Effects of paravertebral block on postoperative analgesia in children undergoing lateral incision cardiac surgery with cardiopulmonary bypass: a randomized controlled trial

Research Plan

Project source: The Top-level Hospital Clinical Research Project by Chinese Academy of Medical Sciences (2023-GSP-QN-7)

Principal Investigator: Guo Jingfei

Sponsor (if applicable): Not involved

Statistical unit (if applicable): Not involved

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Abstract

Research Name	Effects of paravertebral block on postoperative analgesia in children undergoing lateral incision cardiac surgery with cardiopulmonary bypass: a randomized controlled trial (PVB research)
Research Goal	This study aims to determine whether postoperative PVB has better postoperative analgesic effect, lower complication rate and quicker recovery process compared to local infiltration anesthesia for children undergoing side-incision cardiac surgery with cardiopulmonary bypass.
Research Design	Single-center, randomized, controlled, double-blinded
Study population	Children aged 6-14 years who undergo side-incision atrial septal defect repair and/or ventricular septal defect repair surgery with cardiopulmonary bypass
Study intervention	After surgery, patients in the experimental group undergo paravertebral block using drug A, and local infiltration anesthesia using drug B. For the experimental group, drug A is 3mg/kg of 0.375% ropivacaine and drug B is normal saline solution of the same volume. After surgery, patients in the control group undergo paravertebral block using drug A, and local infiltration anesthesia using drug B. For the control group, drug B is 3mg/kg of 0.375% ropivacaine, and drug A is normal saline solution of the same volume.
Inclusion criteria	(1) Children aged 6-14 years old; (2) Children who have atrial septal defect or ventricular septal defect scheduled for lateral incision cardiac surgery with cardiopulmonary bypass; (3) Inform consent signed by the parent or legal guardian.
Exclusion criteria	(1) Patients who were intubated, on mechanical circulatory support, or with intravenous inotropes before surgery; (2) Emergency surgery or redo cardiac surgery; (3) Body weight more than 50 kg; (4) Diagnosed as severe pulmonary hypertension; (5) Left ventricular ejection fraction less than 45% in most recent echocardiography before surgery; (6) Allergic to ropivacaine or other regular anesthetics, analgesics or other medications regularly used in the study; (7) Preoperative platelet counts less than 100*109/L, coagulopathy

	or bleeding tendency ; (8) Preoperatively using antiplatelets or anticoagulants; (9) Diagnosed with scoliosis or other contraindications for PVB.
Primary outcome	Total opioid consumption within 24 hours after surgery (ug/kg)
Secondary outcome	(1) FPS-R scores at 6 hours, 12 hours, 18 hours, and 24 hours after surgery (2) The rate of opioid treatment for remedial analgesia between groups. (3) The first time of FPS-R≥4 postoperatively. (recorded by bedside nurse) (4) Length of postoperative mechanical ventilation, length of ICU stay and hospital stay. (5) The rate of postoperative nausea and vomiting (PONV) 24 hours after surgery (6) The incidence of respiratory depression in the two groups
Study period	2024.3.11-2024.12.31
Sample size	100（50 cases each for experimental group and control group）

1. Research Background

   Postoperative pain after cardiac surgery is severe, and adequate postoperative analgesia is crucial for quick recovery for cardiac surgery patients. The traditional postoperative analgesia model for cardiac surgery is mainly based on opioids. However, the use of large doses of opioids can lead to delayed postoperative recovery. In recent years, the promotion and application of accelerated recovery surgery theory have led to an overall improvement in medical quality (1, 2). The theory of Enhanced Recovery After Surgery emphasizes postoperative multimodal analgesia to reduce opioid use. Postoperative intravenous analgesia combined with regional anesthesia is one of them, such as combined epidural anesthesia, spinal anesthesia, sacral anesthesia, thoracic paravertebral nerve block (PVB), etc.

   However, there are risks associated with epidural anesthesia, spinal anesthesia, or sacral analgesia after cardiac surgery. Cardiac surgery requires systemic blood heparinization, which despite neutralization with protamine, can leave patients more susceptible to serious complications such as epidural hematoma than with other types of surgery. Therefore, new regional blocks such as PVB have gradually emerged in recent years. Compared with epidural block, PVB is easier to operate and can avoid complications

such as epidural abscess, hematoma, general spinal anesthesia, spinal cord, or spinal nerve injury.

An RCT of patients undergoing central sternotomy for cardiac surgery showed that patients who underwent bilateral PVB had the same postoperative pain scores, shorter postoperative ICU length of stay, less nausea and vomiting, and less urinary retention compared to those who underwent epidural blockade (3). Another RCT showed that during side-incision cardiac surgery, patients who underwent unilateral PVB had no significant difference in postoperative pain scores and had lower rates of nerve block failure and nausea compared with patients who underwent epidural blockade. The incidence of complications such as vomiting, urinary retention, and hypotension is also lower (4). However, there are currently no RCT studies in side-incision cardiac surgery comparing postoperative paravertebral blockade with intravenous analgesia alone/incisional local anesthetic infiltration. In thoracic surgery, similar studies have been conducted with positive results (5, 6). An RCT study of PVB for lung surgery showed (6) that compared with simple intravenous analgesia, the PVB group had lower postoperative pain scores and less morphine consumption; while local infiltration analgesia had no significant difference compared with intravenous analgesia alone (5). At present, the number of minimally invasive cardiac surgeries with side incisions is gradually increasing. In order to cooperate with the development of surgery and enhanced recovery process , it is crucial to develop postoperative PVB analgesia technology. This study aims to determine whether postoperative PVB has better postoperative analgesic effect, lower complication rate and faster recovery process compared with simple local infiltration anesthesia for children undergoing side-incision cardiac surgery with cardiopulmonary bypass.

2. Research purpose

This study aims to determine whether postoperative PVB has better postoperative analgesic effect, lower complication rate and faster recovery process compared with simple local infiltration anesthesia for children undergoing side-incision cardiopulmonary bypass cardiac surgery.

3. Research Method

3.1 Overview of experimental design

This study is a single-center, randomized, double-blind trial that aims to determine whether post-operative PVB provides better postoperative analgesia, lower incidence of complications, and faster recovery process compared with simple local infiltration anesthesia for children undergoing side-incision cardiac surgery with cardiopulmonary bypass. This trial will be registered on ClinicalTrials.gov before starting. A detailed statistical analysis plan will be developed before starting data analysis. Results reporting

will strictly follow CONSORT guidelines.

3.2 Subject selection

3.2.1 Inclusion criteria

(1) Children aged 6-14 years old;

(2) Children who have atrial septal defect or ventricular septal defect scheduled for lateral incision cardiac surgery with cardiopulmonary bypass;

(3) Inform consent signed by the parent or legal guardian.

3.2.2 Exclusion criteria

(1) Patients who were intubated, on mechanical circulatory support, or with intravenous inotropes before surgery;

(2) Emergency surgery or redo cardiac surgery;

(3) Body weight more than 50 kg;

(4) Diagnosed as severe pulmonary hypertension;

(5) Left ventricular ejection fraction less than 45% in most recent echocardiography before surgery;

(6) Allergic to ropivacaine or other regular anesthetics, analgesics or other medications regularly used in the study;

(7) Preoperative platelet counts less than 100*109/L, coagulopathy or bleeding tendency ;

(8) Preoperatively using antiplatelets or anticoagulants;

(9) Diagnosed with scoliosis or other contraindications for PVB.

3.2.3 Subject withdrawal criteria and procedures

The researcher may ask the subject to withdraw from the trial at any time during the research process. At the same time, the subject may also spontaneously request to withdraw from the trial at any time. The reasons for withdrawal include but are not limited to: 1) the subject revokes informed consent; 2) the subject is lost to follow-up; 3) the researcher fully assesses the subject from a safety perspective and deems the subject not suitable to continue the trial.

Withdrawal of informed consent means that after obtaining relevant information about the subject's trial, the subject refuses to have further contact with the researcher or his authorized person. The subject should try to inform the researcher in writing that he or she is withdrawing his or her consent for future follow-up. In case of informed consent, the researcher should specify the specific reasons for the subject's withdrawal of informed consent in the case report form (CRF). Subjects may withdraw from the trial at any time at their own request, or may be asked to withdraw from the trial at any time by the investigator, the Data Safety Monitoring Board or the Clinical Events Committee for safety or behavioral reasons, or if the subject is unable to comply with specific trial procedures. In this case, subjects should be encouraged to stay in contact with the investigators and continue to be followed up by telephone and other means during the

remainder of the trial to better assess the safety indicators of the trial. If a subject withdraws from the trial and withdraws informed consent for future disclosures, no further assessments should be conducted and additional data should not be collected, but the investigator may retain and continue to use any data collected before the withdrawal of informed consent.

Loss to follow-up refers to the inability to contact the subject at the end of the trial. No subject should be considered lost to follow-up until the trial is completed. If the subject does not see the doctor as planned, every effort should be made to contact the subject, which can be by phone, email, text message, social media, or if necessary, by letter and/or registered call if necessary. If the subject has died, the date and cause of death should be obtained. If follow-up of this information is not possible, the last known date of survival determined should be reported and recorded on the subject's CRF form.

3.3 Intervention or product introduction

Patients in the experimental group received paravertebral block with 3 mg/kg of 0.375% ropivacaine. Paravertebral block is a commonly used regional block technology. Compared with traditional epidural anesthesia, it has the advantages of relatively stable circulation, lower requirements for coagulation function, and lower complication rate. Paravertebral block can be used for all surgeries from the chest to the pubic symphysis. This study used the thoracic paravertebral block. Specific implementation methods of paravertebral block include blind exploration method, nerve stimulator guidance method, ultrasound guidance method, etc. This study adopts ultrasound-guided paravertebral block technology, which enables accurate positioning and reduce the occurrence of complications such as anesthetic injection into blood vessels and pneumothorax.

3.4 Research process

3.4.1 Research flow chart

3.4.2 Research implementation (method, content, steps, etc.)

1) Before surgery:

The investigator will conduct a pre-screening process to assess whether potential subjects are suitable for inclusion in this study. After pre-screening, the investigator will conduct a screening process to assess whether the subjects meet the inclusion criteria. Before the process of screening subjects, researchers need to obtain informed consent. Our assessment mainly collects the following information:

A. Informed consent: When contacting the subject for the first time, the researcher should explain the entire process of the trial to the subject or their legal representative and obtain their informed consent;

B. Demographic information: gender, date of birth, race, height and weight;

C. Medical history: Medical history relevant to this study, including primary diagnosis, NYHA classification, diabetes, hypertension, hyperlipidemia, infective endocarditis,

COPD, peripheral vascular disease, cerebrovascular disease, previous cardiac surgery history, smoking history, allergy history and current medications (beta blockers, ACE inhibitors, ARBs, statins, diuretics);

D. Basic vital signs: body temperature, heart rate, blood pressure, oxygen saturation

E. Related examinations: echocardiography, routine blood tests, liver and kidney function tests, and coagulation function tests

2) Intraoperative:

Implementation of intervention: After the operation, patients in the experimental group and the control group were treated with drug A for paravertebral block, and drug B for local infiltration block through the incision. Paravertebral block is performed under ultrasound guidance, and right T4 paravertebral nerve block is performed. It is recommended to use the needle insertion method in the sagittal plane. Use 0.375% ropivacaine at a dosage of 3 mg/kg. The rest of the intraoperative anesthesia protocol is the same as the clinical routine.

Intraoperative anesthesia management: Give anesthetic drugs and perform intraoperative management according to the routine of the anesthesia center.

Intraoperative record information: basic intraoperative information such as type of operation, operation time, etc.

3) After surgery:

Routine postoperative analgesia plan: Children are not routinely given analgesic pumps and other analgesic measures after surgery. The ICU bedside nurse observes the patient's pain condition at any time. When the patient shows any signs of discomfort or pain (such as crying, painful expression, body twisting, etc.), the ICU bedside nurse conducts a FPS-R pain score on the child. If the FPS-R score is ⩾4, sufentanil 0.05 μg/kg/h will be continuously pumped intravenously. If 0 < FPS-R score < 4, than Non-opioid analgesics will be given.

Postoperative follow-up information: record the total amount of opioids taken by the patient within 24 hours after surgery; FPS-R scores at 6 hours, 12 hours, 18 hours, and 24 hours after surgery; the time when the first FPS-R ⩾ 4 points after surgery; incidence of nausea and vomiting 24 hours after surgery, the incidence of serious complications such as respiratory depression, postoperative mechanical ventilation time, ICU stay time, postoperative hospital stay.

3.5 Criteria for suspension/termination of studies

The researcher has the right to suspend/terminate this study at any time during the trial. The reasons for suspension/termination include but are not limited to, 1) The incidence and severity of adverse events reported in this study or other similar studies indicate that continuing this trial will be harmful to the subjects. The subjects pose potential health threats; 2) The subjects are not satisfied with the enrollment.

The researcher has the right to replace any research center at any time during the trial.

The reasons for suspending/terminating the research center's continued participation in this study include, but are not limited to, 1) extremely slow recruitment of subjects and insufficient recruitment; 2) poor trial compliance; 3) inaccurate or incomplete data recording; 4) non-compliance with the GCP guidelines of the International Conference on Harmonization (ICH).

3.6 Endpoint evaluation

3.6.1 Effectiveness evaluation

1) Primary endpoint: total opioid consumption within 24 hours after surgery (ug/kg)

2) Secondary endpoints: other postoperative analgesic indicators.

A. FPS-R scores at 6 hours, 12 hours, 18 hours, and 24 hours after surgery. (See attachment 1)

B. Rates of postoperative opioid rescue analgesia use in both groups.

C. Time to first postoperative FPS-R ⩾ 4 points (recorded by bedside nurse)

D. Postoperative mechanical ventilation time, ICU stay time, and postoperative hospitalization time

3.6.2 Safety evaluation

The incidence of vomiting in two groups of children within 24 hours after surgery

The incidence of serious complications including respiratory depression in the two groups of children

3.7 Randomization method and blinding method

3.7.1 Blinding

For children who signed informed consent and screened into the group, their baseline information is recorded, and randomization is conducted after entering the operating room. The children are randomly grouped using the block randomization method. After the random numbers are generated by the computer, all the random numbers are coded and sealed into opaque envelopes. The code, that is, the selection number, was written on the outside of the envelope, and the random number was placed inside the envelope. The children were randomly divided into the experimental group (PVB group) and the control group (local infiltration group). This study is blinded to the intraoperative anesthesiologists, patients, data collectors and analysts, and study result evaluators. Before surgery, a pharmacist who is not involved in the follow-up process opens the envelope and prepares medications based on the grouping results. The pharmacist prepares two medications, A and B for each patient. Drug A for patients in the test group is 3 mg/kg of 0.375% ropivacaine, while for patients in the control group, drug A is the same volume of normal saline. Drug B for patients in the control group is 0.375% ropivacaine at 3 mg/kg, and drug B for patients in the test group is the same volume of normal saline. The anesthesiologists all use drug A to perform paravertebral block on the patients, and drug B to perform local infiltration on the patients. The intraoperative anesthesia management plans of the two groups of patients are exactly

the same, so they are blinded. All patients undergo paravertebral block and local infiltration twice, so they are blinded. The anesthesiologists who collect intraoperative and postoperative data do not know the patient grouping information, so they are blinded. The ICU nurse who evaluates the patient's postoperative pain and adds analgesics does not know the patient's group information and is therefore blinded. Principle of unblinding: If a subject has an adverse event that is suspected to be related to the trial operation and cannot be alleviated by standard clinical treatment methods, for the safety of the subject, emergency unblinding should be carried out. Before the trial begins, each research center will be educated and instructed on the blinding process. If unblinding is necessary, the principal investigator needs to contact the drug dispenser to obtain the trial drug distribution information of the subject, and this unblinding process can only occur when the safety of the subject is threatened. If feasible, before unblinding, it is best for the principal investigator to communicate with members of the trial team to reconfirm the need for urgent unblinding. Once emergency unblinding is carried out, the reason for unblinding must be recorded in detail in the CRF, and the subject is no longer given the trial drug, but the subject can remain in the trial cohort until follow-up is completed.

3.7.2 Randomization method

This study is blinded to the anesthesiologists who performed intraoperative management, patients, and postoperative evaluators. The intraoperative anesthesia management plans of the two groups of patients are exactly the same: drug A is used for paravertebral block and drug B is used for local infiltration anesthesia of the surgical incision. Patients and their families are blinded (both the experimental group and the control group received paravertebral block of the back and local infiltration anesthesia of the wound so that family members and other clinicians ostensibly would not know about the children's grouping). The evaluators are blinded (the person conducting the postoperative pain score does not know the children's grouping and the third-party independent evaluation including the central laboratory does not know the children's grouping either).

4. Statistical considerations

4.1 Sample size estimation

Sample size calculation is based on the primary outcome, total opioid consumption within 24 hours after surgery. Referring to the preliminary test results, the average total opioid consumption within 24 hours after surgery in the traditional low-dose opioid anesthesia group was 850± 180 μg/kg MSE. According to previously published literature (12，13) and the experience of clinical experts, it is assumed that in the PVB group, total opioid consumption within 24 hours after surgery was reduced by an average of 30%，255 μg/kg MSE. At the same time, the combined standard deviation was conservatively estimated to be 425 μg/kg MSE. When the significance level of the

statistical test was taken to be one-sided 0.025, the power level was taken to be 80%. hour. According to statistical principles, 45 children need to be enrolled in each group, and the total number of cases in the two groups is 90. Sample size calculation was performed using the PASS software. Taking into account the maximum possible dropout rate of 10% in the study, this trial will eventually enroll 100 children, 50 children in each group.

4.2 Statistical Analysis Plan

This trial will be analyzed according to the intention-to-treat principle, and any subject who completes randomization will be followed up until the end of the trial (unless the subject withdraws informed consent). This study uses SPSS data analysis software for analysis. Quantitative data will be expressed as mean ± standard deviation or median (interquartile range) depending on whether it conforms to the normal distribution; enumeration data will be expressed as frequency (percentage). Group patients according to intervention measures, compare differences between groups and express them as absolute standard deviations. Comparisons between groups are performed using the two independent sample t-tests for normally distributed measurement data, comparisons between groups are performed using the rank sum test for skewed measurement data, and comparisons between groups are performed using the $\chi 2$ test for enumeration data. All tests are two-sided, and $P<0.05$ means the difference is statistically significant.

5. Data management

5.1 Data collection and CRFs

The data collection of this study is based on paper CRF forms, and all data and its collection process will be completed under the supervision of the trial management center. After the trial is completed, all data and CRF forms will be provided to the principal investigator for long-term storage.

5.2 Saving of test files

The trial documents will be archived securely and confidentially so that they can be reviewed for compliance at any time. The relevant medical documents of the subjects will also be archived in accordance with regulations and saved for the maximum period allowed by the medical institution. If the archive changes, the researcher and the study center need to report to the ethics committee and shall not destroy trial-related documents without the approval of the ethics committee.

5.3 Data quality

The ethics committee and clinical trial institutions will regularly monitor the quality of the data, and the researchers will allow the monitors to obtain any trial-related data at any time.

6. Confidentiality principle

This study will take the following measures to strictly protect the privacy and personal

information of each subject: (1) Confidentiality measures and information security systems for sample providers have been established; (2) Samples and data are stored securely, and all samples and data in the library are /or set access rights for data; (3) When samples or prepared research samples are transferred to other researchers or institutions, all collected samples shall be de-identified (coding management and deletion of all identification information); (4) Data resulting from the research may be published or published publicly, but name or personally identifiable information will not be released.

7. Quality control of research

7.1 Data Security Monitoring Board

The independent Data Safety Monitoring Board (DSMB) will monitor the entire process of this trial. All serious adverse events must be reported to DSMB. If serious clinical safety risks arise, DSMB will give specific opinions to the principal investigator and clinical trial institution. Including 1) continue the trial; 2) continue the trial after adjustment; 3) terminate the trial.

7.2 Researchers and training

Before the trial begins, researchers who can maximize the safety and compliance of the subjects will be selected based on their abilities and experience. In addition, only trained researchers who are familiar with the protocol can participate in this study, and training records will be stored in files.

7.3 Research monitoring

After the study begins, regular monitoring will be conducted to evaluate the progress of the study, adequacy of records, and compliance with the study protocol, and corresponding monitoring records will be provided to the investigators. In addition to regular on-site monitoring, remote monitoring will also be conducted to ensure timely submission of data. Monitors will maintain ongoing communication with researchers through written correspondence, telephone calls, or online conversations.

8. Ethical principles

8.1 Ethical approval

Research can only be implemented after approval by the Ethics Committee. During the research process, the research plan and operating procedures must be strictly followed. At the same time, modifications to the research plan and informed consent must be reviewed and approved by the Ethics Committee before execution.

8.2 Informed consent

Before each research subject is selected for this study, the researcher must provide him or his legal representative with a complete, comprehensive, easy-to-understand content and explanation of the informed consent form approved by the ethics committee in writing, and give it to the research subject or their legal representatives who will be given sufficient time to consider whether to participate in this study. The

research can only be entered after the research subjects or their legal representatives sign the informed consent form. During the study, if new safety information causes significant changes in the risk/benefit evaluation, all updated new information should be provided to the subjects or their guardians and a new informed consent form should be signed.

8.3 Risk-benefit analysis

This study will not bring risks to subjects beyond routine diagnosis and treatment. Most of the clinical outcomes in this study are determined based on questionnaires and routine clinical examination results, and only a small amount of additional blood is drawn from the subjects for the detection of inflammation and pain-related factors. Participants will not receive direct benefit from participating in this study, but if participants are assigned to the intervention group, the intervention may reduce the occurrence of postoperative pain, but it may also have no effect. At the same time, the follow-up personnel during the follow-up period will provide you with treatment and healthcare-related suggestions based on the subject's condition. Subject participation may help us identify safer or more effective diagnosis and treatment methods and expand new scientific knowledge.

8.4 Conflict of interest

not involving

8.5 Subject protection measures

Participants are not required to pay any research-related costs for participating in the study. Subjects' de-identified information and de-identified biological samples may be used to create products or provide health-promoting services. If these situations occur, we will not inform the subjects, pay the subjects, or provide any compensation to the subjects or their families. Most uses of biological samples and biological information do not result in a commercial product or benefit to anyone. No remuneration or compensation will be provided to the subjects in this study.

When the subject's health condition is harmed while participating in this study, the researchers are informed, and we will take necessary measures in a timely manner and determine compensation or compensation liability in accordance with the relevant laws and regulations of our country.

9. Pre-assessment of project risks and risk treatment plan

Investigator reports SAE to the ethics committee

If an SAE occurs during the study, the investigator should immediately report all serious adverse events to the sponsor in writing (within 24 hours after the investigator learns of the event), and then provide a detailed and written follow-up report in a timely manner. At the same time, researchers must fill in the "Serious Adverse Event Report Form" to record the time of SAE occurrence, symptom description, severity, duration, measures taken, outcomes, basis for correlation assessment, and possible explanations for SAE,

etc. If the researcher is unable to learn of a serious adverse event in time (for example, the subject was first treated in another hospital), he or she should report and record the time when the serious adverse event was first learned within 24 hours after becoming informed.

Typically, this information should include a detailed description of the serious adverse event to allow for a complete medical evaluation of the event and an initial independent determination of the possible cause. In addition, information must be provided on other possible causes, such as concomitant medications and concomitant diseases. In the event of death of a subject, the autopsy report must be submitted as soon as possible if available.

Researchers report SUSAR to ethics committee

Researchers should promptly sign and read the relevant safety information of clinical trials such as Suspicious and Unexpected Serious Adverse Reactions (SUSAR) provided by the sponsor, consider the subject's treatment, whether to make corresponding adjustments, and communicate with the subject as soon as possible if necessary , and the SUSAR provided by the sponsor should be reported to the ethics committee.

9.1 Adverse events (AEs)

All AEs need to be reported regardless of whether they occur related to trial procedures or drugs. At the same time, researchers need to follow up closely to determine whether they are related to trial procedures or drugs, patients‘ clinical outcomes, and whether they can be upgraded to serious adverse events (SAEs). This follow-up process needs to continue until the AEs and their related symptoms are reasonably controlled to a stable level.

9.2 Adverse event reporting interval

For SAEs, if they occur within 90 days from the time the subject signs informed consent to the trial operation intervention, they must be reported to the clinical trial institution; if they are not within this interval, but the researcher determines that its occurrence may be related to trials, it also needs to be reported to clinical trial institutions. At the same time, both AEs and SAEs need to be recorded in detail in the CRF.

9.3 Definition of SAEs

SAEs are defined as adverse events with unexpected clinical outcomes during clinical trials, including death, serious life-threatening events, need for readmission, prolonged hospitalization, permanent disability or disability, and teratogenic mutations.

SAEs in this trial included IABP, ECMO, reintubation, tracheotomy, severe respiratory depression, reoperation, perioperative myocardial injury, and stroke.

9.4 Definition of AEs

AEs are unanticipated clinical events that occur in subjects using an investigational drug or device during a clinical trial, and the event does not need to be related to the intervention.

9.5 Severity and relevance assessment

This study will use mild, moderate, and severe to classify the severity of AEs. Mild means that the AEs do not affect the subjects' daily life, moderate means that the AEs affect the subjects' daily lives to a certain extent, and severe means that the AEs significantly affect the subjects' daily lives. In addition, the correlation between AEs and the intervention is assessed and recorded in CRFs.

9.6 Reporting Adverse Events

All SAEs and serious AEs need to be reported to the clinical trial institution within 24 days of occurrence. Non-serious AEs need to be recorded in detail in CRFs.

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Informed Consent

We invite your child to participate in a study initiated/funded by Fuwai Hospital, Chinese Academy of Medical Sciences on " Effects of paravertebral block on postoperative analgesia in children undergoing lateral incision cardiac surgery with cardiopulmonary bypass: a randomized controlled trial". This study has been approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (tel: 010-88396281, 010-88396282). Please read the instructions carefully to understand your rights and obligations in the research, and to understand the nature and risks of the research. Participation in this study is completely voluntary, and whether you participate in this study or not will not affect your treatment and other legitimate rights and interests during your stay in the hospital. While the researcher explains and discusses the informed consent form with you, you can always ask questions and have the researcher explain anything you don't understand. You have plenty of time to discuss your decision with family, friends, and your doctor.

If your child is currently participating in another clinical study, please inform the researchers.

The project leader of this study is Guo Jingfei, attending physician of anesthesiology. The source of funding for this project is: clinical research funding for the top-level medical centers.

1. Why is this study conducted?

Postoperative analgesia regimen after cardiac surgery is critical to a patient's rapid recovery. Traditional opioid-based postoperative analgesia may lead to increased postoperative complications and prolonged recovery time. Currently, multimodal analgesia is advocated for postoperative analgesia, and nerve block, including paravertebral block, is an important part of multimodal analgesia after cardiac surgery. Currently, for lateral-incision cardiac surgery with cardiopulmonary bypass, there are no randomized controlled studies to clarify the postoperative analgesic effect, safety, and impact of paravertebral block on rapid postoperative recovery. This double-blinded randomized controlled trial aims to study whether pediatric patients who underwent paravertebral block have less postoperative pain, fewer complications and faster recovery process compared to patients who underwent local infiltration anesthesia.

2. Why are your children invited to participate in this study?

The inclusion and exclusion criteria for this study are:

Inclusion Criteria:

(1) Children aged 6-14 years old;

(2) Children who have atrial septal defect or ventricular septal defect scheduled for lateral incision cardiac surgery with cardiopulmonary bypass;

(3) Inform consent signed by the parent or legal guardian.

Exclusion Criteria

(1) Patients who were intubated, on mechanical circulatory support, or with intravenous inotropes before surgery;

(2) Emergency surgery or redo cardiac surgery;

(3) Body weight more than 50 kg;
(4) Diagnosed as severe pulmonary hypertension;
(5) Left ventricular ejection fraction less than 45% in most recent echocardiography before surgery;
(6) Allergic to ropivacaine or other regular anesthetics, analgesics or other medications regularly used in the study;
(7) Preoperative platelet counts less than 100*109/L, coagulopathy or bleeding tendency ;
(8) Preoperatively using antiplatelets or anticoagulants;
(9) Diagnosed with scoliosis or other contraindications for PVB.

3. The process and methods of this research

The intervention of this study is paravertebral block, a commonly used perioperative analgesia method that is quite safe when administered under ultrasound guidance.

This study is a randomized controlled clinical trial. After you agree that your child will participate in this study, your child will be randomly assigned to the intervention group or the control group. The probability of entering the two groups is equal. The intervention we take in the two groups are: patients in the experimental group will have paravertebral block using 3 mg/kg of 0.375% ropivacaine after the operation, and patients in the control group will have paravertebral block using the same volume of normal saline to simulate the experimental group after the operation. Patients in the control group will be treated with 3 mg/kg of 0.375% ropivacaine for local infiltration anesthesia after the operation, and patients in the experimental group will be treated with the same volume of normal saline to simulate the control group after the operation.

Throughout the study, your child's demographics, medical history, basic vital signs, test results, information about adverse events, pain scores and opioid dosage, the length of postoperative ICU stay and hospital stay will be recorded. We also need to collect blood samples from your child at certain time points for testing of relevant indicators.

4. Duration of the study and number of participants

This study is a single-center clinical study and plans to recruit 100 research participants at Fuwai Hospital, Chinese Academy of Medical Sciences. The planned duration of this study is from March 2024 to December 2024, and your child is expected to participate until discharge.

5. What do you need to do to participate in this study?

Before enrolling in the study, the doctors will ask and record your child's medical history, comorbid diseases and treatment, and conduct physical examination to determine whether your child meets the research criteria. Then the researchers will obtain your informed consent and sign an informed consent form. Once your child is included in the study, he/she will undergo preoperative, intraoperative and postoperative interventions guided by researchers and doctors. At the same time, you need to provide complete medical history information so that our team members can fully judge your risk and benefits at any time during the study, and decide whether your child should continue participating in the study.

We will record the dosage of analgesic drugs within 24 hours after the operation, and visit your child at 6 hours, 12 hours, 18 hours, and 24 hours after the operation to record pain and complications during the postoperative period. This would require the child's cooperation. We will draw a small amount of blood samples for testing at three time points: before the operation, 6 hours after the operation, and 24 hours after the operation (the total volume of blood collected shall not exceed 20ml), and your child's cooperation is required.

6. What are the risks and adverse events for study participants in this study?

Some side effects may occur during the trial. Complications of paravertebral nerve block are not common, especially when conducted under the guidance of ultrasound. Most complications are transient and do not cause serious damage. However, as a nerve block method, it does have certain risks, such as puncture-caused nerve injury, hypotension after the nerve block, localized hematoma, infection, etc.

7. Are there any direct benefits from participating in this study?

Your child may not benefit directly from participating in this study. Your child's participation may lead to improvements in medical care, the development of safer or more effective treatments, and new scientific knowledge.

8. If I do not participate in this study, are there any other treatment options?

You can choose not to participate in this study, which will not affect your child's regular treatment. At present, the conventional treatment method for postoperative pain after cardiac surgery is intravenous analgesia based on opioids.

9. Fees and compensation for participating in this study

There are no study-related costs for your participation in the study. Your child's de-identified information and de-identified biological samples may be used to create products or provide health promotion services. If these situations occur, we will not tell you, pay you, or provide you or your family with any compensation. Most uses of biological samples and biological information do not result in a commercial product or benefit to anyone.

You will not be paid or compensated for this study.

10. Handling of research-related damages

When your child's health condition suffers research-related damage while participating in this study, please inform the researcher (Dr. Guo Jingfei, contact number: 15810396387). We will take necessary medical measures promptly and compensate you and your child in accordance with the relevant laws and regulations of our country.

11. Will my information be kept confidential?

If you decide to have your child take part in this study, your participation in the study and your child's personal information in the study will be kept confidential. When using research data in this study, your child's personal information will be kept confidential and all information will be kept secure and used only for this study. Information in the research

database and samples will be strictly desensitized to remove personally identifiable characteristics, and information that may identify your child will not be disclosed to anyone other than the researchers without your permission.

In order to ensure that the research is conducted in accordance with regulations, inspectors from the ethics committee, drug regulatory authorities, and health authorities may access the original medical records of research participants to verify the process of clinical research without violating the principle of confidentiality and relevant regulations.

If the research results are published publicly, your child's personal information will not appear in any public medical records or publications, and we will not disclose this information to anyone or any institution.

12. What rights do research participants have?

Participation in this study is voluntary and you are free to decide whether to participate in this study. Regardless of whether you agree to participate in this study, it will not affect the routine clinical diagnosis and treatment you should receive during your hospital stay.

You may refuse to participate at any time or have the right to withdraw from the study at any stage during the study without any reason, and you will not be subject to discrimination or unequal treatment. Medical treatment and rights will not be affected.

If you want to withdraw from the research project during your participation, please notify the researcher, complete relevant pre-exit checks as required by the researcher, and complete the relevant withdrawal procedures as required. After withdrawal, the researcher will no longer continue to collect and use your children's experimental data, but the anonymized data collected before you exit will not be deleted or withdrawn. After you withdraw, your child may choose opioid analgesic treatment. If we discover new information related to your child's health and rights after you withdraw, we may contact you again.

If you want to participate in this study, you need to read this informed consent form carefully and sign it after confirming that you fully understand the relevant issues. You will not lose any legal rights granted to you by law after signing this document.

During the research process, you have the right to obtain new information about this research, and you also have the right to obtain the informed consent form and re-sign the new version of the informed consent form.

If you agree to sign this document, our hospital will obtain your biological samples and research data free of charge. Our researchers and the joint research institutions participating in this study can use your biological samples and research data for the purpose of this research.

13. Circumstances and reasons under which research participants may be terminated

If your child has the following circumstances during the study, the researcher will ask your child to withdraw from this study:

(1) After randomization, serious violations of the inclusion criteria or exclusion criteria are found, affecting the evaluation of intervention efficacy;

(2) Serious complications or special physiological change occurs, and it is not suitable to continue the trial;

(3) If allergic reactions or serious adverse events occur, the trial should be stopped

according to the doctor's judgment;

(4) The blinding is broken midway due to various reasons.

The study sponsor or regulatory agency may also terminate the study during the research period. If this study is terminated prematurely, we will notify you promptly and your researcher will provide recommendations for the next treatment plan based on your child's health condition. For study participants who drop out midway, for safety reasons, we have a final follow-up plan, and you have the right to refuse. In addition, you are expected to return all unused study drugs/study equipment to the researchers. If we find new information related to your health and rights after you drop out, we may contact you again.

Once you withdraw from the study, we won't collect new data about your child. The researcher will closely preserve the relevant information before withdrawing from the study until it is finally destroyed and will not continue to use or disclose it. However, in rare cases, this information needs to be used. For example, when government supervision departments conduct supervision, inspections, and statistics, they will ask to see all research information, which will include information related to your participation in the research at that time.

14. Are you willing to participate in future research?

If you agree, we would like to keep your child's remaining samples for testing during the study. In addition, we would like to follow up with your child long-term after the study ends to learn about health status and medication information (this may be considered if long-term follow-up is involved). Your child's remaining de-identified biological samples, research data, clinical diagnosis and treatment data (including but not limited to medical records, imaging data, clinical examination and monitoring data etc.) and follow-up data will continue to be used for subsequent genetic and non-genetic medical research on cardiovascular diseases in order to explore the causes, mechanisms and influencing factors of disease occurrence and evolvement, and to develop disease prevention, diagnosis and treatment measures. If you do not agree, after completing this study, your child's remaining research samples will be destroyed according to clinical routines, and the research data and clinical diagnosis and treatment data will be kept for a specified number of years in accordance with national regulations and will be kept strictly confidential.

Participating in future research will not increase your additional risk or financial burden. All samples and data from future research will be properly kept at our hospital and kept strictly confidential. You may voluntarily choose whether to participate in future studies and may withdraw from the study at any time by contacting the researchers.

15. Who should I contact if I have questions or difficulties?

You can ask any questions about this study at any time and get corresponding answers, including any discomfort that may occur during the study, please contact researcher Guo Jingfei at 15810396387.

If you have any questions about your rights, please contact the Ethics Committee of Fuwai Hospital, Tel: 010-88396281, 010-88396282.

Thank you for taking the time to read this informed consent form. If you and your family members agree to participate in this study after full consideration, we hope that you and your family members will complete this study in accordance with the requirements of

the researchers. Before participating in this study, please complete and sign the last page of this document (signature page) with your researcher in duplicate, with each of you and the hospital keeping one copy of the signed document.

Signature page

Statement of research participants

I have carefully read, understood and agreed to all the terms of this informed consent form.

I have been informed of the research purpose, content, and procedures of this research/clinical trial, possible risks of the research/trial, research compensation, and my rights, etc.; I have had sufficient time and opportunity to ask questions and have received satisfactory answers.

I agree to participate in this study and authorize your hospital to collect my biological samples and research data for this study.

I promise that the information I provide is true; if I provide false information, I promise to be responsible for the consequences.

I have also been told who to contact if I have questions or want further information.

I confirm that the contact information left at the signature office is my own valid contact information. If I change my contact information, I should inform your hospital in time. Otherwise, I am willing to bear the consequences of being unable to contact and receive notifications.

I know that I can withdraw from this study at any time without affecting my medical treatment and rights. I also know that the researcher may suspend/terminate my continued participation in this study at any time.

I will be given an original copy of this informed consent form, signed by myself and the researcher.

I agree to participate in this study.

Do you agree to participate in future research ☐ Agree ☐ Disagree (please choose) Donate the remaining samples for testing, clinical diagnosis and treatment data, and long-term follow-up data for future research. I authorize researchers and joint research units of related medical research projects use my approved anonymous remaining samples and data for cardiovascular-related genetic and non-genetic medical research. (If there is content for future research in the text, you may consider adding this wording)

Name of the Study Participant: Signature:

Date:

(If the research participant is a person without capacity or with limited capacity, a guardian's signature is required. If the research participant is a person with full capacity for civil conduct, this part can be deleted)

Name of the guardian: Signature:

Date:

I confirm that the information in the informed consent form has been correctly interpreted and understood by the research participant and/or the research participant's

legal representative. Study participants voluntarily agreed to participate in this study.

Signature of impartial witness [if applicable]: Date:

Statement of the investigators

I confirm that the details of this study have been explained to the study participants. Including their rights, benefits and risks, the research participants' questions were answered, and a signed copy of the informed consent form was given to them. The research participants voluntarily participated in this study.

Name of the investigator: Signature:

Date: