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Comparing postoperative analgesia of bilateral serratus anterior plane block and thoracic paravertebral block for children following the Nuss procedure: protocol for a randomised, double-blind, non-inferiority clinical trial

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ABSTRACT

Introduction The Nuss procedure, despite being a minimally invasive surgery, is regarded as one of the most painful surgical procedures in children, and postoperative pain control remains a major clinical issue in this population. Thoracic paravertebral nerve block (TPVB) is reported as excellent pain relief for the Nuss procedure despite its challenging performance and associated adverse effects. Serratus anterior plane block (SAPB) is a simplified and effective method for managing thoracic pain as an alternative to TPVB. However, whether SAPB can provide analgesia comparable with that provided by the TPVB approach in children undergoing the Nuss procedure is unknown.

Methods and analysis This will be a prospective, randomised, double-blind, single-centre, non-inferiority trial that will enrol children aged 7–16 years subjected to the Nuss operation for pectus excavatum. In total, 74 paediatric patients will be randomly assigned to either the SAPB or TPVB group after general anaesthesia to receive ultrasound-guided regional nerve blocks (0.25% ropivacaine 2.5 mg/kg). The primary outcome will be the assessment of postoperative pain intensity at predetermined time points. The secondary outcomes will include assessing intraoperative opioid intake, consumption of analgesics within 24 hours postoperatively, time of first use of rescue analgesics, extubation time, perioperative adverse events and plasma ropivacaine concentrations across the block groups. Demographic and clinical characteristics (eg, pectus severity and the number of bars used) of the patients will be recorded. All data will be collected by investigators who are blinded to the treatment.

Ethics and dissemination Ethical approval was obtained from the Ethics Committee on Biomedical Research of the West China Hospital of Sichuan University (2021-1275). During the period of the study, all procedures will be conducted following the principles of the Declaration of Helsinki. The results of the trial will be published in a peer-reviewed scientific journal.

Trial registration number ChiCTR2200056596.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The thoracic paravertebral nerve block is an effective regional anaesthetic technique for the Nuss procedure; however, it may not be an option for many anaesthesiologists because of potential complications, difficulty in acquisition and time consumption.
⇒ A thorough risk–benefit analysis is needed for anaesthesiologists before implementing nerve blocks to ensure their safety and necessity.

WHAT THIS STUDY ADDS

⇒ This will be a prospective, randomised, double-blind trial to compare the effectiveness and ease of use of serratus anterior plane block with thoracic paravertebral nerve block in paediatric patients undergoing Nuss surgery.
⇒ This study aims to measure and compare the local anaesthetic plasma concentrations in these two blocks, which could help develop a pharmacokinetic model after anaesthetics are injected into the serratus anterior plane, a blanked area.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings may encourage the application of the serratus anterior plane block in pectus excavatum repair surgery as a suitable approach for providing non-inferior postoperative analgesia to the thoracic paravertebral nerve block while avoiding potential hazards and enhancing recovery.
⇒ The data we will collect may help us comprehend the pharmacokinetic dynamics after ropivacaine injection in the serratus anterior plane.

INTRODUCTION

Pectus excavatum (PE) is one of the most common congenital deformities of the chest wall, with an incidence of approximately 0.1–0.25%.[1] The Nuss procedure, also known as minimally invasive repair of PE, is a typical treatment for PE correction.[2] Despite the minimally invasive Nuss technique, paediatric patients may still experience severe or extreme acute postoperative pain due to changes in thoracic morphology caused by pressure from the shaped steel bars applied to the chest wall. Substantial pain may be associated with the inhibition of deep breathing, coughing and secretion clearance, resulting in atelectasis and pneumonia.[3] Furthermore, postoperative pain is likely to evolve into chronic pain, which could negatively impact the quality of life of the paediatric population in the future.

In addition to preventing medical and surgical complications, effective postoperative pain relief helps patients regain function, increases satisfaction and accelerates recovery. For decades, traditional opioid-based analgesics have been the backbone of perioperative pain management in children owing to their valid analgesia and stable haemodynamics.[4] Nevertheless, opioid-related adverse events such as respiratory depression, nausea, vomiting and urinary retention pose novel challenges for paediatric analgesic administration.[4 5]

Various perioperative strategies have been developed and are constantly evolving for managing postoperative pain, including regional nerve block.[6] Thoracic epidural analgesia (TEA) is a traditional method for managing perioperative pain for Nuss surgery.[5] However, it requires anaesthesiologists with extensive training and experience in safe regional techniques, especially in paediatric anaesthesia,[7] and the ability to recognise and respond to high-incidence complications promptly.[8] Several peripheral nerve blocks became available with the widening application of ultrasound-guided techniques. Ultrasound-guided technique of thoracic paravertebral nerve block (TPVB) is reported as a good alternative to TEA.[9] TPVB is also reported as effective and feasible for paediatric Nuss patients.[10] TPVB is a challenging technique, demanding substantial time and presenting the possibility of numerous complications, such as haemodynamic instability and pleural injury, which limits its use in pragmatic clinical settings for children. Serratus anterior plane block (SAPB) targets lateral branches of the T2–T6 intercostal nerves, generating great interest since its first description by Blanco *et al* in 2013.[11] It is a low-risk and easy inter-fascial plane block technique, which has been reported as an effective analgesia for thoracic dermatomes in thoracotomy, a video-assisted thoracic surgery.[12] Bilateral single-injection SAPB reportedly decreased pain and opioid consumption during the early postoperative period in patients undergoing the Nuss procedure in a retrospective study.[13] However, prospective randomised controlled studies are sparse.

The systemic toxicity of local anaesthetics is strongly related to the amount absorbed into the bloodstream. A higher absorption rate of the anaesthetic solution is expected with TPVB because of the highly vascular nature of the paravertebral space.[14] The SAPB target plane for local deposition is superficial with few vessels, which is considered safer for blood absorption. With advanced surgical procedures, a thorough risk–benefit analysis is needed for anaesthesiologists before implementing nerve blocks to ensure their safety and necessity.[15]

Whether SAPB provides analgesia comparable with that of the TPVB approach remains unknown. Therefore, we will conduct this randomised, non-inferior study to compare SAPB and TPVB for pain management following the Nuss procedure in paediatric patients. As a further step, pharmacokinetic analysis of ropivacaine plasma concentrations will be conducted to measure and compare the differences in local anaesthetic absorption in these two blocks.

METHODS

Trial design and setting

This will be a prospective, randomised, double-blind, single-centre, non-inferiority, parallel-group, two-arm study with a 1:1 allocation ratio conducted at the West China Hospital, China. A flow chart of this study is shown in figure 1. The protocol was developed following the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement, as well as the schedules of patient enrolment, study interventions and outcome assessments (table 1). All the patients will receive general anaesthesia per a standard anaesthetic programme. Regional nerve blocks will be performed by an experienced anaesthesiologist. For all patients, surgery will be performed by a fixed surgical team using the same surgical technique.

Trial population and informed consent

In the ward, preoperative recruitment will occur 1 day before surgery by an independent investigator considering the inclusion/exclusion criteria. Table 2 outlines the eligibility criteria for this study. Patients and their guardians will be informed of the purpose, procedure, follow-up methods, benefits and possible risks of this study in understandable language. Informed consent will be obtained from all the participants and their guardians before recruitment. During the trial, all guardians of patients who voluntarily participated will be able to obtain all pertinent information and withdraw from the trial at any time.

Randomisation and blinding

A computer-generated number will be used to allocate patients to the SAPB or TPVB group, with a 1:1 allocation ratio. This number will be generated by an independent statistician not involved in the data analysis. The code and group allocation of each patient will be placed in an envelope and sealed. Researchers not involved in nerve block or intraoperative management during surgery

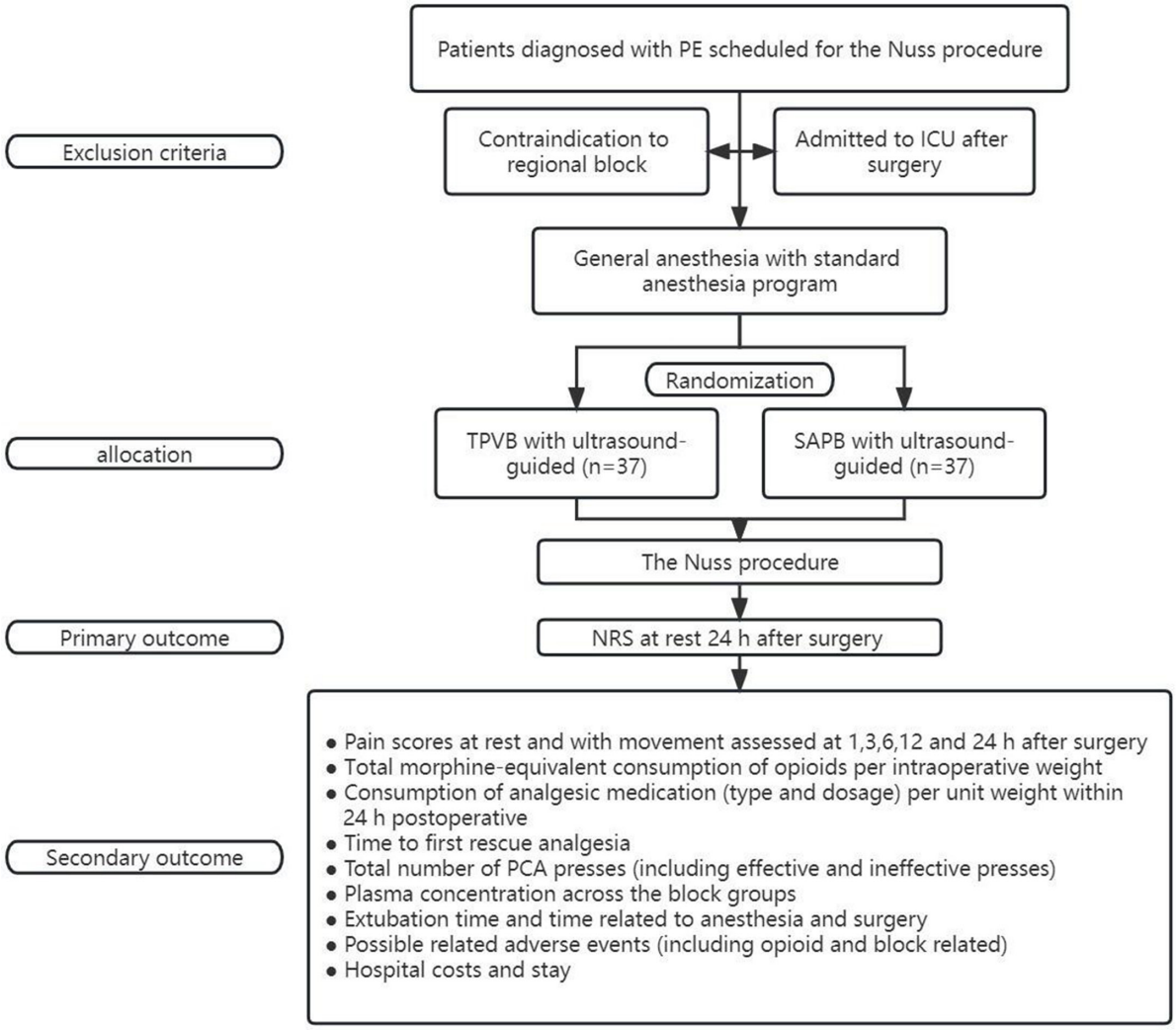

Figure 1 Trial design overview. ICU, intensive care unit; NRS, Numerical Rating Scale; PCA, patient-controlled analgesia; PE, pectus excavatum; SAPB, serratus anterior plane block; TPVB, thoracic paravertebral nerve block.

conducted the postoperative follow-up. Allocation will be blinded to the anaesthesiologists (responsible for intraoperative management/conduct follow-up), participants, surgeons and statisticians, and will be maintained until the final analyses are completed.

Interventions

After the patients arrive at the induction room, routine ECG, pulse oximetry and non-invasive blood pressure monitoring will be performed. Standard general anaesthesia will be induced in both groups with intravenous midazolam 0.05 mg/kg, sufentanil 0.3–0.5 µg/kg, propofol 2.5 mg/kg and cisatracurium 0.1–0.2 mg/kg to facilitate tracheal intubation. After intubation, all blocks will be performed by an experienced anaesthesiologist familiar with TPVB and SAPB (0.25% ropivacaine with 1:200 000 epinephrine 2.5 mg/kg in total) who did not participate in the data collection and analysis. Radial artery cannulation will be performed to facilitate the early identification and management of serious pitfalls during the Nuss procedure. Anaesthesia will be maintained with 1.5 MAC sevoflurane, to keep the bispectral index monitor at 40–60, along with a 50% air/oxygen mixture with volume control ventilation (6–8 mg/kg). The end-tidal carbon dioxide pressure will be maintained at approximately 35–45 mm Hg in both groups. Sufentanil and muscle relaxants will be administered intermittently at the discretion of the anaesthesiologists responsible for intraoperative management to maintain the haemodynamic parameters within 20% of the preoperative baseline values. The haemodynamic monitoring results will be used to adjust the fluid volume, infusion speed and transfusion. Neostigmine will be administered before extubation to reverse neuromuscular block in all patients. A patient-controlled analgesia (PCA) pump will be connected to the intravenous line 30 min before the expected end of the surgery.

Ultrasound-guided TPVB

Children in the TPVB group will be placed in the prone position. A 6–14 MHz linear transducer (M9, Mindray Bio-Medical Electronics, Shenzhen, China) will be used to laterally scan the midline to identify the spinous and transverse processes, and paravertebral space at the fifth

Table 1 Schedules of patient enrolment, study interventions and outcome assessments

Time point	Enrolment	Randomisation	Interventions	Follow-ups	
				Within 24 hours postoperatively	From 24 hours postoperatively to discharge
Eligibility criteria	•				
Informed consent	•				
Physical examination	•				
Demographic characteristics	•				
Allocation		•			
Drug administration			•		
Procedure			•		
Primary outcome assessment				•	
Secondary outcome assessment				•	•

vertebral level. Using an in-plane technique, a nerve block needle (B Braun Aesculap, Japan Co; 0.71×80 mm) will be inserted advancing from a lateral to a medial direction under ultrasound guidance following strict aseptic conditions. After perforating the costotransverse ligament, with a good view of the needle, 0.5–1 mL of normal saline will be administered to observe the anterior movement of the pleura, and then 0.25% ropivacaine with 1:200 000 epinephrine 0.5 mL/kg will be injected into the paravertebral space. The paravertebral block will be performed on the contralateral side using the same technique.

Ultrasound-guided SAPB

With the patient in the supine position and the upper arm resting slightly over the head, SAPB will be performed using the ultrasound-guided technique described by Blanco *et al*.[11] A 6–14 MHz linear probe will be scanned in the sagittal plane along the midaxillary line to check the orientation of the third and fourth ribs while locating the pleura, latissimus dorsi, serratus anterior and intercostal muscles (from superficial to the deepest). Under direct visualisation of the ultrasound probe, a nerve block needle will be inserted in the plane between the serratus anterior and latissimus dorsi muscles after preparing the block area with a 10% povidone-iodine solution. Once an adequate view of the needle is obtained, normal saline (0.5 mL) will be administered to observe plane separation by hydro-dissection, and then 0.25% ropivacaine with 1:200 000 epinephrine, 1 mL/kg in total, will be deposited bilaterally in the fascial plane.

Table 2 Inclusion and exclusion criteria of the study

Overview of eligibility criteria	
Inclusion criteria	Exclusion criteria
► Aged 7–16 years	► Withdraw informed consent
► Patients diagnosed with PE and scheduled Nuss procedure of PE	► Admitted to intensive care unit after surgery
► American Society of Anesthesiologists physical status classification I–III	► Contraindication to regional block (eg, local anaesthetic allergy, anatomical abnormalities, infection at the injection site or coagulation disorders)
► Signed informed consent form	

PE, pectus excavatum.

Ropivacaine concentration

Arterial blood samples will be obtained at 10, 30 and 60 min after the regional block. Within 1 hour of collection, the separated plasma samples will be frozen and kept at −80°C before analysis. Ropivacaine concentrations will be evaluated using liquid chromatography-tandem mass spectrometry.[16]

Postoperative period

Patients will be transferred to a post-anaesthesia care unit (PACU) for continuous monitoring of vital signs after extubation and discharged to a surgical ward after a full assessment of their conscious state and vital signs. During the first 72 hours following surgery, all patients will receive intravenous sufentanil via a PCA pump containing sufentanil 2 µg/kg and ondansetron 0.1 mg/kg diluted in 100 mL of normal saline. It will be programmed to provide a background infusion at a rate of 2 mL/hour

while providing boluses (0.5 mL) on demand. The PCA button can be repeatedly pressed with a lockout period of 15 min if the patient feels pain. A rescue analgesic will be provided via intravenous sufentanil 0.1 µg/kg in the PACU or oral ibuprofen suspension drops (10 mg/kg) in the ward if a top-up dose fails to provide adequate pain relief (Numerical Rating Scale (NRS) scores >4). The online electronic pain management database system records all rescue drugs as well as data from the PCA pumps (number pressed, time pressed, total drug and rescue drug).

Study outcomes

Main outcome

The primary objective of this study is to evaluate the analgesic effect of ultrasound-guided bilateral SAPB compared with that of TPVB in children diagnosed with PE scheduled for Nuss. The primary outcome of this study will be the pain score assessed at rest, 24 hours after surgery. Pain severity will be registered using the NRS (no pain=0, mild pain=1–3, moderate pain=4–6 and severe pain ≥7).

Secondary outcomes

This study expects to assess the following secondary outcomes:

- Pain scores at rest and with movement assessed at 1, 3, 6, 12 and 24 hours after surgery.
- Total morphine-equivalent consumption of opioids per intraoperative weight.
- Consumption of analgesic medication (type and dosage) per unit weight within 24 hours postoperatively.
- Time to first rescue analgesia.
- Total number of PCA presses (including effective and ineffective presses).
- Plasma concentration across the block groups.
- Extubation time and time related to anaesthesia and surgery.
- Possible related adverse events (including opioid and block related).
- Hospital costs and stay.

Data collection, management and monitoring

Demographic data (including age, sex, height, weight and body mass index) and clinical characteristics (including comorbidities, diagnosis (such as pectus severity and Haller Index), allergic history, baseline mean arterial pressure (MAP)/heart rate (HR) values, and the American Society of Anesthesiologists status) will be collected before the procedures. Preoperative, intraoperative (MAP/HR values, medications, adverse events, number of steel bars used, etc) and postoperative follow-up data will be recorded in order in case report forms (CRFs) devised for each patient included in the study for the proper storage of raw materials. The paper-version data will be input into the electronic case report file by two research assistants, and double entry will be conducted to ensure data accuracy. All withdrawals will be documented in the CRF. All patient information and data will be stored and coded in the archives. Study supervisors will oversee the trial conduct while performing monthly audits.

Statistical analysis

Data analysis will be completed by a researcher blinded to the randomisation using SPSS software (V.23.0, IBM SPSS). Data from the included patients will be used in the statistical analysis; missing data will not be imputed. Normally distributed variables will be expressed as mean (SD), and non-normally distributed variables will be expressed as median and IQR. Categorical variables will be reported as numbers and/or percentages of the total. Student's t-test (normally distributed variables) or Mann-Whitney U test (non-normally distributed data) and cross-tabulation or the Pearson $\chi 2$ test (categorical variables) will be used when appropriate. Repeated-measures analysis of variance will be used to assess the pain score of the primary outcome between the two groups. Secondary outcomes will be analysed per the data type, as appropriate. We will consider performing a predefined subgroup analysis on primary endpoints according to age, pectus severity (Haller Index) and the number of steel bars used during the surgical procedure, if necessary. Differences between the two groups will be considered statistically significant at $p<0.05$. Interim analyses will not be performed. Any changes to the statistical analysis plan will be described in a subsequent publication.

Sample size calculation

This is a non-inferiority study protocol, and the NRS 24 hours after surgery at rest will be regarded as the main outcome to calculate the sample size using PASS software V.15.0.5. Considering our previous study and preliminary experimental data, we found that the average pain score at 24 hours after TPVB was 2.58, with an SD of 0.92.[10] Assuming SAPB decreases the NRS by an SD of 0.45, and the non-inferiority margin is set at 0.5, 70 participants (N1=N2=35) will be recruited to achieve an alpha (one-side) 0.025 and 90% power. With a dropout rate of 5%, the final predicted sample size is 74 (N1=N2=37).

Safety considerations

Nerve blocks are administered in the operating room under close monitoring of vital signs, allowing for early detection and treatment of adverse events. Ropivacaine administration will be immediately discontinued if adverse events occur. Any unexpected adverse events that occur during the trial will be immediately reported to the principal investigator or, if necessary, to the hospital patient safety board.

Trial status

The trial is ongoing. The recruitment process began in December 2021, and 30 patients are enrolled. The results of this trial have been publicly disclosed and submitted for publication in a peer-reviewed scientific journal.

CONCLUSION

SAPB has gradually become accepted in clinical practice owing to its simplified application acquisition and use, low risk of pneumothorax and local anaesthetic toxicity.[17] Thus, this study is designed to investigate whether the simple-to-use SAPB could be an appropriate alternative to TPVB, especially in the setting of multimodal therapy for the Nuss procedure in paediatric patients. Our findings may encourage the application of SAPB in PE repair surgery as a suitable approach for providing non-inferior postoperative analgesia to TPVB while avoiding potential hazards and enhancing recovery.

Contributors YH and BD conceived the idea for this trial. All the authors (YH, ZL, MX, BD and XJ) participated in the trial design. The manuscript was drafted by YH and revised by BD. ZL, MX and XJ coordinated the trial, data collection and analysis. All the authors contributed to the research and agreed to be responsible for all aspects of this study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University (2021-1275). All procedures will be conducted following the principles of the Declaration of Helsinki (Fortaleza, 2013). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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