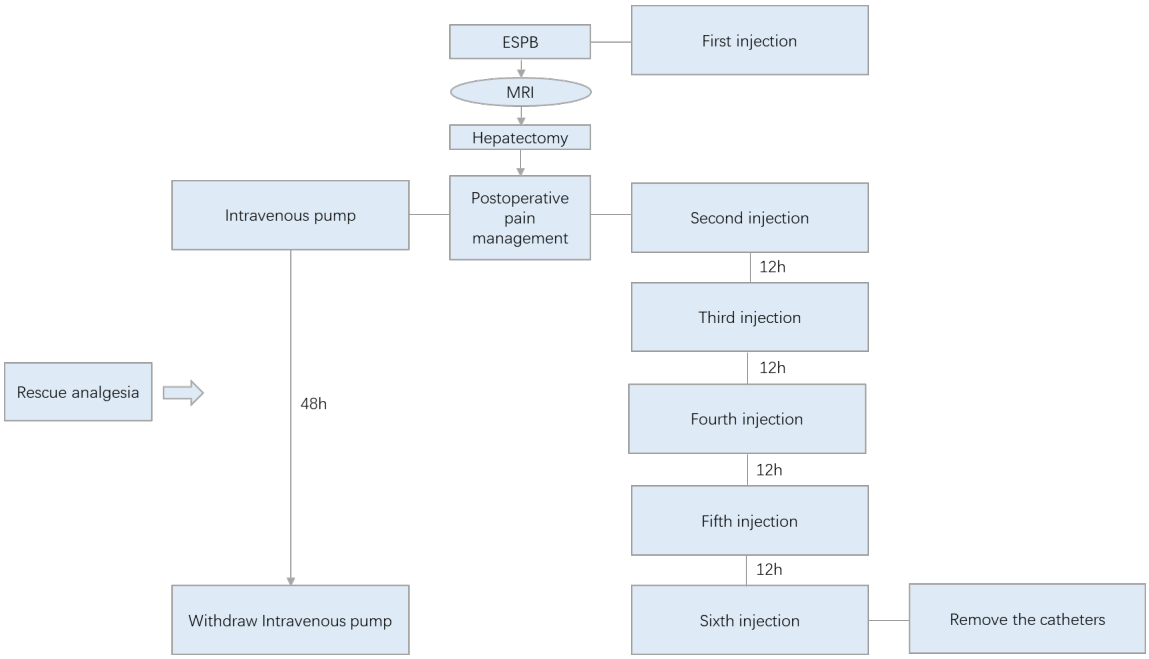
General anesthesia

General anesthesia was maintained by a total intravenous anesthesia approach and performed by another experienced anesthesiologist. All patients were transferred to the operation room without any premedication and received standard monitoring, including electrocardiogram (ECG), noninvasive and invasive systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), saturation of pulse oxygen (SpO_2), respiratory rate (RR), and partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) intraoperatively. Furthermore, bispectral index score (BIS) monitoring of electroencephalograms was routinely used in the two groups. Central venous catheterization was performed in the right internal jugular vein before anesthesia induction. A forced-air rewarming blanket and core temperature monitoring were routinely used to maintain the patient's temperature (>36 °C - <37 °C). Both the ESPB group and conventional group were induced with midazolam 0.06 mg/kg, sufentanil 0.5 mg/kg, propofol 0.2 mg/kg, and rocuronium 0.6 mg/kg. Target-controlled infusion of propofol was started immediately after anesthesia induction to maintain the BIS between 40 and 55. Intermittent intravenous injections of cisatracurium were used to maintain muscle relaxation. Remifentanil was loaded in a target-controlled infusion pump with an initial concentration of 2 ng/ml (adjusted to the maximum concentration of 8 ng/ml) to maintain blood pressure and HR fluctuation within 20% of the baseline value intraoperatively. If the HR and mean arterial pressure (MAP) exceeded 20% of the baseline value, an additional 10 μg dose of sufentanil was used. When starting the incision suture, 5 mg tropisetron, 100 mg flurbiprofen axetil, and 0.1 μg/kg sufentanil were used. Moreover, remifentanil infusion was immediately withdrawn when the sheath of the rectus abdominis and linea alba was sutured, and propofol infusion was gradually decreased to maintain the BIS between 55 and 65 until all the incision sutures were completed. Fluid management (maintenance of low CVP below 5 cmH_2O) with close monitoring hepatectomy) to ERAS guideline and preventing intraoperative hypothermia by using forced air warming systems were administrated according to ERAS guideline.

Postoperative pain management

For postoperative pain management, 30 ml of the postoperative injection drugs was administered via the bilateral fixed catheters every 12 hours from the PACU to 48 hours after the operation in all patients (5 postoperative injections in total) in prone. All intravenous analgesia pumps were initiated after tracheal extubation. Considering previous opioid poisoning events and further strict bias control for patients, all intravenous analgesia pumps were locked with only the basic dose, of which additional self-controlled use PCA was invalid. The operation parameters of the intravenous pumps were 2 ml/h without additional PCA. Furthermore, the surgeon considered the use of rescue analgesia only when the patient asked and when the immediate VAS at rest was greater than or equal to 4 points. Flurbiprofen was the first choice for NSAID rescue analgesia. The intravenous pump and ESPB catheters were removed 48 hours after the operation. All patients received Postoperative glycaemic control (<8.3mmol/l), and

encouragement to early mobilization according to ERAS guideline.



Flow chart of the intervention

Management of loss to follow-up

If a patient refused to attend the scheduled follow-up according to this protocol, he or she was recorded as lost to follow-up and was not analyzed with the cases that finished the study.

Early study termination

Participants were allowed to withdraw from the study at any time, and the study could be terminated at any time for any reason by the principal investigators (PI). The PI and coinvestigators ensured that adequate consideration was given to the protection of the patient's interests and were responsible for informing the Independent Ethics Committee [IEC] of early termination of the study **(eAppendix 5)**.

Data collection

During the data collection, the completeness of the data must be checked before signing the name of the collector to ensure that the data will not be missing.

Characteristics (eAppendix 6)

(1) Baseline characteristics were collected by the assistant (Chaoqun Li), including age, sex, BMI, ASA grade, ECOG performance status, cardiovascular comorbidities, diabetes, previous liver resection, preoperative laboratory tests within one week (albumin, bilirubin, ALT, AST, ALP, GGT, platelets, creatinine, INR, lactate, AFP), etiology (HBV, HCV or others), Child-Pugh class, and ICG-15 min.

(2) Operation-related characteristic data were collected by Chengyu Liao and included radiologically-diagnosed cirrhosis, SLV, calculated SRLV, surgical procedure, liver resection difficulty level, and pathological characteristics (lesion number, maximum tumor size, macrovascular invasion,

microvascular invasion, satellite lesions, METAVIR grade of liver fibrosis).

Outcomes

ESPB events (eAppendix 7)

Danfeng Wang recorded ESPB events, including the VAS after catheterization (both the VAS before catheterization and preoperative abdominal pain complaints were considered and evaluated), preoperative decannulation, suspected allergies, local site paresthesia, local site hemorrhage, local site infection, pneumothorax, rash, cardiopalmus, dyspnea, nausea, vomiting, fever, shock, and death).

MRI check for local anesthetics diffusion (eAppendix 8)

Diffusion was evaluated by a professional radiologist and recorded by Jiawei Su.

Intraoperative surgical outcomes (eAppendix 9)

Intraoperative surgical outcomes were recorded by the chief surgeon after the surgery (Yifeng Tian, Yaodong Wang), including the adjusted incision length (adjusted by height), operative time, blood loss, number of Pringle maneuvers, transfusion, hepatic parenchyma section class (A, B, C class), and negative margins (pathologically).

Intraoperative anesthesia outcomes (eAppendix 10)

Intraoperative surgical outcomes were recorded by the anesthesiologist who performed the general anesthesia (Xiaochun Zheng, Ting Zheng, Chaoqun Li), including the duration of anesthesia, awaking time, opioid use (remifentanil, sufentanil), and anesthetic rehydration volume (crystal liquid, colloid liquid, urine output).

Postoperative anesthesia outcomes and events (eAppendix 11)

Postoperative anesthesia outcomes and events (follow-up) were recorded by Huazhen Ye, including the postoperative VAS score (PACU, 12 h, 24 h, 48 h, 72 h, 96 h) at rest and during movement, the number of postoperative rescue analgesia administrations with NSAIDs, and the use of pethidine within the first postoperative 48 hours and beyond the first postoperative 48 hours. Postoperative anesthesia events: postoperative VAS score (PACU, 12 h, 24 h, 48 h, 72 h, 96 h) at rest and during movement, the number of postoperative rescue analgesia administrations with NSAIDs, the use of pethidine within the first postoperative 48 hours and beyond the first postoperative 48 hours, flushing, nausea, vomiting, dizziness, bradycardia, respiratory depression, delirium, and spasticity.

Postoperative recovery outcomes and complications (eAppendix 12)

Surgeons (Shi Chen, Yifeng Tian, Yaodong Wang, Long Huang, Tiansheng Lin, Chengyu Liao) recorded their own patients' postoperative recovery outcomes and complications, including the postoperative length of hospital stay (from operative day to discharge), time to off-bed (the time to walk or other out-of-bed activities after surgery), time to bowel movement (the time to first bowel movement after surgery), time to oral intake (the time to first semiliquid intake), bile leakage, hemorrhage, abscess, ileus, wound infection, liver failure, pneumonia, pleural effusion, arrhythmia, renal insufficiency, sepsis, major complications (Clavien-Dindo grading of grade III or higher), 30-d reoperation or readmission, and 30-d death. All the involved data definitions are presented in eAppendix 3 or the Outcomes Assessment section.

Privacy/Confidentiality

All the data were summarized by a third party (Zenggui Yu, who signed a confidentiality agreement) and marked with the subject number. All data containing identifying information were hidden and inputted into the dedicated encrypted database.

Throughout the study, several measures were taken to minimize any breaches of personal information, including:

(1) The collection, transmission, handling, and storage of the study patient data complied with data protection and privacy regulations. This information was provided to the study patients when informed consent was obtained for treatment procedures.
(2) Only the principal investigators and coinvestigators who signed confidentiality agreements had access to the dedicated database during the study.
(3) The principal investigators and coinvestigators could not view the corresponding grouping and treatment information until the final unblinding.

Statistics

Statistical software

SPSS 26.0 (IBM Corporation, NY, United States) and JASP software (version 0.16.3) was used to analyze the data.

Statistical analysis plan

The continuous variables are presented as the mean with standard deviation or median with range (IQR) and compared using the t-test or Mann-Whitney U test, as appropriate; categorical data are presented as a number with percentage and compared using the Pearson $\chi 2$ test or the Fisher exact test, as appropriate. Logistic Analysis was use to analyze the factors for textbook outcome. Statistical significance was reported at $P < 0.05$.

Information and informed consent

The investigator was responsible for obtaining written informed consent from each participant after an adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator used the IRB-approved written informed consent form. Each informed consent form was appropriately signed and dated by the subject or the subject's legally authorized representative and the person who obtained the consent.

Compensation

If the participant had an accident or emergency during the study, the research doctors provided corresponding medical treatment immediately. Compensation was available to the patients in the event of trial-related health injuries; the PIs were responsible for compensation based on the contract and relevant laws.

Treatment of the subjects after the end of the clinical trial

The subjects who finished the study followed the standard treatment for hepatocellular carcinoma. Subjects who withdrew in the middle of the study received the same standard treatment for hepatocellular carcinoma. Specific treatments were determined according to the subjects' clinical status and the surgeon's discretion.

Additional considerations for the study

Compliance and modification of the clinical trial protocol

The study was conducted following the clinical trial protocol, including the written notification consent form approved by the Institutional Review Board. All protocol modifications were discussed upfront among the investigators. All protocol modifications, except those intended to reduce immediate risk to the subjects, were submitted to and approved by the Institutional Review Board. Approvals were obtained before changes were implemented.

References

[1] Kehlet H. Postoperative pain, analgesia, and recovery-bedfellows that cannot be ignored. Pain 2018:159 Suppl 1: S11-S16.

[2] Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet 2019:393: 1537-1546.

[3] Nimmo SM, Foo ITH, Paterson HM. Enhanced recovery after surgery: Pain management. J Surg Oncol 2017:116: 583-591.

[4] Forero M, Adhikary SD, Lopez H, et al. The Erector Spinae Plane Block: A Novel Analgesic Technique in Thoracic Neuropathic Pain. Reg Anesth Pain Med 2016:41: 621-627.

[5] Huang W, Wang W, Xie W, et al. Erector spinae plane block for postoperative analgesia in breast and thoracic surgery: A systematic review and meta-analysis. J Clin Anesth 2020:66: 109900.

[6] Luis-Navarro JC, Seda-Guzman M, Luis-Moreno C, et al. Erector spinae plane block in abdominal surgery: Case series. Indian J Anaesth 2018:62: 549-554.

[7] Gurkan Y, Aksu C, Kus A, et al. Ultrasound guided erector spinae plane block reduces postoperative opioid consumption following breast surgery: A randomized controlled study. J Clin Anesth 2018:50: 65-68.

[8] Abu Elyazed MM, Mostafa SF, Abdelghany MS, et al. Ultrasound-Guided Erector Spinae Plane Block in Patients Undergoing Open Epigastric Hernia Repair: A Prospective Randomized Controlled Study. Anesth Analg 2019:129: 235-240.

[9] Singh S, Choudhary NK, Lalin D, et al. Bilateral Ultrasound-guided Erector Spinae Plane Block for Postoperative Analgesia in Lumbar Spine Surgery: A Randomized Control Trial. J Neurosurg Anesthesiol 2019.

[10] Paladini G, Musella G, Farris G, et al. Erector spinae plane block to enhance recovery after thoracoscopic lung lobectomy in infants. Minerva Anestesiol 2019:85: 1247-1249.

[11] Tsui BCH, Mohler D, Caruso TJ, et al. Cervical erector spinae plane block catheter using a thoracic approach: an alternative to brachial plexus blockade for forequarter amputation. Can J Anaesth 2019:66: 119-120.

[12] Ayub A, Talawar P, Gupta SK, et al. Erector spinae plane block: A safe, simple and effective alternative for knee surgery. Anaesth Intensive Care 2019:47: 469-471.

[13] Bagaphou TC, Santonastaso DP, Rispoli M, et al. Bilateral continuous erector spinae plane block: an alternative to epidural catheter for major open abdominal surgery. Minerva Anestesiol 2020.

[14] Kot P, Rodriguez P, Granell M, et al. The erector spinae plane block: a narrative review. Korean J Anesthesiol. 2019;72(3):209-220.

[15] Shein-Chung Chow, Jun Shao, Hansheng Wang, and Yuliya Lokhnygina. *Sample Size Calculations in Clinical Research, Third Edition*. Taylor & Francis Group, Boca Raton, FL 33487-2742, 2018; pp.50(3.12).

[16] Fu J, Zhang G, Qiu Y. Erector spinae plane block for postoperative pain and recovery in hepatectomy: A randomized controlled trial. *Medicine (Baltimore)*. 2020;99(41):e22251.

[17] Tamura T, Kitamura K, Yokota S, Ito S, Shibata Y, Nishiwaki K. Spread of Quadratus Lumborum Block to the Paravertebral Space Via Intramuscular Injection: A Volunteer Study. Reg Anesth Pain Med. 2018;43(4):372-377.

[18] Abu Elyazed MM, Mostafa SF, Abdelghany MS, Eid GM. Ultrasound-Guided Erector Spinae Plane Block in Patients Undergoing Open Epigastric Hernia Repair: A Prospective Randomized Controlled Study. Anesth Analg. 2019;129(1):235-240.

[19] Kim D, Kim JM, Choi GS, Heo G, Kim GS, Jeong JS. Ultrasound-guided erector spinae plane block for postoperative analgesia in laparoscopic liver resection: A prospective, randomised controlled, patient and observer-blinded study. Eur J Anaesthesiol. 2021;38(Suppl 2):S106-S112.

[20] Fu J, Zhang G, Qiu Y. Erector spinae plane block for postoperative pain and recovery in hepatectomy: A randomized controlled trial. Medicine (Baltimore). 2020;99(41):e22251.

[21] Kang R, Chin KJ, Gwak MS, et al. Bilateral single-injection erector spinae plane block versus intrathecal morphine for postoperative analgesia in living donor laparoscopic hepatectomy: a randomized non-inferiority trial [published online ahead of print, 2019 Oct 23]. Reg Anesth Pain Med. 2019;rapm-2019-100902.

[22] Aydın T, Balaban O, Acar A. Ultrasound guided continuous erector spinae plane block for pain management in pulmonary malignancy. J Clin Anesth. 2018;46:63-64.

eAppendix1. Complete list of the enrollment and exclusion criteria.

Enrollment criteria:

(1) Patients who were diagnosed with hepatocellular carcinoma and planned to undergo open extended hepatectomy (≥3 segments) including extended left hepatectomy (left hemihepatectomy, left trisectionectomy), extended right hepatectomy (right hemihepatectomy, right trisectionectomy) and central hepatectomy (S4\5\8);
(2) Patients aged 18–80 years old;
(3) Patients with a Eastern Cooperative Oncology Group performance status of 0 to 1;
(4) Patients with an American Society of Anesthesiologists (ASA) physical status I – III.

Exclusion criteria:

(1) Patients who clearly asked for laparoscopic surgery;
(2) Patients with a body mass index ≥30 kg/m^2 or <18.5 kg/m^2;
(3) Patients with an allergic history to any local anesthetics (ropivacaine, lidocaine, bupivacaine, procaine, tetracaine, benzocaine, dacronin etc.);
(4) Patients with an allergic history to any anesthetics (propofol, remifentanil, sufentanil etc.);
(5) Patients with an allergic history to any CT or MRI contrast medium (iodinated contrast, gadolinium-containing contrast, etc.)
(6) Patients with an allergic history to any ultrasonic couplant;
(7) Patients with obvious renal insufficiency (serum creatinine >2 times the normal upper limit);
(8) Patients with severe spinal deformities;
(9) Patients with distant tumor metastases;
(10) Patients who had undergone hepatectomy (segment ⩽2);
(11) Patients who required emergency surgery, such as spontaneous tumor rupture and massive hemorrhage;
(12) Patients with a skin infection, furuncle, abscess, or paraspinal tuberculosis close to the punctuation site;
(13) Patients with a history of a cerebrovascular accident within the past 6 months before inclusion;
(14) Patients with a history of unstable angina pectoris, myocardial infarction, or heart failure within the past 6 months before inclusion;
(15) Patients with severe lung diseases (e.g., pulmonary fibrosis, severe emphysema, pulmonary heart disease); or a forced expiratory volume in 1 second (FEV1) < 50% of predicted values, arterial O_2 ≤ 60 mmHg, or arterial CO_2 > 50 mmHg;
(16) Patients with poorly controlled acute or active infections (infection-induced fever >38℃);
(17) Patients with poorly controlled hypertension or diabetes;
(18) Patients with severe mental diseases or disorders;
(19) Patients with suspicious systemic or regional nervous system diseases;
(20) Patients with receiving systematic administration of corticosteroids;
(21) Patients requiring concomitant surgical treatment for other diseases;
(22) Women who were pregnant or breastfeeding;
(23) Patients with other underlying serious diseases;
(24) Patients who were unable or refused to comply with the treatment and monitoring required by the study;

(25) Patients participating in other clinical trials;
(26) Patients who refused to provide informed consent.

eAppendix 2. Involved definitions.

(1) ASA grade [1]

ASA grade I: No organic, physiologic, biochemical or psychiatric disturbance

ASA grade II: a patient with mild systemic disease that results in no functional limitation

Examples: well-controlled hypertension, uncomplicated diabetes mellitus

ASA grade III: a patient with severe systemic disease that results in functional impairment

Examples: diabetes mellitus with vascular complications, prior myocardial infarction, uncontrolled hypertension

(2) ECOG performance status [2]

0: Fully active, no restrictions on activities

1: Unable to do strenuous activities but able to complete light housework and sedentary activities

2: Able to walk and manage self-care but unable to work. Out of bed more than 50% of waking hours

3: Confined to a bed or chair more than 50% of waking hours. Capable of limited self-care

4: Completely disabled. Totally confined to a bed or chair. Unable to do any self-care

5: Death

(3) Liver resection difficulty level [3]

Grade I (Low complexity): Peripheral wedge resection <3 cm; left lateral sectionectomy

Grade II (Medium complexity): Left hepatectomy without caudate resection; right hepatectomy without caudate resection; right posterior sectionectomy; left hepatectomy with caudate resection; isolated caudate resection; right trisectionectomy without caudate resection

Grade III (High complexity): Right anterior sectionectomy; right hepatectomy with caudate resection; right hepatectomy with hepaticojejunostomy; anatomical middle hepatectomy; right trisectionectomy with caudate resection; left trisectionectomy without caudate resection; right trisectionectomy with hepaticojejunostomy; left trisectionectomy with caudate resection; right hepatectomy with hepaticojejunostomy; right trisectionectomy with hepaticojejunostomy; right hepatectomy with inferior vena cava reconstruction

(4) Child-Pugh class

Measures	Points			
	1	2	3	
Total bilirubin	< 2 (<34)	2–3 (34–50)	> 3 (>50)	mg/dL (mmol/L)
Serum albumin	> 35 (>3.5)	28–35 (2.8–3.5)	< 28 (<2.8)	g/L (g/dL)
PT (INR)	< 3 (< 1.70)	4–6 (1.71–2.20)	> 6 (>2.20)	sec
Ascites	None	Mild	Moderate to Severe	
Hepatic encephalopathy	None	Grade I-II	Grade III-IV	
	Class A: 5–6, B: 7–9, C: 10–15 points			

(5) Standard liver volume (SLV) [4] and calculated-SRLV

SLV (mL) = 706.2 x BSA (m^2) + 2.4 = 2.223 x Weight (kg)$^{0.426}$ x Height (cm)$^{0.682}$

The remnant standard liver volume was calculated by the surgeon in charge under CT according to the planned operation.

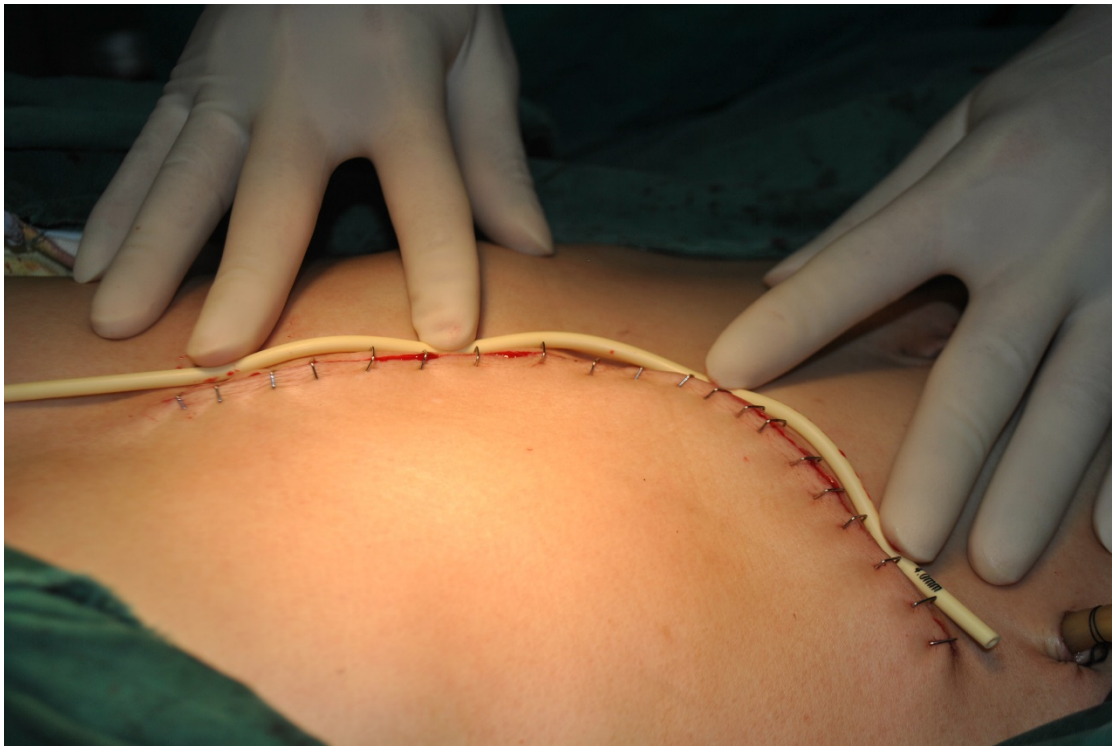
(6) METAVIR grade of liver fibrosis [5-6]

Stage	Name	Septa (thickness and number)	Criteria	score
0	No definite fibrosis			0
1	Minimal fibrosis	+/−	No septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis	1
2	Mild fibrosis	+	Occasional thin septa; may have portal expansion or mild sinusoidal fibrosis	2
3	Moderate fibrosis	++	Moderate thin septa; up to incomplete cirrhosis	3
4A	Cirrhosis, mild, definite, or probable	+++	Marked septation with rounded contours or visible nodules Most septa are thin (one broad septum allowed)	4
4B	Moderate cirrhosis	++++	At least two broad septa, but no very broad septa and less than half of biopsy length composed of minute nodules	5
4C	Severe cirrhosis	+++++	At least one very broad septum or more than half of biopsy length composed of minute nodules (micronodular cirrhosis)	6

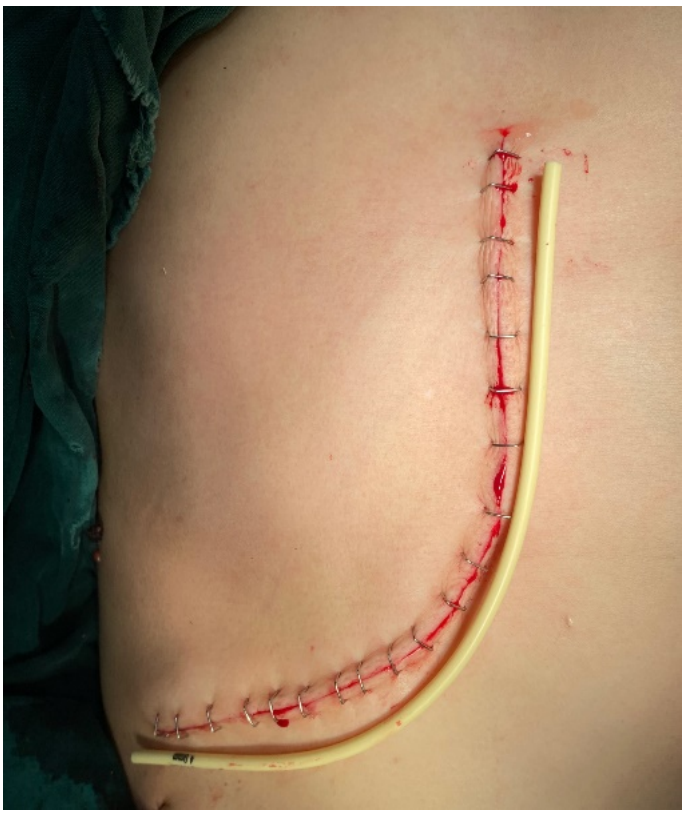
(7) Adjusted incision length

Adjusted incision length (cm/m) = length of incision (cm)/height (m)

Measurement of the length of the incision was estimated through a drainage tube, as shown in the figures below.



Measurement of the length of the incision



Measurement of the length of the incision

(8) Hepatic parenchyma section class

The hepatic parenchyma section class was judged and recorded by the chief surgeon according to the condition of the liver section during the hepatectomy procedure.

Class A: a dry section with a small amount of bleeding

Class B: a moist section but without permeating bleeding

Class C: a very moist section with permeating bleeding

(9) Transfusion

This means intraoperative blood transfusion, including plasma, erythrocyte suspending liquid, and cryoprecipitate.

(10) Negative margins

R0 resection, which is defined as complete removal of macroscopic nodules and the absence of microscopic diseases at the surgical margin, has been more frequently used to report the optimal degree of curative hepatic resection in HCC.

(11) Duration of anesthesia

The time from the induction anesthesia to recovery of consciousness whereby the patient could answer simple questions.

(12) Awakening time

Time from extubation of the endotracheal tube to recovery where the patient could answer simple questions.

(13) Postoperative length of stay (PLOS)

PLOS was recorded from the operative day to discharge.

(14) Time to off-bed

Time to off-bed was defined as the time to walking or other out-of-bed activities after surgery.

(15) Time to bowel movement

Time to bowel movement was defined as the time to first bowel movement (measured in days) after surgery.

(16) Time to oral intake

Time to oral intake was defined as the time to first semiliquid intake.

(17) Major complications

Major complications were indicated by a Clavien-Dindo grading of grade III or higher.

(18) Hemorrhage

Hemorrhage means postoperative hemorrhage requiring additional treatment beyond medicine.

(19) Abscess

An encapsulated or nonencapsulated abdominal abscess or ascites confirmed on imaging (CT or ultrasonic).

(20) Ileus

A flatulent and gas-liquid filled intestinal loop shown on abdominal plain film X-ray examination, accompanied by related symptoms and requiring further treatment.

(21) Liver failure [7]

Early:

(1) Severe gastrointestinal symptoms such as extreme fatigue, anorexia, vomiting and abdominal distension;

(2) Progressive jaundice (serum TBIL ≥ 171 μ 1 mol/L or daily rise ≥ 17 μ mol/L);

(3) 30% < PTA ≤ 40% (or 1.5 < INR ≤ 1.9);

(4) No hepatic encephalopathy or other complications.

Medium term: On the basis of the early manifestations of liver failure, the disease further developed, and one of the following two appeared:

(1) Hepatic encephalopathy below grade II and/or obvious ascites infection;

(2) Obvious bleeding tendency (bleeding point or ecchymosis), 20% < PTA ≤ 30% (or 1.9 < INR ≤ 2.6).

Late stage: On the basis of the mid-term manifestations of liver failure, the patient's condition was further aggravated, with a severe bleeding tendency (ecchymosis at injection site, etc.), PTA ≤ 20% (or INR ≥ 2.6), and one of the following four symptoms: hepatorenal syndrome, massive hemorrhage of the upper digestive tract, severe infection, or hepatic encephalopathy above grade II.

(22) Pneumonia

Patients meeting the criteria below (at least 4 and any one of 1-3) and in whom other diseases that could cause fever, cough and expectoration were excluded:

1) Clinical symptoms include cough, expectoration, fever and chest tightness

2) Physical examination with or without rales or tubular breathing

3) White blood cells greater than 10×10^9/L or less than 4×10^9/L

4) Large infiltrations on the imaging examination

(23) Renal insufficiency

Acute renal insufficiency after surgery was defined as that requiring dialysis treatment, or original chronic renal insufficiency was defined as requiring emergency dialysis treatment.

(24) Sepsis [8]

Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to

infection. The clinical criteria were according to the sepsis 3.0 guidelines.

(25) Pleural effusion

Pleural effusion was confirmed by ultrasound or other imaging examinations, and was defined as effusions not expected to be wholly absorbed and requiring further drainage.

(26) Textbook outcome [9]

The textbook outcome was defined as the absence of ESPB events, positive margins, anesthesia events, complications, prolonged postoperative length of hospital stay (≥10 d), readmission, and mortality.

(27) Clavien-Dindo classification [10-11]

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions.
II	Requiring pharmacological treatment with drugs other than those needed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention.
IIIa	Intervention not under general anesthesia.
IIIb	Intervention under general anesthesia.
IV	Life-threatening complications (including CNS complications) requiring IC/ICU management.*
IVa	Single organ dysfunction (including dialysis).
Vb	Multiorgan dysfunction.
V	Death of a patient.
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*: brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

References

[1] ASA Physical Classification System. [Internet]. American Society of Anesthesiologists. [Cited December 6, 2013]. Available at http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System/.

[2] Hensing T, Cella D, Yount S. The impact of ECOG performance status on quality of life symptoms in patients with advanced lung cancer. J Clin Oncol. 2005 23:16_suppl, 8099-8099

[3] Kawaguchi Y, Hasegawa K, Tzeng CD, et al. Performance of a modified three-level classification in stratifying open liver resection procedures in terms of complexity and postoperative morbidity. Br J Surg. 2020;107(3):258-267.

[4] Urata K, Kawasaki S, Matsunami H, et al. Calculation of child and adult standard liver volume for liver transplantation. Hepatology. 1995;21(5):1317-1321.

[5] Kim SU, Oh HJ, Wanless IR, Lee S, Han KH, Park YN. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol. 2012;57(3):556-563.

[6] Kim MY, Cho MY, Baik SK, Park HJ, Jeon HK, Im CK, et al. Histological subclassification of cirrhosis using the Laennec fibrosis scoring system correlates with clinical stage and grade of portal hypertension. J Hepatol. 2011;55:1004-1009.

[7] Chinese Liver Failure and Artificial Liver Group, Severe Liver Diseases and Artificial Liver Group. Diagnostic and treatment guidelines for liver failure (2012 version). Chinese Journal of Hepatology. 2013,21(3):177-183.

[8] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-810.

[9] van Roessel S, Mackay TM, van Dieren S, et al. Textbook Outcome: Nationwide Analysis of a Novel Quality Measure in Pancreatic Surgery. Ann Surg. 2020;271(1):155-162.

[10] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205e213.

[11] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187e196.

eAppendix3. Calculation of the Area Under the Curve (AUC).

The trapezoidal area calculation method was used to obtain the AUC of the Time-VAS curve [1].

$$AUC = \sum (A_i + A_j) \times (t_j - t_i) \div 2 (j > i)$$

A_i and A_j are the corresponding VAS scores at two adjacent observation postoperative time points, tj and ti, respectively.

For example, if the VAS scores of a patient in the PACU, and 12-h and 24-h postoperatively are 5, 4 and 3, respectively, the calculation method of the cumulative AUC is as follows:

cumulative $AUC_{PACU\text{-}12h} = (5+4) \times (12–0) \div 2 = 54$

cumulative $AUC_{12h\text{-}24h} = (4+3) \times (24–12) \div 2 = 42$

cumulative $AUC_{PACU\text{-}24h} = 54 + 12 = 66$

Reference

[1] Dingju Pan, Hao Cui, Zhu Liang, et al. Analysis of the Clinical Value of Traditional Chinese Medicine Based on Symptoms Effect-Time Area Under Curve. JOURNAL OF GUIZHOU UNIVERSITY OF TRADITIONAL CHINESE MEDICINE. 2020;42(1):50-53.

eAppendix 4. Patient Information Sheet

Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial

Principal investigator: Xiaochun Zheng, MD, PhD; Danfeng Wang, MD; Shi Chen, MD, PhD; Yifeng Tian, MD

Research center: Department of Anesthesiology, Fujian Provincial Hospital, Fuzhou, China

Department of Hepatobiliary Pancreatic Surgery, Fujian Provincial Hospital, Fuzhou, China

Dear Sir/Madam,

You are being invited to take part in a clinical study.

This study will compare the postoperative analgesic efficacy and recovery outcomes between ESPB and conventional opioid-based pain management for open major hepatectomy.

Before you decide whether to participate, it is vital for you to understand why the research is being done and what your involvement will be. Your doctor will discuss the study with you and allow you to ask any questions you may have.

This information sheet provides essential information about why and how to participate in this research study; you may take this sheet with you. Please read the following information carefully and discuss it with your family members, friends, doctors or others if you wish.

Please feel free to ask us questions if there is anything that is unclear or if you would like more information. Please take time to decide whether or not you wish to take part in this study. Participation in this study is entirely voluntary.

The background and purpose of the research project:

Background

Good intraoperative management of anesthesia and postoperative analgesia is essential to promote the recovery of patients and improve quality of life. Routine use of intravenous or epidural analgesia after open liver resection is effective. However, it can be accompanied by several adverse events, such as excessive sedation, nausea, vomiting, itching, respiratory depression, peripheral nerve injury, etc. Coagulation dysfunction, infection, spinal deformity, and the patient's nonacceptance or cooperation are contraindications to epidural puncture. In addition, poor management of acute postoperative analgesia may lead to chronic postoperative pain. Erector spinae plane block (ESPB) was first reported by Forero in 2016 and applied to the treatment of thoracic and back neuropathic pain. At present, ESPB under ultrasound guidance is used for compound anesthesia and postoperative analgesia for cardiothoracic, abdominal, and lower extremity operations. It can reduce the consumption of anesthetics during and after surgery and promote the recovery of patients after surgery. However, the postoperative analgesia time for a single ESPB is approximately 8 hours. For patients undergoing open hepatectomy, analgesia is generally required for more than 48 hours. Therefore, we attempted to apply continuous ESPB to extend the postoperative analgesia time.

Purpose

In this study, patients undergoing open major hepatectomy were selected to observe the effects of

general anesthesia combined with ESPB analgesia compared with general anesthesia combined with intravenous opioid-based analgesia on postoperative pain VAS scores and the incidences of postoperative outcomes including nausea, vomiting, the time to off-bed, the time to bowel movement, the length of postoperative hospital stay and other related surgical and anesthesia indicators. At the same time, ultrasound-guided continuous ESPB was further evaluated via a fasting T1-MRI check. Some of the clinical operations in this study, such as ESPB before surgery, require your cooperation. Please follow the instructions of your doctor. Once arranged to implement the corresponding treatment group, please maintain maximum compliance during the trial process and cannot change the group at will, otherwise will be quit from the clinical trial.

Rights and compensation

If there are any adverse reactions or severe adverse reactions related to the trial drug in this study, you will be offered free treatment and corresponding financial compensation; any expenses incurred will be paid by the sponsor.

Use of the research results and personal privacy

With the understanding and assistance of you and other subjects, the results of the research study may be published in medical journals, but the personal information of the study participants will be protected with strict confidentiality. No one will be allowed to obtain your information except the hospital ethics committee and relevant researchers, who will be allowed access to your information. Participation in the entire research process is voluntary. If you decide not to participate in this study, it will not affect any other treatments you require. If you decide to participate, you will be asked to sign this written informed consent form.

Subject's risk

Subjects will receive ESPB combined with intravenous general anesthesia in this study; ESPB may cause several adverse outcomes, including toxic reactions to local anesthetics, pneumothorax, allergies, and skin paresthesia.

There are very few complications, such as toxic reactions, but regional block methods have related complications. This trial does not increase the risk of anesthesia, and we will have corresponding preventive measures.

We sincerely invite you to participate in this study entitled "Ultrasound-guided continuous erector spinal muscle plane block for rapid postoperative rehabilitation of patients undergoing open hepatectomy and cost analysis." Before you decide to participate, it is essential that you understand the purpose and content of the study. Please read this informed consent form carefully and discuss it with your doctor, family, and friends. If anything is unclear or you want to know more, please ask the researcher who signed this consent form.

Informed consent

Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial

Patient Name		**Trial No.**

Patient Statement and Signature *to be completed by the patient*

Please **tick** each box below ☐ if you agree with the corresponding statement

☐ I voluntarily participate in this clinical research project.

☐ I can withdraw from this study at any time, and doing so will not hinder my future diagnosis and treatment at Fujian Provincial Hospital.

☐ The research physician has explained this clinical study to me, and I have had the opportunity to ask questions. All my questions have been answered, and I understood all the answers.

☐ I understand that data collected prior to this date may still be used by responsible individuals taking part in this research.

☐ I have carefully read and fully understood the content of the informed consent form and agreed to participate in this research work.

My signature confirms that I have had an opportunity to ask questions, and all of my questions have been answered.

Patient signature		**Date signed**	
Guardian's signature		**Date signed**	
Contact number			

Investigator Statement and Signature

to be completed by the person taking consent

I have discussed withdrawal from the clinical research study with the patient, using language that is understandable and appropriate. The patient has had the opportunity to ask questions.

Investigator signature		**Date signed**	

eAppendix 5. Consent Withdrawal Form

Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial

Patient Name		**Trial No.**	

Patient Statement and Signature ***to be completed by the patient***

Please **tick** each box below ☐ if you agree with the corresponding statement

☐ I have decided to withdraw from this study and all follow-up related to the trial. I understand that withdrawal from the study will not affect any future care I will receive from my medical and nursing team in the hospital.

☐ I understand that data collected prior to this date may still be used by responsible individuals taking part in this research.

☐ I no longer permit any new information from my medical records to be used to obtain information for this study, unless it is used specifically to assess any safety concerns related to my participation in the trial. This will apply to all records made on or after the date of this form.

☐ My doctor has discussed withdrawal from the clinical research study with me, using language that is understandable and appropriate.

☐ I understand that the investigators will need to be notified about my withdrawal.

My signature confirms that I have had an opportunity to ask questions, and all of my questions have been answered.

Patient signature		**Date signed**	

Investigator Statement and Signature

to be completed by the person taking consent

I have discussed withdrawal from the clinical research study with the patient, using language that is understandable and appropriate. The patient has had the opportunity to ask questions.

Investigator signature		**Date signed**	

eAppendix 6. Characteristic form

Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial			
Characteristic			
Patient Name		**Trial No.**	
Basic characteristic			
Age	**Y**		
Sex	☐ **Male**	☐ **Female**	
Height	**cm**	**Weight**	**kg**
BMI	**kg/m^2**		
ECOG performance status	☐ **0**	☐ **1**	
ASA grade	☐ **I**	☐ **II**	☐ **III**
Comorbidities	☐ **Hypertension**	☐ **Diabetes**	☐ **Others:**
Previous liver resection	☐ **Yes:**	☐ **No**	
Laboratory tests			
Albumin, g/dL			
Bilirubin, mmol/L			
ALT, U/L			
AST, U/L			
ALP, U/L			
GGT, U/L			
Platelets, 10^9/L			
Creatinine, mmol/L			
INR			
Lactate, mmol/L			
AFP, ng/mL			

ICG-15min, %			
Etiology	☐ **HBV**	☐ **HCV**	☐ **Other:**
Child-Pugh class	☐ **A**	☐ **B**	☐ **C**
Investigator signature	☐	☐ **Date**	☐
Operation-related characteristics			
Radiological cirrhosis	☐ **Yes**	☐ **No**	
SLV, mL			
Calculated SRLV, mL			
Surgical procedure			
Left hepatectomy			
Right hepatectomy			
Central hepatectomy			
Liver resection difficulty level	☐ **Grade I**	☐ **Grade II**	☐ **Grade III**
Pathological characteristics			
Lesions	☐ **Unifocal**	☐ **Multifocal**	
Macrovascular invasion	☐ **Yes**	☐ **No**	
Microvascular invasion	☐ **Yes**	☐ **No**	
Satellite lesions	☐ **Yes**	☐ **No**	
Maximum tumor size, cm			
METAVIR grade of liver fibrosis	**F0**	**F1**	**F2**	**F3**	**F4**
AJCC stage	☐ **I**	☐ **II**	☐ **III**	☐ **IV**
BCLC stage	☐ **0**	☐ **A**	☐ **B**	☐ **C**
Please tick each corresponding statement box ☐			
Investigator signature		**Date**	

eAppendix 7. Catheterization events form

Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial		
Patient Name		**Trial No.**
Catheterization evaluation		
Preoperative abdominal pain complaint	☐ **Yes**	☐ **No**
VAS before catheterization		
VAS after catheterization		
Depth of catheterization		
Catheterization events		
Suspected allergy	☐ **Yes**	☐ **No**
Local site paresthesia	☐ **Yes**	☐ **No**
Local site hemorrhage	☐ **Yes**	☐ **No**
Local site infection	☐ **Yes**	☐ **No**
Pneumothorax	☐ **Yes**	☐ **No**
Rash	☐ **Yes**	☐ **No**
Cardiopalmus	☐ **Yes**	☐ **No**
Dyspnea	☐ **Yes**	☐ **No**
Nausea	☐ **Yes**	☐ **No**
Vomiting	☐ **Yes**	☐ **No**
Fever	☐ **Yes**	☐ **No**
Shock	☐ **Yes**	☐ **No**
Death	☐ **Yes**	☐ **No**
Other	☐	
Preoperative decannulation	☐ **Yes**	☐ **No**
Please tick each corresponding statement box ☐		
Investigator signature		**Date**

eAppendix 8. MRI anesthetics diffusion check form

<table>
<tr><td colspan="4">Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial</td></tr>
<tr><td>Patient Name</td><td colspan="2"></td><td>Trial No.</td></tr>
<tr><td colspan="4">MRI check result</td></tr>
<tr><td>Anesthetics diffusion</td><td colspan="2">☐ Positive:
☐ T1
☐ T2
☐ T3
☐ T4
☐ T5
☐ T6
☐ T7
☐ T8
☐ T9
☐ T10
☐ T11
☐ T12</td><td>☐ Negative</td></tr>
<tr><td colspan="4">Please tick each corresponding statement box ☐</td></tr>
<tr><td>Investigator signature</td><td colspan="2"></td><td>Date</td></tr>
</table>

eAppendix 9. Intraoperative surgical outcomes form

Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial				
Patient Name		**Trial No.**		
Intraoperative outcomes				
Incision length, cm				
Adjusted incision length, cm/m				
Operative time, min				
Blood loss, ml				
Number of Pringle maneuvers				
Transfusion				
Transfusion	☐ **Yes:** ☐ **RBC** ☐ **Plasma** ☐ **Other**		☐ **No**	
Hepatic parenchyma section class	☐ **Grade I**	☐ **Grade II**	☐ **Grade III**	
Negative margins	☐ **Yes**		☐ **No**	
Investigator signature		**Date**		

eAppendix 10. Intraoperative anesthetic outcomes form

Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial		
Patient Name		**Trial No.**

Intraoperative anesthetic outcomes	
Duration of anesthesia, min	
Awaking time, min	
Remifentanil consumption, mg	
Sufentanil consumption, ug	
Crystal liquid, ml	
Colloid liquid, ml	
Urine output, ml	
Other adverse events	
Preoperative lactate, mmol	
Postoperative lactate, mmol	

Intraoperative hemodynamics				
Time	**SBP (mmHg)**	**DBP (mmHg)**	**MAP (mmHg)**	**HR (bpm)**
Operation room				
1 min after intubation				
5 min after intubation				
Incision				
Abdominal exploration				
First-cut (hepatectomy)				
5 min after suture				
5 min after extubation				

Investigator signature		**Date**	

eAppendix 11. Postoperative anesthetic outcomes and events form

Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial		
Patient Name		**Trial No.**
Postoperative anesthetic outcomes		
RestVAS-PACU		
RestVAS-12h		
RestVAS-24h		
RestVAS-48h		
RestVAS-72h		
RestVAS-96h		
MoveVAS-PACU		
MoveVAS-12h		
MoveVAS-24h		
MoveVAS-48h		
MoveVAS-72h		
MoveVAS-96h		
PACU duration		
Rescue analgesic NSAIDs	☐ **Yes**	☐ **No**
Within 48 h	☐ **Yes:** ☐ **1** ☐ **2** ☐ **3** ☐ **4** ☐ _____	☐ **No**
After 48 h	☐ **Yes:** ☐ **1** ☐ **2** ☐ **3** ☐ **4** ☐ _____	☐ **No**
Postoperative anesthesia events		

Flushing	☐ **Yes**	☐ **No**
Nausea	☐ **Yes**	☐ **No**
Vomiting	☐ **Yes**	☐ **No**
Dizziness	☐ **Yes**	☐ **No**
Bradycardia	☐ **Yes**	☐ **No**
Respiratory depression	☐ **Yes**	☐ **No**
Delirium	☐ **Yes**	☐ **No**
Spasticity	☐ **Yes**	☐ **No**
Please tick each corresponding statement box o		
Investigator signature		**Date**

eAppendix 12. Postoperative surgical outcomes form

Title: Analgesic efficacy of an opioid-free postoperative pain management strategy versus a conventional opioid-based strategy following open major hepatectomy: an open-label, randomised, controlled, non-inferiority trial				
Patient Name		**Trial No.**		
Postoperative recovery outcomes				
Postoperative length of hospital stay				
Time to off-bed				
Time to bowel movement				
Time to oral intake				
Postoperative recovery outcomes				
Postoperative day	**ALT (U/L)**	**AST (U/L)**	**ALP (U/L)**	**GGT (U/L)**
POD1				
POD3				
POD5				
Postoperative complications				
Bile leakage	☐ **Yes**	☐ **No**		
Hemorrhage	☐ **Yes**	☐ **No**		
Abscess	☐ **Yes**	☐ **No**		
Ileus	☐ **Yes**	☐ **No**		
Wound infection	☐ **Yes**	☐ **No**		
Liver failure	☐ **Yes**	☐ **No**		
Pneumonia	☐ **Yes**	☐ **No**		
Pleural effusion	☐ **Yes**	☐ **No**		
Arrhythmia	☐ **Yes**	☐ **No**		
Renal insufficiency	☐ **Yes**	☐ **No**		
Sepsis	☐ **Yes**	☐ **No**		
Major complications	☐ **Yes**	☐ **No**		

30d-reoperation or readmission	☐ **Yes**	☐ **No**	
30d-death	☐	☐	
Other	☐		
Please tick each corresponding statement box ☐			
Investigator signature		**Date**	