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Goal-directed perfusion to reduce acute kidney injury after paediatric cardiac surgery (GDP-AKIp): study protocol for a prospective randomised controlled trial

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ABSTRACT

Introduction Cardiac surgery-associated acute kidney injury (CS-AKI) occurs in up to 40%~60% of paediatric patients and increases postoperative morbidity and mortality. A goal-directed perfusion (GDP) strategy aimed at maintaining indexed oxygen delivery (DO_2i) above the critical threshold (reported to be 260~300 mL/min/m^2 in adults) during cardiopulmonary bypass (CPB), is effective in reducing the incidence of CS-AKI. However, no clear standards of paediatric critical DO_2i exist. Our prior prospective cohort study exploring the critical DO_2i threshold during paediatric CPB has found the nadir DO_2i <353 mL/min/m^2 was an independent risk predictor of CS-AKI. Based on this background, this trial is designed to further determine whether the implementation of the GDP initiative aimed at maintaining DO_2i ≥360 mL/min/m^2 would reduce the rate of CS-AKI in paediatrics and improve clinical outcome.

Methods and analysis This is a prospective, single-centre, randomised controlled trial. In total, 166 paediatric patients undergoing cardiac surgery will be randomly allocated to the GDP group or control group. Patients in the GDP arm will be treated with a GDP strategy during CPB aimed to maintain DO_2i at ≥360 mL/min/m^2 (to ensure safely above the risk DO_2i threshold we found). The perfusion strategy for patients in the control arm will be factored on body surface area and temperature. The primary outcome is the rate of postoperative CS-AKI (it is defined according to paediatric Risk, Injury, Failure, Loss of renal function and End-stage renal disease criteria). The secondary end points include: (1) the other oxygen metabolism parameters during CPB; (2) major complication and all-cause mortality (in-hospital or within 30 days postoperatively); (3) short-term clinical outcomes (ie, time to extubation, mechanical ventilation time, hospital stay).

Ethics and dissemination The study has been approved by the Biomedical Research Ethics committee of West China Hospital of Sichuan University (approval number: 2019(863)). Results will be disseminated through peer-reviewed publications and conferences.

Trial registration number ChiCTR2000029232.

Strengths and limitations of this study

- This will be the first randomised controlled trial to explore the clinical effects of goal-directed perfusion (GDP) for postoperative cardiac surgery-associated acute kidney injury (CS-AKI) in paediatrics.
- This perfusion strategy is specifically tailored to the infants.
- We choose the target of 360 mL/min/m^2 as the indexed oxygen delivery (DO_2i) threshold which is safely above the critical DO_2i obtained from our prior prospective cohort study.
- A limitation of the study is the lack of a precise and quantifiable measures of diagnosing early CS-AKI.

INTRODUCTION

Infants or children undergoing open cardiac surgery are at high risk of developing cardiac surgery-associated acute kidney injury (CS-AKI), with the incidence of 40%–60%.[1–3] Paediatric CS-AKI increases postoperative morbidity and mortality, which also adversely affects the long-term prognosis. CS-AKI has a complex pathophysiology with many risk factors,[4 5] and therefore no single medication or therapy has been demonstrated to be effective for treatment or prevention.[6 7] However, it has been established that the associated low oxygen delivery is one of the important predicators of CS-AKI.[8–10] Therefore, in the absence of an intervention to prevent CS-AKI, a reasonable strategy to identify modifiable risk factors and to meet physical oxygen demand may reduce the risk of CS-AKI.

Oxygen delivery (DO_2) during CPB is calculated by multiplying the pump flow rate and the arterial oxygen content, which is more comprehensive in reflecting tissue oxygen supply than the independent parameters of arterial oxygen saturation (SaO_2), cardiac output and haemoglobin concentration.[11]

So, indexed DO_2 (DO_2i) is one of the most important determinants of 'optimal perfusion' during CPB.[11] The minimal safe DO_2i during CPB, termed 'critical DO_2i', is the point when the maximal oxygen extraction is reached, and the whole body oxygen consumption (VO_2) and tissue oxygenation begin to decrease, and anaerobic metabolism and lactic acidosis begin to develop.[11] In recent years, the concept of goal-directed perfusion (GDP) aimed at maintaining the nadir DO_2i on CPB above the critical value has been proved to be effective to reduce the incidence of CS-AKI.[8–10] Therefore, nadir DO_2i is a stronger predictor of CS-AKI than nadir haemoglobin or perfusion flow rate alone.[12]

Several clinical studies have explored the 'critical DO_2i' threshold in adult cardiac surgeries. Ranucci *et al*[13] reported that DO_2i value <260 mL/min/m^2 was associated with increased lactate formation. Subsequently, numerous retrospective and prospective observational studies have confirmed the association between nadir DO_2i on CPB and postoperative AKI, with the identification of a 'critical DO_2i' in the range of 262–272 mL/min/m^2 for adult patients undergoing CPB.[8–10] In 2018, a multicentre randomised controlled trial (RCT) showed that a GDP strategy, with maintenance of DO_2i >280 mL/min/m^2, was effective in reducing Acute Kidney Injury Network (AKIN) stage 1 postoperative AKI.[14] Moreover, in 2019, Mukaida *et al*[15] has tested that the time-dose response of DO_2i during CPB was a better indicator than nadir DO_2i in evaluating AKI risk, and maintaining DO_2i level >300 mL/min/m^2 may result in decreased risk for postoperative AKI. However, all the studies about the critical DO_2i thresholds on CPB and the relationship between the nadir DO_2i and CS-AKI are all limited to the adult population. The literature in paediatric patients is scarce and no evidence-based paediatric critical DO_2i threshold is universally accepted. Given that infants have a much higher metabolic rate and oxygen demand, consequently they require a much higher pump flow rate (3.2 L/min/m^2 body surface area (BSA) vs 2.4 L/min/m^2 BSA) and haematocrit (HCT) than adults. So, the critical DO_2i in infants cannot be referred to the existing adults' standard, otherwise it will cause severe hypoperfusion and hypoxia.

Therefore, our research group has innovatively conducted a pilot prospective cohort study to explore the critical DO_2i threshold in paediatric cardiac patients, with the association of postoperative AKI (trial registration number: ChiCTR1900028683). The results showed that nadir DO_2i was significantly different between the non-AKI and AKI groups. And the nadir DO_2i on CPB less than the critical value threshold of 353 mL/min/m^2 was an independent risk predictor of CS-AKI in infants. However, further studies are needed to define the effects of GDP approach in paediatrics.

Based on this background, the current RCT of GDP strategy to reduce AKI after paediatric cardiac surgery (GDP-AKIp) is designed to further study whether the GDP approach aimed at avoiding the nadir DO_2i less than the critical threshold of 360 mL/min/m^2 will reduce the rate of postoperative AKI in paediatric patients undergoing mild hypothermic CPB, and improve the clinical outcome.

OBJECTIVE

To demonstrate that the implementation of the GDP initiative aimed at maintaining DO_2i ≥360 mL/min/m^2 compared with standard CPB flow rate management factored on BSA and temperature would reduce the rate of CS-AKI in paediatrics and improve clinical outcome, we will test the following hypothesis:

- The implementation of the GDP initiative would be associated with a reduced AKI incidence within 7 days of paediatric cardiac surgery compared with control patients.

METHODS/DESIGN

Study design

The GDP-AKIp study is a single-centre, prospective, double-blinded, two-armed, RCT with a 1:1 allocation ratio, testing whether the GDP strategy will reduce the rate of CS-AKI and improve clinical outcome in paediatric patients. The protocol structure is written according to the Consolidated Standards of Reporting Trials 2010 Statement guidelines and follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement. The SPIRIT checklist can be found in online supplemental additional file 1. Figure 1 is the trial flow chart. The schedule of enrolment, interventions and assessments follows the SPIRIT Statement (figure 2).

This trial will be undertaken in West China Hospital of Sichuan University, where >300 infant open-heart procedures with CPB are performed each year. Recruitment will be commenced in April 2020.

Participants

We plan to enrol 166 paediatric participants aged <3 years undergoing CPB for any elective cardiac surgical procedure via a median sternotomy.

Inclusion criteria

Participants must meet all the inclusion criteria:

1. aged ≤3 years;
2. undergoing elective cardiac surgery via a median sternotomy under CPB;
3. American Society of Anesthesiologists I–IV level;
4. there is a written informed consent.

Exclusion criteria

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

1. chronic kidney disease stage 5 (receipt of kidney replacement therapy or estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2)[16];
2. expected nadir CPB temperature <32°C;
3. heart transplantation;
4. suffering perioperative cardiac arrest;

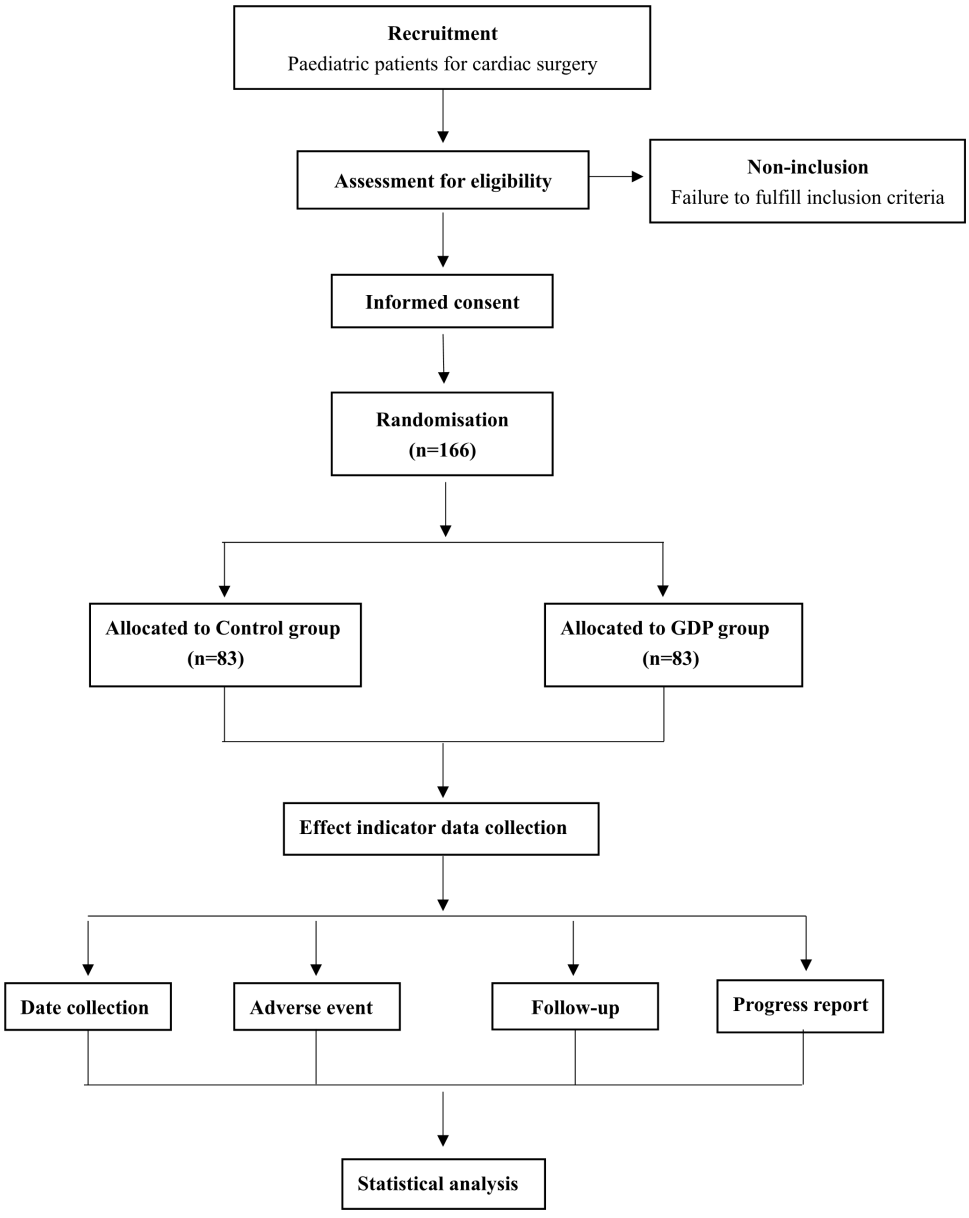

Figure 1 Flow chart. GDP, goal-directed perfusion.

5. aortic arch and other deep hypothermic circulatory arrest surgery;
6. preoperative treatment with extracorporeal life support;
7. postoperative treatment with extracorporeal life support or ventricular auxiliary device (VAD);
8. participating in other interventional studies;
9. premature infants and those with pre-existing brain or kidney abnormalities.

Randomisation/Blinding

Once informed consent has been received and the preoperative assessments completed, patients will be enrolled into the trial. In this study, a statistician in the study will use the IBM SPSS Statistics V.19.0 software to generate a table of random numbers. The ratio of test-to-control is 1:1 and the block size is 2. Patients will be randomly assigned to either GDP or control arms according to enrolment sequence. A table of random numbers will be placed in sequentially labelled opaque envelopes. The distribution order will be kept by a research assistant who is not involved in recruitment, intervention, outcome evaluation or statistical analysis. After the subjects have met the study criteria, the research assistant will notify the appropriate perfusionist to intervene by telephone of the assignment (GDP group or control group).

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, the anaesthesiologists, the paediatric intensive care unit (PICU) physicians, the data collectors and the data analysts are blinded to treatment allocation in the whole process. To ensure these people are blinded to the perfusion strategy,

	STUDY PERIOD							
TIMEPOINT	Day before surgery	Day of surgery	Before CPB	During CPB	After CPB	ICU	Ward	1 momth after surgery
ENROLLMENT:								
Eligibility screen	X							
Informed consent	X							
Random allocation		X						
INTERVENTIONS:								
Goal-directed perfusion strategy				X				
Routine perfusion strategy				X				
ASSESSMENTS:								
Preoperative information	X							
Intraoperative information		X	X	X	X			
The incidence of CS-AKI						X	X	X
The body metabolism parameters				X		X		
Major complication and all-cause mortality						X	X	X
Short-term outcomes during hospitalisation						X	X	
Follow-up								X

Figure 2 Schedule of enrolment, interventions, assessments according to Standard Protocol Items: Recommendations for International Trials (SPIRIT). CPB, cardiopulmonary bypass; CS-AKI, cardiac surgery-associated acute kidney injury; ICU, intensive care unit.

the patient files typically the perfusion records will not be involved information related to the study arm.

Interventions

Patients who meet the enrolment criteria will be randomised 1:1 to either control or GDP group.

Patients in the control group will receive arterial pump flow based on BSA and temperature, with a target value of 2.8~3.2 L/min/m^2. Ultrafiltration and transfusion of packed red blood cell (PRBC) during CPB will be triggered by the HCT value, according to local institutional standards.

Patients in the GDP group will receive a GDP strategy during CPB aimed to maintain DO_2i at ≥360 mL/min/m^2. The main intervention will be based on adjustment of the arterial pump flow according to the HCT value so as to reach and maintain a DO_2i above the prespecified threshold. In the event of low HCT values and an inability to maintain the DO_2i above the threshold, transfusing PRBC or ultrafiltration could be considered.

With respect to the other perfusion details, the patients will be treated according to our hospital standards. The DO_2i levels of patients in both study arms during CPB are reported at 10 min intervals. For patients in the GDP group, the perfusionist will have a direct view of the GDP monitor data to achieve compliance with the GDP protocol. For patients in the control group, the DO_2i value will be excluded from the record form to avoid any intervention based on values in the control group.

Study end points

The primary end point is the rate of AKI after cardiac surgery. AKI is defined according to paediatric Risk, Injury, Failure, Loss of renal function and End-stage renal disease (pRIFLE) classification at the risk or greater level as any increase in estimated creatinine clearance (eCrCl) >25% from baseline (obtained within 1 week before surgery) to peak value within the first 7 days postsurgery.[17] Moreover, to accurately reflect changing renal function, adjusting serum creatinine (SCr) values for fluid balance will be used. Adjusted SCr=measured SCr×(1+[cumulative net fluid balance (L)/total body water (kg)]). Postoperative SCr will be recorded daily for 7 days. We will also record peak SCr during hospital stay and SCr before discharge on all patients. We will calculate pRIFLE scores using the eGFR calculated from the eCrCl with the Schwartz formula[18]: eGFR (mL/min per 1.73 m^2)=0.413×height (cm)/SCr (mg/dL). Our AKI definition will not include urine output as urine output is frequently influenced by modified ultrafiltration and diuretic use.

The secondary end points include: (1) the other oxygen metabolism parameters during CPB, including mixed venous oxygen saturation (SvO_2), the peak lactate concentration and regional cerebral and renal oxygen

saturation, (2) major complication (ie, low cardiac output syndrome; typically based on two or more of the following: cardiac index ≤2.2 L/min/m^2, blood lactate >3 mmol/L or increase in blood lactate of at least 2 mmol/L from baseline, SvO_2 <50% or increase in SaO_2 to SvO_2 difference by at least 20% from baseline, urine output <1 mL/kg/hour, peripheral skin temperature to core body temperature difference of >7°C),[19] severe respiratory failure based on blood gas, treatment for pneumonia (ie, antibiotics), sepsis, deep sternal wound infection and all-cause mortality (in-hospital or in-hospital or within 30 days postoperatively), (3) short-term clinical outcomes including time to extubation, mechanical ventilation time, PICU time, length of hospital stay.

Perioperative management and monitoring

General anaesthesia will be induced with midazolam, sufentanil and propofol as necessary. Tracheal intubation will be facilitated with either rocuronium or cisatracurium. There is no restriction on the type or dose of anaesthetic used to induce anaesthesia. The trachea will be intubated, and mechanical ventilation starts to achieve an end-tidal carbon dioxide tension of 35~45 mm Hg. After the induction, anaesthesia will be maintained with continuous infusion of propofol or inhalation of sevoflurane until the end of surgery. Midazolam, sufentanil and cisatracurium will be given as needed.

A standard CPB equipment with a disposable hollow-fibre membrane oxygenator (Pixie, Medtronic, USA) and a roller pump (Stockert-5, Sorin Group, Germany) will be selected. The pump circuit will be primed with 150~200 mL acetated Ringer's solution, 1–2 units PRBC, 10 g albumin, 1.25 mL/kg 20% mannitol and 10–20 mL 5% sodium bicarbonate. Cold modified St. Thomas blood cardioplegia (1:4) at the dose of 30 mL/kg will be used for all patients. The cardioplegia will be repeated half dose every 20~25 min during surgery. Pump flow rate will be targeted between 2.8 and 3.2 L/min/m^2. Surgery will be performed under mild hypothermia (33°C–34°C), with mean arterial pressure 30~45 mm Hg and HCT 25%~30% during CPB. Blood gases and haemoglobin values will be measured at the following detailed time points. After the cardiac surgical procedure and aortic unclamping, the heart will be defibrillated if sinus rhythm does not resume spontaneously. And after weaning from CPB, modified ultrafiltration (MUF) will be routinely performed and the HCT will be maintained at 30%~35%. Then, protamine will be used to reverse the effect of heparin. Postoperatively, all patients will be transferred to the PICU.

The blood gases will be routinely monitored at the following time points, that is, after anaesthesia induction, CPB initiation, 5 min after aortic clamping, every 10 min during the periods of aortic cross-clamping, at rewarming, before CPB weaning and after MUF. Moreover, during CPB, blood gases should be re-examined 5 min after the completion of any intervention measures, such as adjustment of pump flow rate and ventilation parameters, blood transfusion, ultrafiltration and so on.

The DO_2i will be calculated based on the blood gases during the period of aortic cross-clamping. The nadir DO_2i will be taken as the lowest of all calculated values. And the DO_2i will be computed using the following formula[13]: DO_2i (mL/min/m^2)=pump flow (L/min/m^2) ×(1.36×haemoglobin (g/L)×haemoglobin saturation (%)+0.031×partial pressure of arterial oxygen (mm Hg))/BSA (m^2).

SvO_2 and lactate concentration should also be recorded every 10 min from blood gas during CPB. Renal and cerebral regional oxygen saturation (rSO_2) will be continuously measured every 2 s (EGOS-600A) from the time of anaesthesia to the time of transfer from the operating room to PICU. Baseline rSO_2 levels (before CPB) and both average and nadir levels for the intraoperative period will be recorded. We will also evaluate cumulative time spent during CPB at or below a rSO_2 value 20% less than baseline and cumulative time spent at or above a rSO_2 value 20% more than baseline.

Data collection

All the related data will be collected on the case report form. Preoperative data include patient demographics (sex, age, weight, presence of cyanotic lesions and Fontan candidates), preoperative cardiovascular profile (ejection fraction, New York Heart Association functional class, Society of Thoracic Surgeons–European Association for cardiothoracic surgery congenital heart surgery mortality score (STAT) score,[20] pulmonary hypertension and the use of ACE inhibitor, diuretics and β-blockers prior to cardiac surgery), presence of comorbidities (lung infection, hypothyroidism, previous cerebrovascular accident) and laboratory assays (SCr value and haemoglobin). Operative data including type of operation, CPB duration, aortic cross-clamp time, nadir body temperature during CPB, number of PRBC units transfused during surgery, rSO_2 value, nadir SvO_2, nadir DO_2i and the peak blood glucose and lactate concentration on CPB will be assessed. We will record postoperative data including SCr value, AKI stage, the peak lactate and blood glucose concentration in the PICU, the number of PRBC units transfused in the PICU, the maximum VIS score, urine output (mL/kg/hour), maximum fluid overload (FO) (ie, (daily (fluid in (L)–fluid out (L))×100/PICU admission patient weight (kg)) within the first week of PICU admission and cumulative FO (cFO) (eg, cFO=%FO day of surgery (DOS)+%FO postoperative day 1; also, for DOS, the cFO includes intraoperative fluid status.[21] We will also evaluate the association between CS-AKI and postoperative short-term outcomes (major complication and all-cause mortality, time to extubation, mechanical ventilation time, PICU time, hospital stay).

Statistical considerations

Sample size estimate

The sample selected for this study is based on the finding of our prior pilot cohort study exploring the critical DO_2i threshold in paediatric patients undergoing cardiac

surgery with CPB. That study showed that 38.5% paediatric patients developed CS-AKI postoperatively. A non-inferiority threshold of 10% is considered according to previous studies.[14] A sample size of 75 per group will yield 80% power to obtain a significant difference between the two groups, using a two-sample t-test at a one-sided 0.025 level of significance. To account for an approximately 10% dropout rate, a total of 166 subjects (83 subjects for each group) will be enrolled.

Statistical analyses

Continuous variables will be described as the mean (SD), median (IQR) when not normally distributed and categorical variables with count (n) and proportions (%). The normality of distribution will be tested with the Kolmogorov-Smirnov test. Baseline characteristics will be compared using χ^2 or Fisher's exact tests and a Student's t-test. The primary outcome, the occurrence of AKI after surgery, will be compared using χ^2 or Fisher's exact tests, and the relative risks and the 95% CI will be calculated. The secondary outcomes, which are the continuous variables, will be performed using unequal-variance Student's t-test. The other secondary outcomes, including the major complication and all-cause mortality will be compared using χ^2 or Fisher's exact tests. In addition, a multiple logistic regression analysis will be used to identify relevant covariates (the oxygen metabolism parameters such as DO_2i, SvO_2, lactate, rSO_2 value and other risk factors such as CPB duration, age, %FO) associated with the primary outcome. Analyses of morbidity and mortality will be conducted using the intention-to-treat approach. Logistic regression or Cox proportional hazard model will be carried out for different subgroups. We plan a prespecified subgroup analysis in: (1) patients with CPB duration ≥90 min and (2) patients with CPB duration <90 min. For all the statistical tests, a p value <0.05 will be considered significant. Statistical analyses will be done using statistical software SPSS V.19.0.

Missing data

Missing data for the primary outcome (baseline and peak SCr levels) will be assumed to be missing completely, and these patients will be excluded from the efficacy analysis. If data are 'missing at random' and accounting for a small proportion, we will first perform analysis by excluding missing values; if data are 'not missing at random', we will attempt to contact authors, investigators to obtain data. Nevertheless, if there is no reply, we will then perform multiple imputations to impute missing values and conduct subsequent analysis to estimate the robustness of the findings.

DISCUSSION

To our knowledge, this will be the first prospective RCT to investigate the prevention of CS-AKI with CPB for paediatric patients receiving GDP strategy aimed at maintaining DO_2i ≥360 mL/min/m^2 compared with those receiving standard CPB flow rate management factored on BSA and temperature. The results of this RCT will fill the gap of GDP strategy in paediatric cardiac surgery patients, and provide new ideas for optimising the perfusion strategy and improving the prognosis in paediatrics, which has significant clinical value.

CS-AKI is defined as eCrCl >25% of baseline within the first 7 days postsurgery. Although several standardised definitions for CS-AKI have been developed, no consensus exists regarding which to use in children. In our study, pRIFLE criteria is selected due to following reasons. First, pRIFLE is more sensitive, identifying a greater number of mild AKI cases.[22 23] The pRIFLE criteria are based on changes in eCrCl while AKIN and The Kidney Disease: Improving Global Outcomes are mainly based on changes in SCr. Many studies reported that eCrCl in infants better reflects renal function than SCr alone due to their insufficient renal function.[24 25] Second, small children, compared with older children and adults, have very low baseline SCr owing to the dependency of SCr on muscle mass. Thus, the advantage of the 'increase in SCr >0.3 mg/dL' criterion in the AKIN disappears with regard to children with baseline Cr ≤0.5 mg/dL.

GDP is a refined and individualised CPB perfusion strategy proposed in recent years. It involves aggressive patient management and incorporates continuous monitoring of oxygen metabolism parameters, such as DO_2i, carbon dioxide production and oxygen extraction index, so as to tailor perfusion to each patient's specific needs.[26] Several clinical studies have shown that a GDP strategy aimed at maintaining DO_2i above the critical threshold (reported to be 260~300 mL/min/m^2 in adults) during CPB, is associated with reduced risk of CS-AKI.[8–10 13] However, no clear standards of paediatric critical DO_2i exist. Our prior prospective cohort study has found that the nadir DO_2i <353 mL/min/m^2 was an independently risk predictor of CS-AKI in infants. We chose a conservative target of 360 mL/min/m^2 in our RCT to remain safely above the risk threshold we found. The main intervention in this study is to tailor the perfusion flow according to the HCT value so as to maintain a DO_2i above the prespecified threshold. In the event of low HCT values, an increasing perfusion flow was unable to maintain the DO_2i above the threshold, and ultrafiltration and/or PRBC transfusion could be considered.

Our research has certain limitations. First, our study lacks patients treated under hypothermic conditions <32°C, when different limits of critical DO_2i are likely to occur. Second, CS-AKI is certainly a multifactorial event, and we could not include all of the possible determinants in our analyses. Third, although adjusting SCr values for fluid balance will be used in our study, SCr has several limitations for diagnosing early AKI and the incidence of CS-AKI may be underestimated. Biomarkers of renal cell injury might help us identify additional patients at an earlier stage.[27]

Patient and public involvement

Patients' priorities, experience and preferences will be not involved in the development of the research question and outcome measures, the design of this study or the recruitment and conduct of the study. The results will be not disseminated to study participants.

ETHICS AND DISSEMINATION

The study has been approved by the Biomedical Research Ethics committee of West China Hospital of Sichuan University on 5 December 2019 (approval number: 2019(863)). Written informed consent will be obtained from all patients before inclusion. Trial oversight will be performed by an independent Data Safety and Monitoring Board (Biomedical Research Ethics committee). The task is to oversee the safety of the trial subjects and to monitor integrity and validity of the conduct of the clinical trial. Results will be disseminated through peer-reviewed publications and conferences.

Contributors YZ helped designing the trial, collected and analysed the data and drafted the manuscript. XZ helped designing the trial, performed the study. BW collected data and analysed the data. LG performed study coordination and collected date. RZ conceived the study, designed the trial and drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

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26 Groom RC. Is it time for goal-directed therapy in perfusion. *J Extra Corpor Technol* 2017;49:P8–12.
27 Yoneyama F, Okamura T, Takigiku K, *et al*. Novel urinary biomarkers for acute kidney injury and prediction of clinical outcomes after pediatric cardiac surgery. *Pediatr Cardiol* 2020;41:695–702.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	Page 14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 14
	5b	Name and contact information for the trial sponsor	Page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pages 2-4
	6b	Explanation for choice of comparators	Pages 4
Objectives	7	Specific objectives or hypotheses	Page 4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Pages 7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 6-7 & Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Pages 11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Pages 8–11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	NA
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pages 11-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Pages 12

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Pages 14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file consent form
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.