Intralipid postconditioning in patients of Cardiac surgery undergoing cardioPulmonary Bypass (iCPB): study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background: Intralipid is a necessary fatty acid carrier that has been safely used as an energy supplier in the clinic. It has played an important role in rescuing the cardiac arrest caused by local anesthetic toxicity. In recent years, experimental studies have shown that intralipid postconditioning (ILPC) could reduce myocardial ischemic/reperfusion (I/R) injuries. Our research group has innovatively conducted a pilot randomized controlled trial (RCT) and the results showed that ILPC could reduce the release of cTnT and CK-MB, biomarkers of myocardial I/R injury, in valve replacement surgery. However, the potential effects of ILPC on the clinical outcome of adult cardiac surgery patients are unclear. Intralipid postconditioning in patients of cardiac surgery undergoing cardiopulmonary bypass (iCPB) trial is aimed to further study whether ILPC could improve short-term and long-term clinical outcome, as well as cardiac function in adult cardiac surgery patients.

Methods: The iCPB trial is an ongoing, single-center, prospective, double blinded, large sample RCT. In total, 1000 adults undergoing cardiac surgery will be randomly allocated to either ILPC group or the control group. Intervention group received an intravenous infusion of 2 mL/kg of 20% intralipid (medium-chain and long-chain fat emulsion injection C6~C24, Pharmaceutical) within 10 minutes before aortic cross-unclamping, and the control group received an equivalent volume of normal saline. The primary endpoints are complex morbidity of major complications during hospitalization, and all-cause mortality within 30 days after surgery. The secondary endpoints include: (1) all-cause mortality 6 months and 1 year postoperatively, (2) the quality of life within 1 year after surgery using QoR-15 questionnaire, (3) the postoperative cardiac function evaluated by LVEF, LVEDs, LVEDD, and the myocardial injury evaluated by CK-MB, cTnT, BNP, (4) short-term clinical outcomes during hospitalization and total cost are also detailed evaluated.

Discussion: The iCPB trial is the first to explore ILPC on the clinical outcome of adult cardiac surgery patients. The results are expected to provide potential evidences about whether ILPC could reduce the morbidity and mortality, improve the cardiac function and quality of life. Therefore, provide a rationale for the evaluation of the potentially clinically relevant benefit of intralipid therapy.

Trial registration: Chictr.org.cn, ChiCTR1900024387. Prospectively registered on 9 July 2019.

Background

Myocardial ischemia/reperfusion (I/R) injury[1] is an important factor affecting cardiac function and prognosis in patients of cardiac surgery. The underling mechanisms include oxidative stress, inflammatory reaction, calcium overload, ion channel dysfunction and increased membrane permeability, energy metabolism disorders, etc[1]. These mechanisms interrelated with each other, and most importantly, the energy metabolism disorders are the initial link. Improving myocardial energy metabolism can reduce myocardial I/R injury[2]. Since the myocardium relies mainly on fatty acid oxidation (FAO) instead of glycometabolism to provide energy, some experimental studies indicated that supplementing

the exogenous FAO substrate can increase the supply of myocardial ATP and thus exert cardioprotection[3-7]. However, preischemic exposure of fatty acids will lead to insufficient FAO during the period of ischemia and cause cardiotoxicity injury subsequently. In the meanwhile, clinically, the myocardial ischemic processes are unpredictable, so the intervention of FAO during the period of reperfusion is more controllable and valuable.

Intralipid, a necessary fatty acid carrier, has been safely used as an energy supplier in the clinic for more than 50 year. It has also played an important role in rescuing the cardiac arrest caused by local anesthetic toxicity, which has been incorporated into several clinical guidelines[8-11]. In recent years, experimental studies have shown that lipid emulsion infusion just before reperfusion (i.e., intralipid postconditioning, ILPC) could reduce myocardial infarct sizes, improve cardiac function and reduce myocardial I/R injuries[12-16]. Subsequent mechanistic studies define that ILPC acts through the phosphorylation of glycogen synthase kinase-3β via PI3K/Akt/ERK pathways[12-14], Caveolin2/STAT3/GSK-3β pathway[15], and ultimately inhibits the opening of mitochondrial permeability transition pore (mPTP), which is essential to mitochondrial calcium overload and reactive oxygen species (ROS). Meanwhile, Umar[16] reported that the cardioprotective effects of lipid emulsion are mediated through G-protein coupled receptor-40 (GPR40) in two animal models of I/R injury and bupivacaine-induced cardiotoxicity. On the other hand, it could simply be a metabolic switch from glucose to fatty acid metabolism that paradoxically protects the heart [5,17]. Therefore, despite these interesting experimental findings, the potential clinical usage of intralipid in preventing myocardial I/R injury needs to be further investigated.

Based on the above background, our research group has innovatively conducted a pilot randomized controlled trial (RCT) to investigate whether ILPC would display the same cardioprotective effects in patients of cardiac surgeries, who were inevitably subject to I/R during cardiopulmonary bypass (CPB) [18,19]. The results showed that ILPC could reduce the release of myocardial damage biomaker of serum cardiac troponin T(cTnT) and creatine kinase-MB (CK-MB) after cardiac valve replacement surgery, and the total 72-hour postoperative area under the curve (AUC) of cTnT and CK-MB were significantly reduced by 32.3% and 26.4% compared with control, respectively[18]. However, due to the relatively small sample content, there were no significant differences between the short-term clinical prognostic parameters such as LVEF, vasoactive inotropic drug score (VIS score), ICU time, length of hospital stays (LOS), morbidity and mortality within 3-months after surgery.

Therefore, we design a large sample RCT to further study whether intralipid postconditioning could improve the short-term and long-term clinical prognosis as well as cardiac function of adult cardiac surgery patients undergoing cardiopulmonary bypass.

Objective

Despite the numerous studies on the myocardial protective effects of different drugs and measures, there are only a handful of drugs and measures that can be safely and effectively used in clinic[1, 20]. Moreover, few studies focused on the clinical outcome. Intralipid postconditioning in patients of cardiac

surgery undergoing cardiopulmonary bypass (iCPB) trial is a large sample RCT conducted to further study whether ILPC could reduce mortality and morbidity, improve the cardiac function and the quality of life in adult cardiac surgery patients, not limited to valve replacement surgery. The outcome is expected to be the foundation for the future multicenter clinical trial to evaluate the potentially clinically relevant benefit of intralipid therapy. As has been safely and widely used in clinical practice, intralipid may play a novel and important role as a therapeutic intervention for ischemic heart diseases, if similar cardioprotective effects and better clinical outcomes are demonstrated clinically.

Methods And Design

Study design

This iCPB study is a large sample, single-center, prospective, double-blinded, two-armed, randomized controlled trial with a 1:1 allocation ratio, testing the clinical outcome of intralipid postconditioning in adult cardiac surgery patients undergoing cardiopulmonary bypass. The protocol structure is written according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement guidelines and follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement. The SPIRIT checklist can be found in Additional file 1. The SPIRIT figure is illustrated in Fig. 1, and the Flow chart in Fig.2. The study will be conducted in West China Hospital of Sichuan University, China. More than 2500 open-heart procedures with CPB are performed at there each year.

Ethical approval and trial registration

This clinical study protocol has been approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University on 4 July 2019 (Approval number: 2019(324)). Written informed consent will be obtained from all patients before inclusion. The trial has been prospectively registered in the Chinese Clinical Trials Registry (ChiCTR)(www.chictr.org.cn) with the Registration number ChiCTR1900024387 on 9 July 2019.

Participants

We plan to enroll 1000 participants undergoing a cardiopulmonary bypass (CPB) for any elective cardiac surgical procedure via a median sternotomy such as procedures that involve the valves, coronary arteries, or aorta, or combined procedures.

Inclusion criteria

Patients will be eligible for enrollment if they meet all the following criteria:

1. Aged 18-70 years old
2. Scheduled to undergoing selective cardiac surgery with median sternotomy under CPB
3. Classified by the American Society of Anesthesiologists (ASA) physical status classification scheme of class I -

4. Signed informed consent

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participation

1. Redo cardiac surgery
2. Experienced cardiogenic shock or cardiac arrest, , left ventricular ejection fraction (LVEF) less than 30%, positive baseline serum cTnT or CK-MB
3. Aortic arch and other deep hypothermic circulatory arrest surgery, such as pulmonary thromboendarterectomy
4. Heart transplantation
5. Uncontrolled hypertension
6. Hyperlipidemia
7. Significant hepatic (international normalized ratio>2.0), pulmonary (forced expiratory volume-1<40% predicted, PaO2/FiO2<120) or renal disease (serum creatine level>150μmol/L)
8. Severe coagulation dysfunction
9. Any disorder associated with immunological dysfunction (e g, malignancy or positive serological test for the HIV) in the last 6 months
10. Current infections
11. Pregnant women
12. Preoperative treatment with intralipid in the last 1-month
13. Preoperative treatment with nicorandil (an adenosine triphosphate-sensitive potassium channel opener) or sulfonylurea (an adenosine triphosphate-sensitive potassium channel blocker)
14. Participating in other interventional studies

Randomization/Blinding

Patients who meet the enrollment criteria will be randomized 1:1 to either control or ILPC group. Randomization will be performed with the use of a computer-generated randomization sequence from random number table. The investigator who is responsible for grouping visits the patients the day before surgery and gets the informed consents. Once the patient is qualified, he determines the serial number and random number of the patient and writes on the Case Report Form (CRF). Allocation concealment was maintained until the time of CPB initiation by using opaque, numbered and sealed envelopes. The perfusionists will be aware of patients' group allocation because they will provide the trial intervention, but they will not be involved in either the postoperative treatment or the analysis.

The patients, the surgeons, ICU physicians, the data collectors and data analysts are not aware of the trial grouping in the whole process. Any intraoperative event or deviation from the protocol is recorded on the CRF.

Interventions

Patients who meet the enrollment criteria will be randomized 1:1 to either control or intralipid postconditioning (ILPC) group.

Patients in the ILPC group will receive an intravenous infusion of 2 mL/kg of 20% intralipid (medium-chain and long-chain fat emulsion injection C6~C24, Pharmaceutical) less than 10 min before aortic cross-unclamping. Intralipid should be infused over 10 min in constant speed. The dose of intralipid is chosen on the basis of the bolus dose when it is used in rescuing the cardiac arrest caused by local anesthetic toxicity[8-11].

Patients in the control group received an equivalent volume of normal saline 10min before aortic cross-unclamping.

Study endpoints

The primary endpoints are complex morbidity of major complications during hospitalization (all systemic organ complications are grade as I-V in Table 1), and all-cause mortality within 30 days after surgery.

The secondary endpoints include: (1) all-cause mortality 6 months and 1 year postoperatively, (2) the quality of life within 1 year after surgery, using 15-item Quality of Recovery Questionnaire (QoR-15)[21], (3) the postoperative cardiac function evaluated by LVEF, LVEDS, LVEDD at time points of 1 week, 1 month, 6 month and 1 year postoperatively, and the myocardial injury evaluated by CK-MB, cTnT, BNP at time point of 2h, 24h postoperatively, (4) short-term clinical outcomes during hospitalization (postoperative awakening time, mechanical ventilation time, ICU time, length of hospital stay) and total cost are also detailed evaluated.

Perioperative management and monitoring

Upon arrival in the operating room, standard monitoring includes 5 lead electrocardiogram (ECG), pulse oximeter. A peripheral venous cannula will be inserted, and patients will be sedated with midazolam intravenously. A radial arterial cannula will be inserted before anesthesia. Intravenous anesthesia is induced with midazolam (0.1-0.2 mg/kg), sufentanil (0.5-1μg/kg) and rocuronium (0.6 mg/kg).The trachea will be intubated, and mechanical ventilation will start to achieve an end-tidal carbon dioxide tension of 35-45 mm Hg, with limited inhaled oxygen concentration (FiO_2) 0.4-0.6, tidal volume (VT) 10ml/kg during operation. After the induction, anesthesia will be maintained with continuous infusion of propofol 80-100μg/kg/min or inhalation anesthesia 0.5-2mininal alveolar concentration (MAC) combined with dexmedetomidine 0.5ug/kg/h. Midazolam, sufentanil and rocuronium will be given as needed. Arterial blood pressure, central venous pressure and nasopharyngeal temperature will be recorded continuously. After systemic heparinization (3mg/kg, activated clotting time >480s), the ascending aorta, superior and inferior lumen (or right atrium) will be cannulated. Standard CPB with a disposable hollow fiber membrane oxygenator (Affinity NT 541; Medtronic, USA) and a roller pump (Stockert-5, Sorin Group,

Germany) will be started with a target output of 2.4–2.8 L/min.m^2 of body surface area. After aortic cross-clamping, cardio protection will be provided by cold-blood cardioplegia (1:4) at the dose of 20 mL/kg. The cardioplegia will be repeated half dose every 25 min during surgery. Surgery will be performed under mild hypothermia (33℃), with MAP 50-70 mmHg and HCT 20-30% during CPB. After the cardiac surgical procedure, the heart will be defibrillated after aortic unclamping, if sinus rhythm does not resume spontaneously. After weaning from CPB, protamine will be used to reverse the effect of heparin. Patients will be transferred to ICU after surgery and extubated at the earliest clinically appropriate time when their ventilation, hemodynamics, and neurological status are considered stable by the attending physician.

Postoperative follow-up

Each patient will receive follow-up calls at 1month, 6 months and 1year after surgery to answer questions regarding presence, quality using the 15-item Quality of Recovery Questionnaire (QoR-15)[21], and to provide the cardiac function data. Each patient will leave at least three phone numbers and receive a maximum of three telephone calls if contact could not be made.

Data collection

All the related data are collected on the CRF. Preoperative data include general information about age, height, weight, current and past medical history, especially heart diseases history. Using the classification of American Society of Anesthesiologists (ASA) to assessment risk within 24 hours before surgery. Intraoperative data include type and duration of surgery procedure, duration of CPB and aortic cross clamp, method of anesthesia and the duration of anesthesia. Post-operative data include the morbidity and mortality, cardiac function evaluated by LVEF, LVEDS, LVEDD, myocardial injury evaluated by CK-MB, cTnT, BNP, short-term clinical outcomes during hospital stay (postoperative awakening time, mechanical ventilation time, ICU time, length of hospital stay) and total cost. The follow-up data include quality of life at three time points (1month, 6 months, and 1-year), using the 15-item Quality of Recovery Questionnaire (QoR-15) and the echocardiography to evaluate the cardiac function.

Statistical Considerations

Sample size estimate

The sample selected for this trial was based on the results of a meta-analysis published by our research team, exploring the influences of inhalation anesthesia compared with total intravenous anesthesia on the patients' outcomes after valve surgery the effects of inhaled anesthesia and intravenous anesthesia on the clinical outcomes of heart valve surgery[22]. The study included 13 randomized controlled trials (a total of 962 patients undergoing heart valve surgery) and found that the 30-day mortality rate was 5.3%, complex morbidity of major postoperative complications was 27% (including post-arrhythmia, acute kidney injury, pulmonary complications, neurological complications, postoperative bleeding and myocardial infarction)[22]. Taking the complex morbidity of major complications in the meta-analysis as a control, the study has 80–90% power to detect a 25 relative risk reduction for the primary outcome of

complex morbidity at a significance level (alpha) of 0.05 (two-sided), with an allowance of 10% of patients lost to follow-up or withdrawn from the study, finally the calculated sample size of this study is about 1000 cases (500 cases each group).

Data analysis

Data will be expressed as means ± standard deviation or numbers (percentages). Baseline characteristics will be compared using chi-squared or Fisher's exact tests, a Student's t test, or a nonparametric test as appropriate. The primary outcomes, the complex morbidity of major postoperative complications and all-cause mortality within 30 days after surgery, will be compared using chi-squared or Fisher's exact tests, and the relative risks and the 95% confidence interval will be calculated. The secondary outcomes, which are the continuous variables that followed a normal distribution, will be performed using unequal-variance Student's t-test or nonparametric test. The other secondary outcomes, including the all-cause mortality 6 months and 1 year postoperatively, and data of QoR-15 will be compared using chi-squared or Fisher's exact tests. All analyses of morbidity and mortality will be conducted using the intention-to-treat approach. A sensitivity analysis using the per-protocol approach will also be performed. In addition, a multiple logistic regression analysis will be used to identify relevant baseline covariates associated with the primary outcome. Variables tested in the model will be selected if $P < 0.10$ or if they are clinically relevant. Logistic regression or Cox proportional hazard model will be carried out for different subgroups. Results are considered statistically significant if $P < 0.05$. Two-sided significance tests will be used throughout. Statistical analyses are performed using statistical software SPSS 17.0.

Discussion

The morbidity and mortality associated with cardiac surgery using CPB remains high despite advances in surgical technique, anesthesia management and CPB technology. However, myocardial I/R injury is still an important factor affecting patients' cardiac function and clinical prognosis. Ischemic preconditioning and/or postconditioning[23,24] has been reported to be effective in reducing myocardial I/R injury. This method did not translate into clinical practice partially due to difficulty in application of ischemic conditioning[24]. Remote ischemic preconditioning (RIPC) prior to cardiac surgery is non-invasive, but recent clinical studies and meta-analysis did not show its benefits on clinical outcomes[25]. Therefore, pharmacological preconditioning or postconditioning has better research and clinical prospects. Even multiple drugs were assessed[1,20], but none proved to be beneficial in large scale studies for myocardial protection. Now, intralipid may play a novel and potential role in cardioprotection with bright prospect[3-7].

Intralipid, a safe fat emulsion for human use, is used commonly as a component of parenteral nutrition in clinical practice. It also is used as therapy for severe cardiotoxicity secondary to accidental overdose of local anesthetics, an effect that has been confirmed in animals and humans[8-11]. Because patients with local anesthetic-induced cardiac arrest are considered to be less responsive for standard resuscitation methods, currently infusion of lipid emulsion is considered the primary treatment for local anesthetic

toxicity[10,11]. In recent years, another striking experimental finding is that intralipid postconditioning(ILPC) could reduce myocardial I/R injuries and thus improve cardiac function, where intralipid was administered as a bolus at the onset of reperfusion[12-17]. So, intralipid may represents a novel and clinically feasible cardioprotective strategy that is highly effective in remodeled hearts. Does the protective effect of lipid emulsion play some role in the effects of propofol (where 10% lipid emulsion is the vehicle) that have been noted in myocardial I/R injury[26]? Therefore, it is necessary that the cardioprotective effects of intralipid need to be clinically verified separately.

Our research group has conducted a pilot study and showed promising results that ILPC induced a significant reduction of postoperative cTnT and CK-MB release in patients undergoing cardiac valve replacement surgery[18,19]. Moreover, a single intravenous bolus of intralipid(2 mL/kg, 20% intralipid) did not bring abnormal lipid metabolism and was found to be safe, with no perioperative hepatic or renal dysfunction or any other significant related complications[18,19]. However, the sample size of the pilot study is small, and it is uncertain to know its influence on patient outcome. Here, we continue to conduct a large sample RCT to further study whether it could improve the cardiac function, the short-term and long-term clinical prognosis of adult cardiac surgery patients, not limited to valve replacement surgery. To our knowledge, this is the first clinical trial investigating the effects of intralipid postconditioning on patient outcome, including mortality, morbidity and long-term life quality. Our data will provide a rationale for the evaluation of the potentially clinically relevant benefit of intralipid therapy.

Our research has certain limitations. First of all, due to intralipid being white emulsion, it was difficult to achieve the blinding of anesthetists and perfusionists. So even they will provide the trial intervention, but they will not be involved in either the postoperative treatment or the analysis. Secondly, since the inhaled anesthetic sevoflurane is considered to be significantly cardioprotective and the high-dose propofol has also been reported to have a certain myocardial protective effect[26-28], both of which are currently widely used in clinical anesthetics, how to reduce their interference on the results of intralipid postconditioning is of great importance. In our previous pilot study[18,19], all included patients were given total intravenous anesthesia to eliminate the interference of sevoflurane. However, this does not rule out the role of propofol and is also not consistent with clinical practice. Therefore, in this large-sample RCT, we do not limit the anesthesia methods, but will make strict statistics on the dosage of various anesthetics in the intervention group and the control group, so as to ensure the baseline data be comparable. Thus, the confounding factors and interference of the anesthetics will be effectively avoided, and at the same time, it was more consistent with the clinical routine.

In summary, this large sample RCT will be the first to explore the intralipid postconditioning on the clinical outcome of adult cardiac surgery patients. The results are expected to provide potential evidences about whether intralipid postconditioning could reduce the morbidity and mortality, improve the cardiac function and quality of life. Therefore, provide a rationale for the evaluation of the potentially clinically relevant benefit of intralipid therapy.

Trial Status

The trial was started after we obtained the approval of local ethics committee and registered in the Chinese Clinical Trials Registry. The current protocol is version 2.0 and was issued on 1 June 2019. The study opened to patient recruitment in July 2019. Completion of this trial is expected in December 2021

Abbreviations

CPB: cardiopulmonary bypass; ILPC: intralipid postconditioning; I/R: ischemic/reperfusion; RCT: randomized controlled trial; FAO: fatty acid oxidation; GPR40: G-protein coupled receptor-40; cTnT: cardiac troponin T; CK-MB :and creatine kinase-MB; AUC: area under the curve; VIS score: vasoactive inotropic drug score; CONSORT: Consolidated Standards of Reporting Trials; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; LOS: length of hospital stays; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; LVEDs: left ventricular end- systolic diameter; BNP: Brain natriuretic peptide; ECG: Electrocardiogram; VT: Tidal volume; VT: Tidal volume ; MAP: mean artery pressure; HCT: hematocrit ; ICU: intensive care unit: ASA: American Society of Anesthesiologists; CRF: Case report form; PaO2: Arterial blood partial pressure of oxygen; FiO2: Inhaled oxygen concentration

Declarations

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Availability of data and materials

Data from the current study is available from the corresponding author upon reasonable request.

Authors’ contributions

YY drafted the first version of the manuscript together with HX. RHZ conceived and designed the trial and requested funding. YZ contribute to enroll patients and to data collection. YH and RHZ critically revised the manuscript. All authors approved the final manuscript.

Authors’ information

See the tilte page.

Ethics approval and consent to participate

This clinical study protocol has been approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee on 9 July 2019 (Approval number 2019 (324)). We will obtain informed consent from patients when recruiting before the experiment. The patients can withdraw from the trial at any time.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table

Table 1. Grade of complication outcome of the subjects

	Grade of complication outcome of the subjects
I	Healed after temporary treatment
II	Lead to longer hospital stay
III	Life-threatening, but can be basically recovered during hospitalization
IV	Resulting in injuries for 30 days or longer after surgery, the quality of life is significantly reduced
V	Death within 30 days after the surgery (during the study period)

Note: The end of the operation until 24:00 on the day is 0 days after surgery, and the next day after surgery is 00:01-24:00. And so on.

Figures

	STUDY PERIOD									
TIMEPOINT	**Day before surgery**	**Day of surgery**	**Before CPB**	**During CPB**	**After CPB**	**ICU**	**Ward**	**30 days after surgery**	**6 months after surgery**	**1 year after surgery**
ENROLLMENT:										
Eligibility screen	X									
Informed consent	X									
Random allocation		X								
INTERVENTIONS:										
Intralipid postconditioning				X						
Placebo				X						
ASSESSMENTS:										
Preoperative information	X									
Intraoperative information		X	X	X	X					
Complex morbidity of major complications						X	X			
All-cause mortality						X	X	X	X	X
Echocardiography	X						X	X	X	X
Biomarkers of myocardial injury	X					X				
Short-term outcomes during hospitalization						X	X			
Follow-up								X	X	X

Fig.1 Schedule of enrollment,interventions,and assessments according to Stardard Protocol Items:Recommendations for Interventional Trials(SPIRIT).

Figure 1

The SPIRIT figure

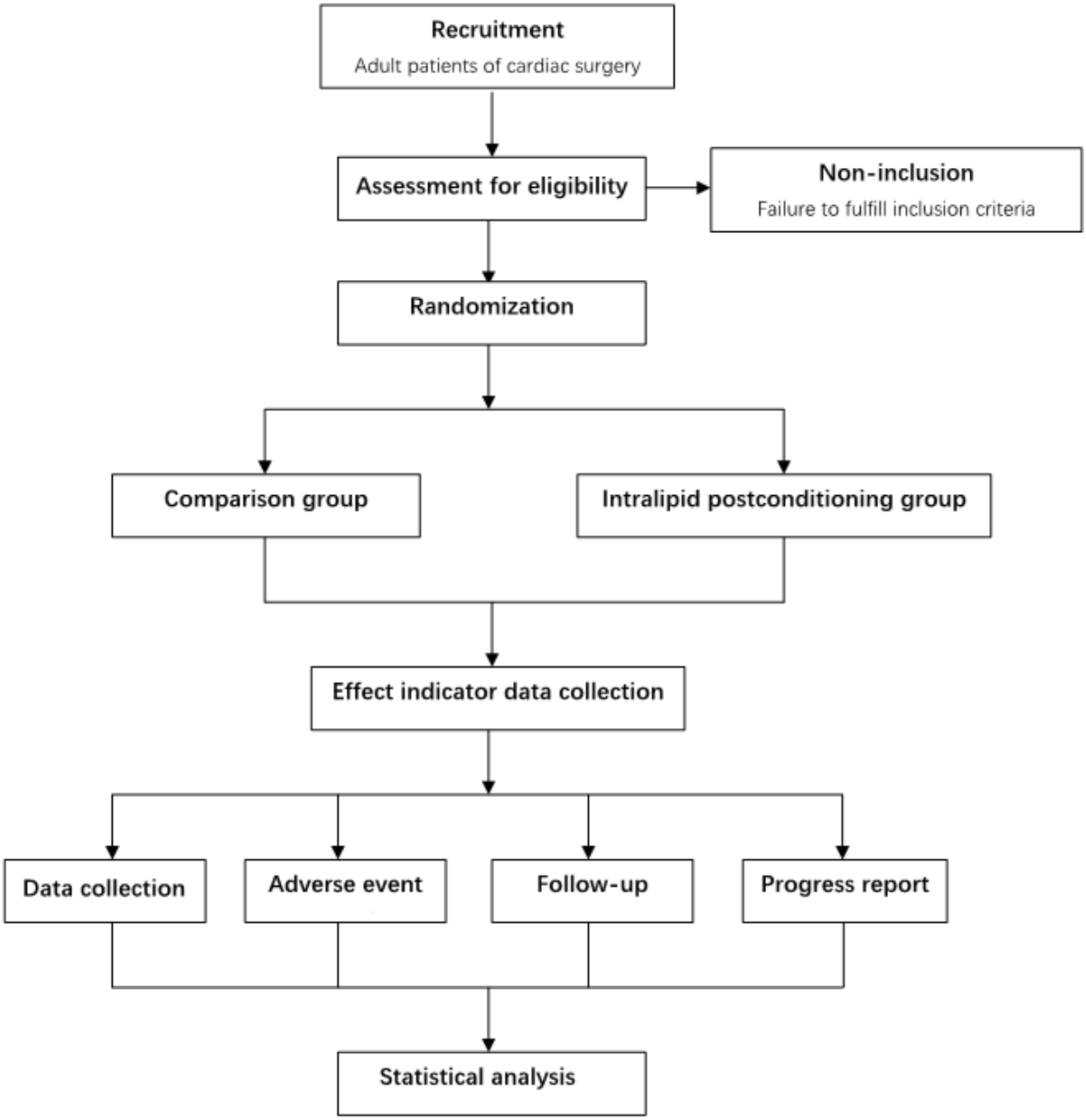

Fig. 2 Flow chart

Figure 2

Flow chart