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Near-infrared spectroscopy to monitor cerebral and renal oxygen saturation during cardiopulmonary bypass surgery for pediatric congenital heart disease: study protocol for a prospective observational cohort trial

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Near-infrared spectroscopy to monitor cerebral and renal oxygen saturation during cardiopulmonary bypass surgery for pediatric congenital heart disease: study protocol for a prospective observational cohort trial

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Abstract

Background: Indicators for monitoring organ function during anesthesia are mostly indirect, lagging and non-specific, especially in pediatric surgery, which is affected by multiple factors, making the monitoring and assessment of organ function more complicated. Related studies suggest that the use of near-infrared spectroscopy technology to continuously monitor the regional oxygen saturation of intraoperative organs can predict the postoperative organ functional status. The aim of the study, regional oxygenation monitoring of the brain and kidney was continuously performed during pediatric surgery for congenital heart disease, and an attempt was made to investigate its relationship with brain injury and acute kidney injury. **Methods:** This study was a prospective, cohort study. Children, aged ⩽18 years, who were to undergo surgery for congenital heart disease under cardiopulmonary bypass were included and signed an informed consent. Psychiatric, renal, and other related disorders were excluded. Cerebral and renal regional oxygen saturation was continuously monitored before induction of anesthesia until the children were transferred to the cardiac care unit at the end of surgery. The children were evaluated preoperatively and postoperatively by the Child Quality of Life Score. Brain injury was assessed using changes in S100 calcium-binding protein B before and after surgery, and acute kidney injury was assessed using the pediatric RIFLE scoring system as measured by changes in

creatinine. **Discussion:** Changes in cerebral oxygen during cardiopulmonary bypass can predict changes in S100 calcium-binding protein B in response to cerebral injury after pediatric preoperative surgery, and changes in renal oxygen saturation during the cardiopulmonary bypass can predict acute postoperative injury after pediatric surgery, as well as validate the impact on the quality of life of children in the postoperative period.

Trial registration: The study was registered with the Chinese Clinical Trial Registry on 18 April 2024. (Number: ChiCTR2400083225)

Keywords

Near-infrared spectroscopy, Regional oxygen saturation, Cardiopulmonary bypass, Brain injury, Acute kidney injury.

Strengths and limitations of this study

- The population for this study was children undergoing surgery for congenital heart disease.
- This is a prospective cohort study to adjust for confounders by regression methods to determine the relationship between regional oxygen saturation and organ injury.
- In addition to analyzing the mean values of regional oxygen saturation for the main predictor variable, we will also analyze desaturation/ oversaturation duration, percentage of time, and AUC separately.
- Relevant prognostic indicators, such as quality-of-life score, length of

postoperative hospital stay, and hospitalization expenditures were also included in the study.

- This is a single-site study; findings need to be tested on a larger scale in multiple sites

Background

The monitoring and assessment of oxygen delivery and oxygen consumption in vital organs in children under general anesthesia during surgery is complicated by their own factors, such as age and body size, as well as possible changes in intraoperative hemodynamics. Although indicators such as lactic acidosis, hypothermia, bradycardia, decreased blood pressure, and reduced urine output are readily available during anesthesia, they remain indirect, nonspecific indicators of the occurrence of impairments in the function of the organs involved. Near-infrared spectroscopy (NIRS) is a noninvasive technique that is increasingly used in surgical and intensive care environments to monitor regional blood flow and regional oxygen saturation(rSO_2)[1 2]. There are studies on brain tissue oxygen saturation, abdominal oxygen saturation, and renal oxygen saturation. Some studies have described trends in normal values of regional oxygen saturation in the brain and internal organs of preterm infants, and changes in regional oxygen saturation indices over time may be indicative of the maturation of physiologic oxygen balance in this tissue[3 4]. In children, regional oxygen saturation of brain tissue below a certain level from

baseline during noncardiac surgery can lead to adverse behavioral changes or delirium in the postoperative period[5,6]. It has been suggested that reduced renal oxygen saturation in preterm infants is associated with acute kidney injury, which is an independent risk factor for mortality and morbidity in hospitalized patients and can lead to chronic kidney disease and adverse long-term health problems. Of all the organs, brain function and kidney function critically impact the prognosis of postoperative children.

Altering the state of organ perfusion, oxygen delivery, and energy expenditure can prevent or promote cellular damage (from oxidative stress and inflammation) and recovery, a state that occurs during cardiac surgery under cardiopulmonary bypass (CPB). Brain regional oxygen saturation, which is characterized by high constant blood flow and high oxygen uptake, and renal tissue oxygen saturation, which is characterized by high blood flow variability and relatively low oxygen uptake, have the potential to be disrupted during cardiopulmonary bypass. In the present study, regional oxygen saturation monitoring of the brain and kidney was continuously performed during surgery for congenital heart disease in children and an attempt was made to investigate its relationship with brain injury and acute renal injury. To evaluate the association between regional tissue oxygen saturation and quality of life after surgery and anesthesia, the Pediatric Quality-of-Life (PedsQL) survey will be given to caregivers on the day of

surgery (baseline), and 30 days after surgery[7].

Methods

Study design

This was a prospective, observational, cohort study. This study was approved by the ethics committee of Beijing Children's Hospital ([2024]-Y-093-D, protocol amendment number:4.0, issue date: 27 Mar 2024) and registered in the Chinese clinical trial registry (ChiCTR2400083225). We strictly adhered to clinical practice guidelines and the Declaration of Helsinki throughout the trial. The study population consisted of pediatric patients with congenital heart disease who were less than or equal to 18 years of age scheduled for surgery requiring CPB. Written informed consent was obtained from parents or guardians of eligible participants by communicating with them before the study was initiated. Being a large pediatric medical center, the number of surgical cases of congenital heart disease can meet the sample size requirement of this study.

Objectives

The primary objective was to determine the relationship of cerebral and renal oxygen saturation to brain injury and kidney injury. The secondary objectives were to determine the perioperative factors associated with brain injury and kidney injury and to explore the effects of brain injury and

kidney injury on patients' quality of life.

Sample size

Based on the relationship between the predictor variable, change in brain rSO_2, and the outcome variable, brain injury, which was the primary objective of this study, approximately 10 predictor variables such as age, sex, weight, Risk Stratification for Congenital Heart Surgery (RACHS-2), preoperative cyanosis or not, baseline hematocrit, preoperative left ventricular ejection fraction (LVEF), CPB time, and mean arterial pressure during CPB, were also proposed to be included. In this study, we expected a sufficient sample size to test the coefficient of determination R^2 of at least 0.25, and the actual value of R^2 was 0.5. The test level of α=0.05, and the test efficacy of 1-β=0.9 were calculated by using the Multiple Regression module of the PASS15.0 software, and the final sample size of 117 cases was calculated by taking into account the 20% dropout rate due to the withdrawal of the patients or the data recording problem.

Eligibility criteria

Inclusion criteria: (1) Age$\leqslant$18 years old. (2) To be operated under CPB for corrective surgery of congenital heart disease. (3) Parental or guardian's permission (signed informed consent). Exclusion criteria: (1) Post-menstrual age $\leqslant$38 weeks. (2) Renal disease or renal insufficiency, (3)

Autism, developmental delay, cognitive impairment, or neuropsychiatric disorders. (4) Heart transplantation, preoperative dialysis, infection, sepsis, preoperative extracorporeal life support, use of contrast media within 7 days before surgery.

Study Procedures

The flow of the study is shown in Figure 1. A baseline quality-of-life survey is collected on the day of surgery. The survey would be repeated at 30 days post-surgery. The patient receives standard anesthetic care for the surgical procedure as administered by the anesthesia provider. From admission to the operating room until the patient is transferred to the pediatric cardiac intensive care unit (CICU) at the end of the surgery, during this time the child is monitored using the SenSmart™ Model X-100 Universal Oximetry System (Nonin Medical, Inc. Plymouth, MN, USA), which continuously measures rSO_2 every 4 seconds. Inhaled oxygen concentration set at 100%. Before placing the sensor electrodes, the study team should assess the skin condition of the forehead and kidney region. One member of the team places the NIRS sensor electrode on the right side of the patient at the level of the right renal region of the spine after localization by point-of-care ultrasound (right side of the spine, approximately at the T10-L2 level), and the other sensor electrode is placed

on the forehead and connected to the monitor to start recording rSO_2 data. To avoid electrode detachment, the renal region electrode can be covered with a 3M film and the forehead electrode can be wrapped with an elastic bandage.

Measurement of cerebral rSO_2(C-rSO_2) and renal rSO_2(R-rSO_2)

The rSO_2 study measurements were not directly visible to the anesthetist/perfusionist. Three distinct periods were evaluated: before induction (baseline), during CPB, and after CPB. All rSO_2 measurements during each operative period were averaged to define a mean rSO_2 for that period. We also evaluated cumulative time spent during CPB at or below a rSO_2 value 10% less than baseline (desaturation) and cumulative time spent at or above a rSO_2 value 10% more than baseline (oversaturation).

Definition of brain and kidney injury

To recognize brain injury, one method is to assess the concentration of specific markers in plasma, among which the most studied in the pediatric population is S100 calcium-binding protein B (S100B), which is the most abundant calcium-binding protein in neural tissues (especially astrocytes) and is one of the injury-associated molecules released early in brain injury or after primary brain injury, which can lead to secondary injury[8]. S100B

is considered a biomarker of traumatic brain injury and has been shown to correlate with the extent of injury, survival, and neurological prognosis [9]. Serum levels of S100B protein are elevated in patients with brain injuries induced by trauma, hemorrhage, and ischemia, and therefore S100B is often used as a biomarker to assess the severity and prognosis of brain injuries[10]. Three-time points are selected for S100B measurement: before CPB, immediately after the surgery, and on the first postoperative day.

Acute kidney injury after congenital heart surgery (pediatric cardiac surgery-associated acute kidney injury, PCS-AKI) is a common complication in children, with reported incidence ranging from 40% to 60% [11-13]. PCS-AKI is an independent risk factor for mortality and morbidity in hospitalized patients [14-16] and can lead to chronic kidney disease and adverse long-term health problems[17 18]. The diagnostic criteria for AKI in children in present study used the pRIFLE system (the pediatric Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease), which is a classification based on estimated creatinine clearance and urine output as criteria and has been validated in pediatric cardiac surgery patients. pRIFLE system is the most sensitive indicator for detecting AKI, and it is particularly suitable for the early recognition of AKI in infants, young children and low-risk patients [19]. AKI is categorized as stage I (risk), stage II (injury) and stage

III (failure). These stages correspond to a decrease in glomerular filtration rate of 25%, 50% or 75%, respectively. Baseline serum creatinine (SCr) is measured within 48 hours preoperatively. The postoperative maximum level of SCr is recorded within 4 days after surgery.

Study duration and safety

Participation in the study begins with submission of the baseline PedsQL questionnaire and ends with completion of the follow-up PedsQL questionnaire. The patient's caregivers are free to withdraw the child from the study at any time. As this is a very low-risk observational study, there are no guidelines for ending the study early, and the safety data (if applicable) will be summarized.

Definitions of study objectives and other terms

Primary study objective

To further characterize and analyze the relationship between variations in rSO_2 and organ injuries, the following five parameters will be used to describe the rSO_2 variations. (a) Occurrence of brain and kidney injuries; (b) A mean rSO_2 for before, during, and after CPB periods (c) Total duration of all desaturation or oversaturation; (d) Percentage of total desaturation or oversaturation time over total CPB time; and (e) The area-

under-the-curve (AUC) for desaturation or oversaturation for each period and the entire surgery.

Secondary study objectives

Identify perioperative factors associated with injury to the brain and kidney. Such factors include patient, anesthetic, surgical, and physiological factors as mentioned in Section variables for analyses. Also, determine whether the brain and kidney injuries are associated with postoperative changes in quality-of-life scores.

Definition of study periods

While NIRS will be performed throughout the entire anesthetic process, the following three time periods are defined to characterize the anesthetic and surgical process during NIRS monitoring. Pre-CPB is from the beginning of anesthesia induction to the onset of CPB; CPB is from the onset to the end of CPB; and post-CPB is defined as from the end of CPB to completion of the surgery.

Variables for analyses

Patient factors

- Gender (M/F)
- Age at study (months)
- Height (cm)
- Weight (kg)
- American Society of Anesthesiologists (ASA) physical status

- Preoperative hemoglobin and hematocrit level
- Preoperative SCr
- Preoperative left ventricular ejection fraction
- Cyanotic lesions (yes/no)

Surgical factors

- Type of surgery: ventricular septal defect repair, patch or primary closure; atrial septal defect repair; tetralogy of Fallot repair, with or without ventriculostomy; total anomalous pulmonary venous connection repair; double outlet right ventricle repair; others.
- RACHS-2, is a new approach to identifying and risk-stratifying pediatric cardiac surgery using ICD-10 administrative data.
- CPB and aortic cross-clamp time
- Number of attempts to end CPB
- Ventricular fibrillation during weaning
- Extubation time

Physiological factors

Mean arterial pressure, temperature, urine output, hemoglobin, and hematocrit during CPB.

PedsQL quality-of-life survey

An age-appropriate pediatric quality-of-life questionnaire will be given to caregivers on the day of surgery and 30 days after surgery. Each question

will be scored on a 5-point scale, with the lower the score, the better the "quality of life".

- Survey for 1-12 months: 36 questions divided into physical functioning (6), physical symptoms (10), emotional functioning (12), social functioning (4), and cognitive functioning (4).
- Survey for 13-24 months: 45 questions divided into physical functioning (9), physical symptoms (10), emotional functioning (12), social functioning (5), and cognitive functioning (9).
- Survey for 24+ months: 27 questions divided into physical functioning (8), emotional functioning (5), social functioning (5), school functioning, if applicable (3), and cognitive functioning (6).

Prognostic indicators

- Length of postoperative hospital stay
- Hospitalization expenditures

Statistical analysis

Description of baseline data

Basic and population demographic characteristics are summarized using standard descriptive statistics (e.g., mean [SD] or median [IQR] for continuous variables such as age, and percentages for categorical variables such as sex).

Analysis of the primary objective

All subjects who meet the inclusion and exclusion criteria and complete the study will be included in the primary analysis. Descriptive statistics will be used to analyze the primary endpoints throughout anesthesia and for each surgical stage.

(1) Occurrence (%) of brain and kidney injuries.

(2) A mean rSO_2 (IQR) for before, during, and after CPB periods.

(3) Total duration (IQR) of all desaturation or oversaturation.

(4) Percentage (IQR) of total desaturation or oversaturation time over total CPB time.

(5) The AUC of desaturation or oversaturation (IQR).

Analysis of secondary study objectives

A continuous variable will be created for change in S100B protein and a binary outcome variable will be created for the presence or absence of an acute kidney injury event (yes/no) based on the criteria defined in the primary objective. To identify perioperative factors associated with the change in S100B protein and acute kidney injury, we will use the chi-square test or Fisher's exact test for categorical variables and the two-tailed independent samples t-test or the Wilcoxon rank sum test for continuous variables, as appropriate. We will accept a Type I error rate (α) of no more than 0.05.

We will then select variables with p-values less than 0.1 from the univariate analyses to build multivariate linear regression models and

logistic models, respectively, to adjust for confounders. In order to test the association between changes in cerebral/renal oxygen during CPB and the results of the PedsQL (quality of life) survey, a multilevel analysis will be performed. In addition to the main predictor, AUC of desaturation or oversaturation, quality of life scores may be influenced by other factors. These factors include, but are not limited to, general medical condition, type of surgery, postoperative extubation time, and ICU length of stay, all of which may be confounders. Therefore, we will assess the relationship between baseline (day of surgery) quality of life scores and these factors using two-sample t-tests, analysis of variance, Pearson's correlation coefficient, or nonparametric alternatives (e.g., Wilcoxon's rank sum, Kruskal-Wallis ANOVA, or Spearman's rank correlation), as appropriate. If the p-value of the test was less than 0.1, the factor was added to the model as a covariate.

A sensitivity analysis will be performed to test the robustness of the results in order to account for loss to follow-up, using patients with complete PedsQL follow-up measures.

Patient and public involvement

Participants in this study were given the opportunity to provide feedback on the study visit (i.e., the visit was too long, too many question entries). In addition, at the end of the baseline visit, we conducted a survey asking

study participants about their about their current quality of life. We will continue to share study results and updates with participants both online and in person. The purpose of the interviews is twofold: to disseminate study results and to provide participants with the opportunity to ask about their research interests and priorities.

Discussion

The issue of organ injuries, especially neurological and renal injuries during pediatric anesthesia and surgery has been a serious concern in cardiac surgery, which contributes to morbidity, mortality, and the increased use of healthcare resources[20-22]. It is known that intraoperative cerebral perfusion insufficiency and ischemia in infants is a potential cause of cognitive impairment later in life. Inconsistent results from current studies on NIRS techniques for monitoring cerebral oxygenation and whether it reveals insufficient perfusion and ischemia and leads to cognitive impairment. One study found that mean intraoperative brain rSO_2 values were lower in children with unfavorable neurologic outcomes after cardiac surgery [23]. Nevertheless, an international, multicenter, observational study shows that cerebral desaturation seems an unlikely explanation for cognitive dysfunction[20]. Similarly, the results of the current study are inconsistent with regard to the relationship between changes in

intraoperative renal oxygenation and postoperative acute kidney injury, a study reveals that higher average rSO_2 during CPB can predict an increased risk of PCS-AKI [24]. However, another study found that decreased intraoperative renal saturation was associated with increased odds of AKI after cardiopulmonary bypass cardiac surgery in infants [25]. In summary, the organ functional status of the brain and kidney is influenced by a variety of factors and is strongly related to the balance of oxygen supply and demand in the organ on its own, and the predictive ability of intraoperative NIRS monitoring on organ functional status needs to be further verified.

Reporting of study results

Please see Tables 1 – 3. The results for cerebral rSO_2 and renal rSO_2 are reported separately, according to the table above.

Trial status

The protocol version number is 3.0, and the protocol date is March 7, 2024. The date recruitment began on April 22, 2024, with an approximate date of July 2025 for completion of recruitment.

List of abbreviations

NIRS: Near-infrared spectroscopy

rSO_2: Regional oxygen saturation

CPB: Cardiopulmonary bypass

PedsQL: Pediatric Quality-of-Life

RACHS-2: Risk Stratification for Congenital Heart Surgery

S100B: S100 calcium-binding protein B

LVEF: Left ventricular ejection fraction

PCS-AKI: Pediatric cardiac surgery-associated acute kidney injury

pRIFLE: The pediatric Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease

SCr: Serum creatinine

AUC: The area under the curve

ASA: American Society of Anesthesiologists

Declarations

Ethics approval and consent to participate

This prospective observational study was approved by the local ethics committee (Beijing Children's Hospital Institutional Review Board, China, March 28, 2024, IRB [2024]-Y-093-D). The trial was registered with http://www.chictr.org.cn (ChiCTR2400083225; date of registration, April 18, 2024). Our methodology followed the international guidelines for observational studies. Written, informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets collected and/or analyzed during the current study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable

Authors' contributions

ZZ. G: Study design, data collection, and manuscript write-up; JM. Z: Study design, analysis, and interpretation of data; LJ. L and F.W: Study design, data analysis, and critical manuscript revision; ZK. G: Study design, data collection. XX.W and L.H: Data collection and analysis, write up of the manuscript. All authors read and approved the final manuscript.

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Table 1. Demographic and clinic characteristics of the participants

Patient characteristics	All patients	rSO_2 desaturation	rSO_2 oversaturation	P value
Male				
Female				
Age (months)				
Height (cm)				
Weight (kg)				
ASA physical status				
1				
2				
3				

Desaturation: below a rSO2 value 10% less than baseline; Oversaturation, above a rSO2 value 10% more than baseline. Abbreviation: ASA, American Society of Anesthesiologists.

Table 2. Perioperative variables and outcomes

	All patients	rSO_2 desaturation	rSO_2 oversaturation	P value
Outcomes				
Changes in S100B				
PCS-AKI				
Preoperative variables				
Pre-hemoglobin				
Pre-hematocrit				
Pre-SCr				
Pre-LVEF				
Pre-Cyanotic lesions (yes/no)				
Pre-S100B				
Type of surgery				
VSD				
ASD				
TOF				
TAPVC				
DORV				
others				
RACHS-2				
Pre-PedsQL score				
Intraoperative variables				
CPB and aortic cross clamp time				
Aortic cross clamp time				
Number of attempts to end CPB				
Ventricular fibrillation during weaning				
MAP during CPB				
Temperature during CPB				
Urine output during CPB				
Hemoglobin during CPB				
Hematocrit during CPB				
Postoperative variables				
Post-SCr				
Post-S100B				
Extubation time (hour)				
Hospitalization costs				
Post-PedsQL score				

Desaturation: below a rSO2 value 10% less than baseline; Oversaturation, above a rSO2 value 10% more than baseline. Abbreviation: S100B, S100 calcium-binding protein B; PCS-AKI, pediatric cardiac surgery-associated acute kidney injury; SCr, serum creatinine; LVEF, left ventricular ejection fraction; VSD, ventricular septal defect repair; ASD, atrial septal defect repair; TOF, tetralogy of Fallot repair; TAPVC, total anomalous pulmonary venous connection repair; DORV, double outlet right ventricle repair; RACHS-2, Risk Stratification for Congenital Heart Surgery for ICD-10 Administrative Data; PedsQL, Pediatric Quality-of-Life; CPB, cardiopulmonary bypass; MAP, mean arterial pressure.

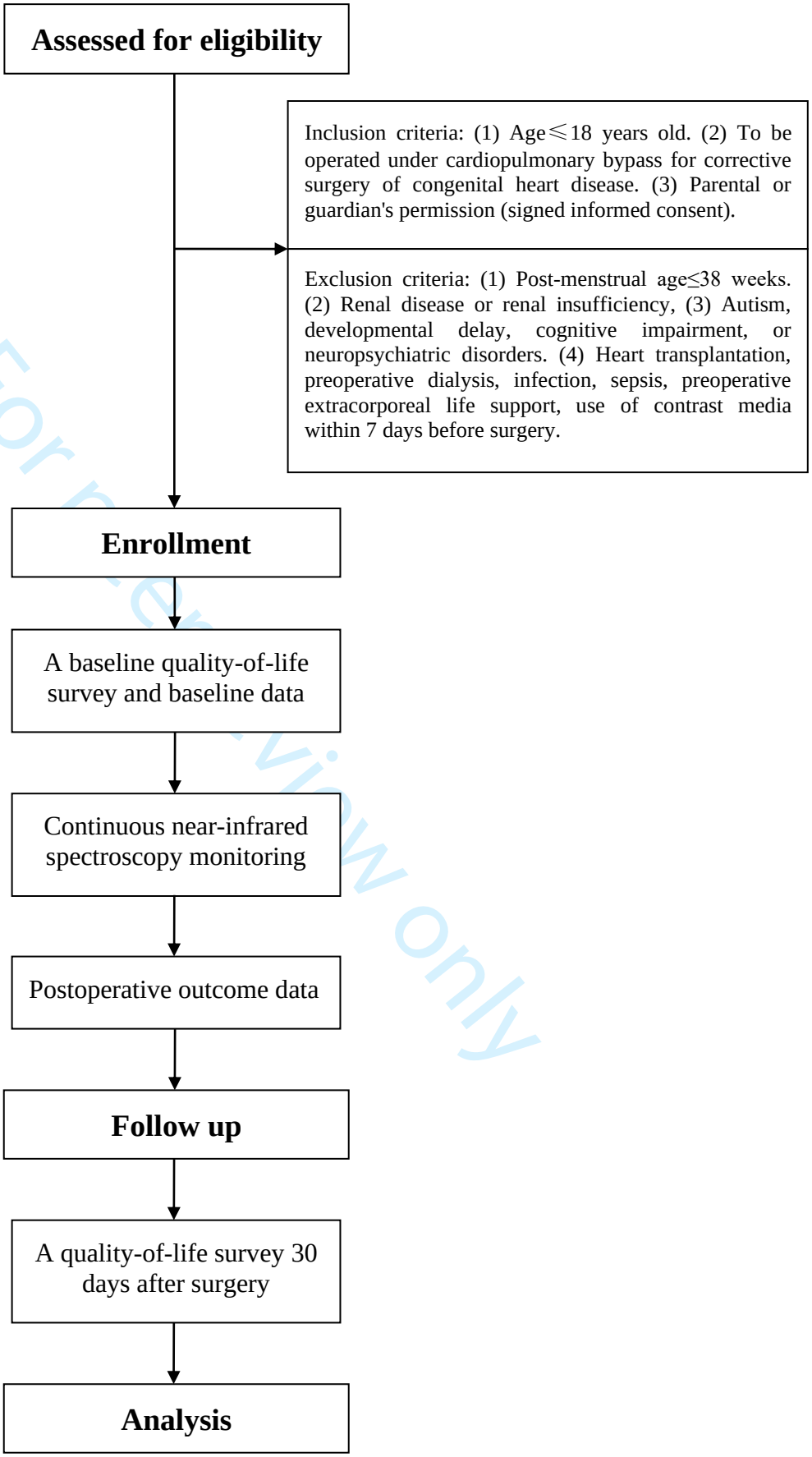
Table3. rSO_2 measurement during surgery

	All	Baseline	Pre-CPB	CPB	Post-CPB
Mean of rSO2					
Desaturation rSO_2 events					
Minimum level					
Total duration					
Percentage of desaturation/total time					
Desaturation AUC					
Oversaturation rSO2 events					
Maximum level					
Total duration					
Percentage of oversaturation/total time					
Oversaturation AUC					

Desaturation: below a rSO_2 value 10% less than baseline; Oversaturation, above a rSO2 value 10% more than baseline. Abbreviation: AUC, area-under-the-curve

Figure Legends

Figure 1. Flow diagram of the patients in the study.



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Near-infrared spectroscopy to monitor cerebral and renal oxygen saturation during cardiopulmonary bypass surgery for pediatric congenital heart disease: study protocol for a prospective observational cohort trial

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Abstract

Background: Current indicators for monitoring intraoperative organ function remain predominantly indirect, delayed, and nonspecific, particularly in pediatric populations undergoing congenital heart surgery, where multifactorial influences further complicate functional assessments. Emerging evidence suggests that the use of near-infrared spectroscopy (NIRS) technology to continuously monitor the regional oxygen saturation (rSO_2) of intraoperative organs can predict the postoperative organ functional status. This study aims to investigate the associations between intraoperative cerebral/renal rSO_2 fluctuations monitored by NIRS and postoperative neurological injury or acute kidney injury (AKI) in pediatric congenital heart disease (CHD) surgery. **Methods:** In this prospective observational cohort study, patients ≤18 years scheduled for CHD surgery under cardiopulmonary bypass (CPB), will be enrolled after obtaining written informed consent. Exclusion criteria include preexisting neuropsychiatric disorders, chronic kidney disease, or other related disorders. Dual-channel NIRS probes will be applied to simultaneously monitor cerebral and renal rSO_2 from anesthesia induction until the patient is transferred to the cardiac care unit. Serum S100 calcium-binding protein B (S100B) levels will be measured before CPB, at the end of the surgery, and on postoperative day 1 to quantify cerebral injury. AKI will be diagnosed using the pediatric Risk,

Injury, Failure, Loss, End-stage renal disease (pRIFLE) criteria based on dynamic creatinine changes. Health-related quality of life will be assessed through the Pediatric Quality of Life Inventory (PedsQL) at preoperative baseline and postoperative day 30. **Discussion:** This protocol hypothesizes that (1) cerebral rSO_2 desaturation during CPB correlates with postoperative S100B elevation (a biomarker of cerebral injury) and (2) renal oxygen saturation changes will predict pRIFLE-defined AKI severity. Furthermore, the study will explore potential linkages between intraoperative rSO_2 variations and quality-of-life outcomes. Successful validation of these associations could establish NIRS as a real-time marker for organ protection strategies in pediatric cardiac surgery.

Ethics and dissemination: This study has been approved by the Institutional Review Board of Beijing Children's Hospital (approval number: [2024]-Y-093-D). Written informed consent will be obtained from all participants before enrollment. The findings of this research will be disseminated through peer-reviewed publications, presentations at relevant conferences, and shared with participating communities via lay summaries and social media platforms.

Trial registration: The study was registered with the Chinese Clinical Trial Registry on 18 April 2024. (Number: ChiCTR2400083225)

Keywords

Near-infrared spectroscopy, Regional oxygen saturation, Cardiopulmonary

bypass, Brain injury, Acute kidney injury.

Strengths and limitations of this study

- This is a prospective cohort study designed to adjust for confounders using regression methods to determine the relationship between regional oxygen saturation and organ injury.
- The study includes detailed monitoring of cerebral and renal oxygen saturation using near-infrared spectroscopy throughout the perioperative period, including desaturation and oversaturation events.
- Multiple prognostic indicators, such as quality-of-life scores, length of hospital stay, and hospitalization costs, are incorporated into the analysis.
- The study is limited by its single-center design, which may affect the generalizability of the findings.
- Data collection relies on continuous NIRS monitoring, which may be subject to technical limitations such as sensor detachment or signal interference.

Background

The intraoperative monitoring of oxygen delivery and consumption in pediatric vital organs faces unique challenges due to developmental factors, including age-dependent physiological variability, body size limitations, and hemodynamic instability. Conventional perioperative indicators, such as lactic acidosis, hypothermia, bradycardia, hypotension,

and oliguria, though routinely monitored perioperatively, provide only indirect and nonspecific warnings of incipient organ dysfunction. Near-infrared spectroscopy (NIRS) has emerged as a noninvasive modality for real-time monitoring of regional tissue oxygen saturation (rSO_2) in both surgical and critical care settings. Accumulating evidence delineates its clinical applications across multiple organ systems.[1 2] There are studies on brain tissue oxygen saturation, abdominal oxygen saturation, and renal oxygen saturation. Some studies have described trends in normal values of rSO_2 in the brain and internal organs of preterm infants, and changes in rSO_2 indices over time may be indicative of the maturation of physiologic oxygen balance in this tissue.[3 4] In children, cerebral rSO_2 below a certain level from baseline during noncardiac surgery can lead to adverse behavioral changes or delirium in the postoperative period.[5 6] It has been suggested that reduced renal rSO_2 in preterm infants is associated with AKI, which is an independent risk factor for mortality and morbidity in hospitalized patients and can lead to chronic kidney disease and adverse long-term health problems. Notably, cerebral and renal functional integrity constitutes pivotal prognostic determinants in pediatric postoperative outcomes.

Altering the state of organ perfusion, oxygen delivery, and energy expenditure can prevent or promote cellular damage (from oxidative stress

and inflammation) and recovery, a state that occurs during cardiac surgery under cardiopulmonary bypass (CPB). Brain regional oxygen saturation, which is characterized by high constant blood flow and high oxygen uptake, and renal tissue oxygen saturation, which is characterized by high blood flow variability and relatively low oxygen uptake, have the potential to be disrupted during cardiopulmonary bypass. In the present study, cerebral/renal rSO_2 monitoring will be continuously performed during surgery for CHD in children and an attempt will be made to investigate its relationship with brain injury and AKI. To evaluate the association between rSO_2 and quality of life after surgery and anesthesia, the Pediatric Quality-of-Life (PedsQL) survey will be given to caregivers on the day of surgery (baseline), and 30 days after surgery.[7]

Methods

Study design

This is a prospective, observational, cohort study. This study has been approved by the ethics committee of Beijing Children's Hospital ([2024]-Y-093-D, protocol amendment number:4.0, issue date: 27 Mar 2024) and is registered in the Chinese clinical trial registry (ChiCTR2400083225). We will strictly adhere to clinical practice guidelines and the Declaration of Helsinki throughout the trial. Participants will include pediatric patients

(age≤18 years) undergoing CHD surgery requiring CPB. Written informed consent will be obtained from legal guardians prior to enrollment.

Objectives

The primary objective is to determine the relationship of cerebral and renal oxygen saturation to brain injury and kidney injury. The secondary objectives are to determine the perioperative factors associated with brain injury and kidney injury and to explore the effects of brain injury and kidney injury on patients' quality of life.

Sample size

The sample size calculation is based on the primary objective of evaluating the relationship between cerebral rSO_2 changes and brain injury. Ten clinically relevant covariates will be included in the multivariate regression model: age, sex, weight, Risk Adjustment for Congenital Heart Surgery-2 (RACHS-2) category, preoperative cyanosis status, baseline hematocrit, left ventricular ejection fraction (LVEF), CPB duration, and mean arterial pressure during CPB. Using the Multiple Regression module in PASS 15.0, the calculation assumes a target coefficient of determination (R^2) of 0.25 with an anticipated effect size of R^2=0.5. With α=0.05 and 90% power, the minimum required sample size is determined to be 117 participants after accounting for 20% attrition (attributable to withdrawal or data collection

errors).

Eligibility criteria

Inclusion criteria: (1) Age⩽18 years old. (2) To be operated under CPB for corrective surgery of congenital heart disease. (3) Parental or guardian's permission (signed informed consent). Exclusion criteria: (1) Post-menstrual age ⩽38 weeks. (2) Renal disease or renal insufficiency. (3) Neuropsychiatric disorders (autism, developmental delay, cognitive impairment). (4) Heart transplantation, preoperative dialysis, infection, sepsis, preoperative extracorporeal life support, use of contrast media within 7 days before surgery.

Study Procedures

The flow of the study is shown in Figure 1. A baseline PedsQL will be administered to caregivers on the day of surgery. A repeat assessment will be conducted at postoperative day 30. All patients will receive standard anesthetic protocols as determined by the attending anesthesiologist. Continuous rSO_2 measurements will be acquired from operating room admission until transfer to the cardiac intensive care unit (CICU). The SenSmart™ Model X-100 Universal Oximetry System (Nonin Medical, Plymouth, MN, USA) will be utilized to record cerebral and renal rSO_2

values at 4-second intervals. Fraction of inspired oxygen will be maintained at 100% throughout the surgery. The forehead and right kidney regions will be inspected for lesions or abrasions prior to electrode application. Under ultrasound guidance, one NIRS sensor electrode will be positioned on the right paravertebral region (T10-L2 vertebral levels), and the other sensor electrode is placed over the forehead and connected to the monitor to start recording rSO_2 data. To avoid electrode detachment, the renal region electrode can be covered with a 3M film and the forehead electrode can be wrapped with an elastic bandage.

Measurement of cerebral rSO_2(C-rSO_2) and renal rSO_2(R-rSO_2)

Real-time rSO_2 values will not be accessible to the anesthesia or perfusion teams to prevent intervention bias. Three distinct perioperative phases will be analyzed: Phase 1: pre-induction baseline. Phase 2: CPB duration. Phase 3: post-CPB period. All 4-second interval measurements within each phase will be averaged to compute mean C-rSO_2/R-rSO_2. We also will evaluate cumulative time spent during CPB at or below a rSO_2 value 10% less than baseline (desaturation) and cumulative time spent at or above a rSO_2 value 10% more than baseline (oversaturation). The 10% threshold for cerebral rSO_2 desaturation is based on established evidence in pediatric populations. While adult studies suggest that a 20% decrease from baseline cerebral

rSO_2 is associated with postoperative cognitive dysfunction,[8] pediatric brains exhibit greater sensitivity to hypoxia. Therefore, we adopted a more conservative threshold of 10%, consistent with Holmgaard et al.'s methods in children undergoing cardiac surgery.[9]

Definition of brain and kidney injury

To recognize brain injury, one method is to assess the concentration of specific markers in plasma, among which the most studied in the pediatric population is S100 calcium-binding protein B (S100B), which is the most abundant calcium-binding protein in neural tissues (especially astrocytes) and is one of the injury-associated molecules released early in brain injury or after primary brain injury, which can lead to secondary injury.[10] S100B is considered a biomarker of traumatic brain injury and has been shown to correlate with the extent of injury, survival, and neurological prognosis.[11] Serum levels of S100B protein are elevated in patients with brain injuries induced by trauma, hemorrhage, and ischemia, and therefore S100B is often used as a biomarker to assess the severity and prognosis of brain injuries.[12] Three-time points are selected for S100B measurement: pre-CPB (baseline), immediate postoperative, and on the first postoperative day.

Acute kidney injury after congenital heart surgery (pediatric cardiac

surgery-associated acute kidney injury, PCS-AKI) is a common complication in children, with reported incidence ranging from 40% to 60%.[13-15] PCS-AKI is an independent risk factor for mortality and morbidity in hospitalized patients[16-18] and can lead to chronic kidney disease and adverse long-term health problems. [19 20]The diagnostic criteria for AKI in children in present study used the pRIFLE system (the pediatric Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease), which is a classification based on estimated creatinine clearance and urine output as criteria and has been validated in pediatric cardiac surgery patients. pRIFLE system is the most sensitive indicator for detecting AKI, and it is particularly suitable for the early recognition of AKI in infants, young children and low-risk patients. [21]AKI is categorized as stage I (risk), stage II (injury) and stage III (failure). These stages correspond to a decrease in glomerular filtration rate of 25%, 50% or 75%, respectively. Baseline serum creatinine (SCr) will be measured within 48 hours preoperatively. The postoperative maximum level of SCr will be obtained within 4 days after surgery.

Study duration and safety

Participation in the study begins with submission of the baseline PedsQL questionnaire and ends with completion of the follow-up PedsQL

questionnaire. The patient's caregivers are free to withdraw the child from the study at any time. As this is a very low-risk observational study, there are no guidelines for ending the study early, and the safety data (if applicable) will be summarized.

Definitions of study objectives and other terms

Primary study objective

To comprehensively evaluate the association between intraoperative rSO_2 fluctuations and organ injuries, five quantitative metrics will be analyzed. (a) Occurrence of brain and kidney injuries; (b) A mean rSO_2 for before, during, and after CPB periods (c) Total duration of all desaturation or oversaturation; (d) Percentage of total desaturation or oversaturation time over total CPB time; and (e) Area-under-the-curve (AUC) for rSO_2 deviations from baseline, calculated separately for each phase and the entire surgical period.

Secondary study objectives

Identify perioperative factors associated with injury to the brain and kidney. Such factors include patient, anesthetic, surgical, and physiological factors as mentioned in Section variables for analyses. Also, determine whether the brain and kidney injuries are associated with postoperative changes in quality-of-life scores.

Definition of study periods

NIRS monitoring will be performed continuously from anesthesia induction until surgery completion. For analytical purposes, the following phases are defined: Pre-CPB: from anesthesia induction to the onset of CPB; CPB: from the onset to the end of CPB; Post-CPB: from the end of CPB to completion of the surgery.

Variables for analyses

Patient factors

- Gender (M/F)
- Age at study (months)
- Height (cm)
- Weight (kg)
- American Society of Anesthesiologists (ASA) physical status
- Preoperative hemoglobin and hematocrit level
- Preoperative SCr
- Preoperative left ventricular ejection fraction
- Cyanotic lesions (yes/no)

Surgical factors

- Type of surgery: ventricular septal defect repair, patch or primary closure; atrial septal defect repair; tetralogy of Fallot repair, with or without ventriculostomy; total anomalous pulmonary venous connection repair; double outlet right ventricle repair; others.

- RACHS-2, is a new approach to identifying and risk-stratifying pediatric cardiac surgery using ICD-10 administrative data.
- CPB and aortic cross-clamp time
- Number of attempts to end CPB
- Ventricular fibrillation during weaning
- Extubation time

Anaesthetic factors

Standard anesthetic medications, including propofol, midazolam, opioids, and end-tidal sevoflurane concentrations, will be recorded and adjusted for as covariates in the analysis.

Physiological factors

Oxyhemoglobin saturation (SpO_2), mean arterial pressure, temperature, urine output, hemoglobin, and hematocrit during CPB.

PedsQL quality-of-life survey

An age-appropriate pediatric quality-of-life questionnaire will be given to caregivers on the day of surgery and 30 days after surgery. Each question will be scored on a 5-point scale, with the lower the score, the better the "quality of life".

- Survey for 1-12 months: 36 questions divided into physical functioning (6), physical symptoms (10), emotional functioning (12), social functioning (4), and cognitive functioning (4).

- Survey for 13-24 months: 45 questions divided into physical functioning (9), physical symptoms (10), emotional functioning (12), social functioning (5), and cognitive functioning (9).
- Survey for 24+ months: 27 questions divided into physical functioning (8), emotional functioning (5), social functioning (5), school functioning, if applicable (3), and cognitive functioning (6).

Prognostic indicators

- Length of postoperative hospital stay
- Hospitalization expenditures

Statistical analysis

Description of baseline data

Basic and population demographic characteristics are summarized using standard descriptive statistics (e.g., mean [SD] or median [IQR] for continuous variables such as age, and percentages for categorical variables such as sex).

Analysis of the primary objective

All subjects who meet the inclusion and exclusion criteria and complete the study will be included in the primary analysis. Descriptive statistics will be used to analyze the primary endpoints throughout anesthesia and for each surgical stage.

(1) Occurrence (%) of brain and kidney injuries.

(2) A mean rSO_2 (IQR) for before, during, and after CPB periods.

(3) Total duration (IQR) of all desaturation or oversaturation.

(4) Percentage (IQR) of total desaturation or oversaturation time over total CPB time.

(5) The AUC of desaturation or oversaturation (IQR).

Analysis of secondary study objectives

A continuous variable will be created for change in S100B protein and a binary outcome variable will be created for the presence or absence of an acute kidney injury event (yes/no) based on the criteria defined in the primary objective. To identify perioperative factors associated with the change in S100B protein and acute kidney injury, we will use the chi-square test or Fisher's exact test for categorical variables and the two-tailed independent samples t-test or the Wilcoxon rank sum test for continuous variables, as appropriate. We will accept a Type I error rate (α) of no more than 0.05.

We will then select variables with p-values less than 0.1 from the univariate analyses to build multivariate linear regression models and logistic models, respectively, to adjust for confounders. In order to test the association between changes in cerebral/renal oxygen during CPB and the results of the PedsQL (quality of life) survey, a multilevel analysis will be performed. In addition to the main predictor, AUC of desaturation or oversaturation, quality of life scores may be influenced by other factors.

These factors include, but are not limited to, general medical condition, type of surgery, postoperative extubation time, and ICU length of stay, all of which may be confounders. Therefore, we will assess the relationship between baseline (day of surgery) quality of life scores and these factors using two-sample t-tests, analysis of variance, Pearson's correlation coefficient, or nonparametric alternatives (e.g., Wilcoxon's rank sum, Kruskal-Wallis ANOVA, or Spearman's rank correlation), as appropriate. If the p-value of the test was less than 0.1, the factor was added to the model as a covariate.

A sensitivity analysis will be performed to test the robustness of the results in order to account for loss to follow-up, using patients with complete PedsQL follow-up measures.

Selection bias

To evaluate potential selection bias, we will conduct a retrospective comparison of baseline characteristics, including age, RACHS-2 score, preoperative LVEF, and orther relevant variables, between enrolled patients and non-participants from the same surgical cohort.

Patient and public involvement

Participants in this study are given the opportunity to provide feedback on the study visit (i.e., the visit is too long, too many question entries). In addition, at the end of the baseline visit, we will conduct a survey asking

study participants about their current quality of life. We will continue to share study results and updates with participants both online and in person. The purpose of the interviews is twofold: to disseminate study results and to provide participants with the opportunity to ask about their research interests and priorities.

Ethics and dissemination

This study has been approved by the Institutional Review Board of Beijing Children's Hospital (approval number: [2024]-Y-093-D), and strictly adheres to the Declaration of Helsinki. Prior to enrollment, written informed consent will be obtained from all participants after detailed disclosure of study objectives, potential risks, and benefits. Participant confidentiality will be ensured through restricted access to anonymized data by authorized investigators only. Participants retain the right to withdraw from the study at any time without penalty. As an investigator-initiated academic trial, the financial compensation is not feasible due to funding limitations. However, participants experiencing treatment-emergent adverse events will receive free medical management at our institution. The results of this research will be presented at academic conferences and published in peer-reviewed journals. The International Committee of Medical Journal Editors guidelines on authorship criteria will be followed, and the manuscript will be drafted and edited by the

authors, not by any professional writers.

Discussion

Organ injuries, particularly neurological and renal complications, remain a significant concern in pediatric cardiac surgery, contributing to increased morbidity, mortality, and healthcare resource utilization.[22-24] It is known that intraoperative cerebral hypoperfusion and ischemia are recognized as potential contributors to long-term cognitive impairment in infants. Despite the widespread use of NIRS for cerebral oxygenation monitoring, its ability to predict perfusion deficits and subsequent cognitive dysfunction remains controversial. One pediatric study demonstrated that lower mean intraoperative cerebral rSO_2 values were associated with unfavorable neurological outcomes.[25] Nevertheless, A large international multicenter study suggested that cerebral desaturation is unlikely to fully explain postoperative cognitive dysfunction.[24] Similarly, the relationship between intraoperative renal oxygenation and postoperative AKI is similarly inconsistent. Higher average renal rSO_2 during CPB has been linked to an increased risk of PCS-AKI.[26] Conversely, another study reported that decreased intraoperative renal saturation was associated with higher odds of AKI in infants.[27] In summary, organ functional status is influenced by multifactorial determinants, including the delicate balance between oxygen supply and

demand. The predictive utility of intraoperative NIRS monitoring for organ outcomes requires further validation through well-designed prospective studies. The identification of reliable NIRS thresholds for organ protection could significantly improve perioperative management strategies in pediatric cardiac surgery.

Reporting of study results

Please see Tables 1 – 3. The results for cerebral rSO_2 and renal rSO_2 are reported separately, according to the table above.

Trial status

The protocol version number is 3.0, and the protocol date is March 7, 2024. The date recruitment began on April 22, 2024, with an approximate date of July 2025 for completion of recruitment.

List of abbreviations

NIRS: Near-infrared spectroscopy

rSO_2: Regional oxygen saturation

CPB: Cardiopulmonary bypass

PedsQL: Pediatric Quality-of-Life

RACHS-2: Risk Stratification for Congenital Heart Surgery

S100B: S100 calcium-binding protein B

LVEF: Left ventricular ejection fraction

PCS-AKI: Pediatric cardiac surgery-associated acute kidney injury

pRIFLE: The pediatric Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease

SCr: Serum creatinine

AUC: The area under the curve

ASA: American Society of Anesthesiologists

Declarations

Ethics approval and consent to participate

This prospective observational study was approved by the local ethics committee (Beijing Children's Hospital Institutional Review Board, China, March 28, 2024, IRB [2024]-Y-093-D). The trial was registered with http://www.chictr.org.cn (ChiCTR2400083225; date of registration, April 18, 2024). Our methodology will follow the international guidelines for observational studies. Written informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets collected and/or analyzed during the current study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

ZZ. G: Study design, data collection, and manuscript write-up; JM. Z: Study design, analysis, and interpretation of data; LJ. L and F.W: Study design, data analysis, and critical manuscript revision; ZK. G: Study design, data collection. XX.W and L.H: Data collection and analysis, write up of the manuscript. All authors read and approved the final manuscript. ZZ.G is the guarantor.

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Table 1. Demographic and clinic characteristics of the participants

Patient characteristics	All patients	rSO_2 desaturation	rSO_2 oversaturation	P value
Male				
Female				
Age (months)				
Height (cm)				
Weight (kg)				
ASA physical status				
1				
2				
3				

Desaturation: below a rSO_2 value 10% less than baseline; Oversaturation, above a rSO_2 value 10% more than baseline. Abbreviation: ASA, American Society of Anesthesiologists.

Table 2. Perioperative variables and outcomes

	All patients	rSO_2 desaturation	rSO_2 oversaturation	P value
Outcomes				
Changes in S100B				
PCS-AKI				
Preoperative variables				
Pre-hemoglobin				
Pre-hematocrit				
Pre-SCr				
Pre-LVEF				
Pre-Cyanotic lesions (yes/no)				
Pre-S100B				
Type of surgery				
VSD				
ASD				
TOF				
TAPVC				
DORV				
others				
RACHS-2				
Pre-PedsQL score				
Anaesthetic durgs				
Propofol				
Midazolam				
Opioid				
End-tidal of sevoflurane				
Intraoperative variables				
CPB and aortic cross clamp time				
Aortic cross clamp time				
Number of attempts to end CPB				
Ventricular fibrillation during weaning				
SPO_2 during CPB				
MAP during CPB				
Temperature during CPB				
Urine output during CPB				
Hemoglobin during CPB				
Hematocrit during CPB				
Postoperative variables				
Post-SCr				
Post-S100B				
Extubation time (hour)				
Hospitalization costs				
Post-PedsQL score				

Desaturation: below a rSO_2 value 10% less than baseline; Oversaturation, above a rSO_2 value 10% more than baseline. Abbreviation: S100B, S100 calcium-binding protein B; PCS-AKI, pediatric cardiac surgery-associated acute kidney injury; SCr, serum creatinine; LVEF, left ventricular ejection fraction; VSD, ventricular septal defect repair; ASD, atrial septal defect repair; TOF, tetralogy of Fallot repair; TAPVC, total anomalous pulmonary venous connection repair; DORV, double outlet right ventricle repair; RACHS-2, Risk Stratification for Congenital Heart Surgery for ICD-10 Administrative Data; PedsQL, Pediatric Quality-of-Life; CPB, cardiopulmonary bypass; MAP, mean arterial pressure.

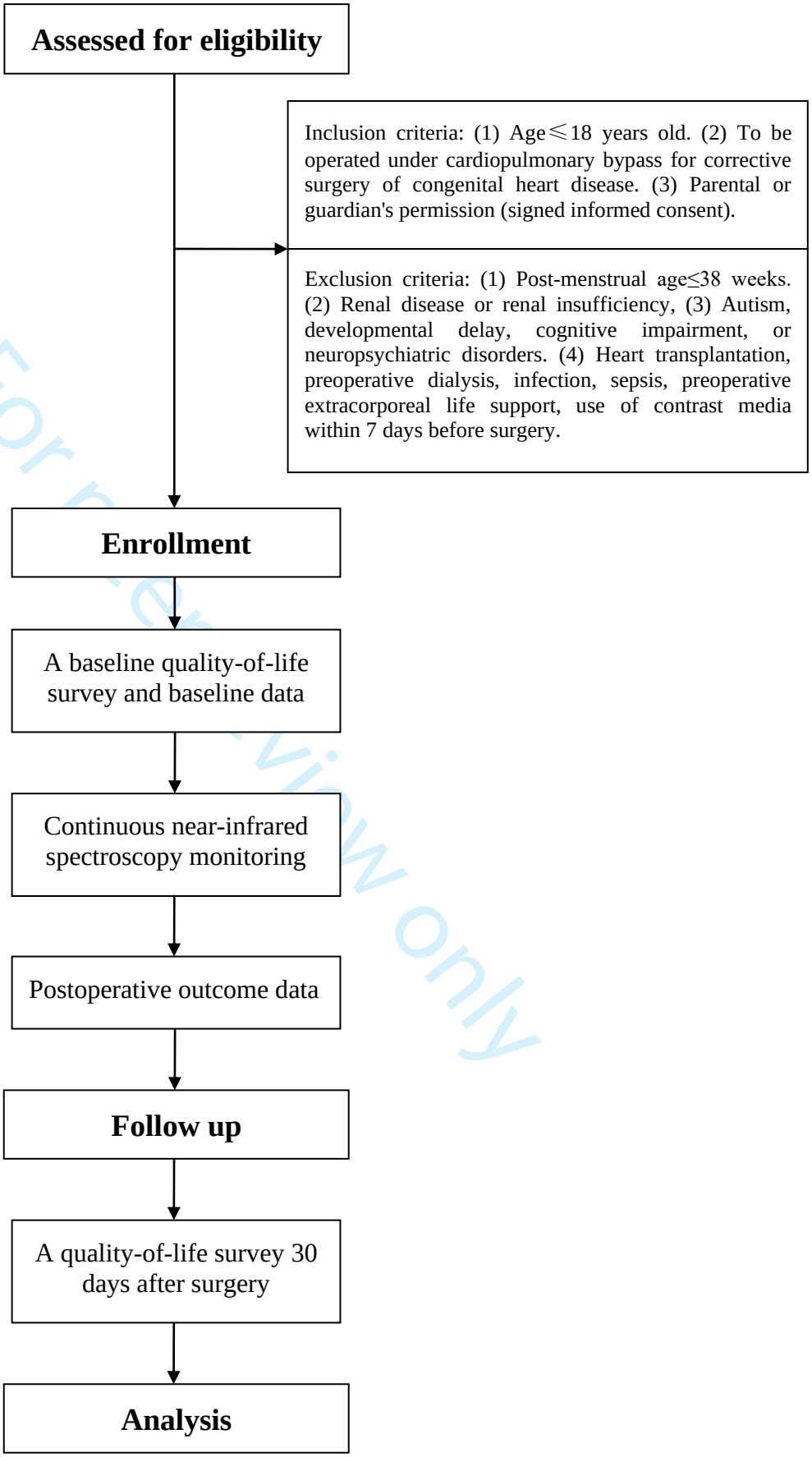
Table3. rSO_2 measurement during surgery

	All	Baseline	Pre-CPB	CPB	Post-CPB
Mean of rSO2					
Desaturation rSO_2 events					
Minimum level					
Total duration					
Percentage of desaturation/total time					
Desaturation AUC					
Oversaturation rSO2 events					
Maximum level					
Total duration					
Percentage of oversaturation/total time					
Oversaturation AUC					

Desaturation: below a rSO_2 value 10% less than baseline; Oversaturation, above a rSO_2 value 10% more than baseline. Abbreviation: AUC, area-under-the-curve

Figure Legends

Figure 1. Flow diagram of the patients in the study.



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Near-infrared spectroscopy to monitor cerebral and renal oxygen saturation during cardiopulmonary bypass surgery for pediatric congenital heart disease: study protocol for a prospective observational cohort trial

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Near-infrared spectroscopy to monitor cerebral and renal oxygen saturation during cardiopulmonary bypass surgery for pediatric congenital heart disease: study protocol for a prospective observational cohort trial

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Abstract

Background: Current indicators for monitoring intraoperative organ function remain predominantly indirect, delayed, and nonspecific, particularly in pediatric populations undergoing congenital heart surgery, where multifactorial influences further complicate functional assessments. Emerging evidence suggests that the use of near-infrared spectroscopy (NIRS) technology to continuously monitor the regional oxygen saturation (rSO_2) of intraoperative organs can predict the postoperative organ functional status. This study aims to investigate the associations between intraoperative cerebral/renal rSO_2 fluctuations monitored by NIRS and postoperative neurological injury or acute kidney injury (AKI) in pediatric congenital heart disease (CHD) surgery. **Methods and Analysis:** In this prospective observational cohort study, patients ≤18 years scheduled for CHD surgery under cardiopulmonary bypass (CPB), will be enrolled after obtaining written informed consent. Exclusion criteria include preexisting neuropsychiatric disorders, chronic kidney disease, or other related disorders. Dual-channel NIRS probes will be applied to simultaneously monitor cerebral and renal rSO_2 from anesthesia induction until the patient is transferred to the cardiac care unit. Serum S100 calcium-binding protein B (S100B) levels will be measured before CPB, at the end of the surgery, and on postoperative day 1 to quantify cerebral injury. AKI will be diagnosed using the pediatric

Risk, Injury, Failure, Loss, End-stage renal disease (pRIFLE) criteria based on dynamic creatinine changes. Health-related quality of life will be assessed through the Pediatric Quality of Life Inventory (PedsQL) at preoperative baseline and postoperative day 30.

Ethics and dissemination: This study has been approved by the Institutional Review Board of Beijing Children's Hospital (approval number: [2024]-Y-093-D). Prior to enrollment, written informed consent will be obtained from the parents or legal guardians of all participating minors. The findings of this research will be disseminated through peer-reviewed publications, presentations at relevant conferences, and shared with participating communities via lay summaries and social media platforms.

Trial registration: The study was registered with the Chinese Clinical Trial Registry on 18 April 2024. (Number: ChiCTR2400083225)

Keywords

Near-infrared spectroscopy, Regional oxygen saturation, Cardiopulmonary bypass, Brain injury, Acute kidney injury.

Strengths and limitations of this study

- This is a prospective cohort study designed to adjust for confounders using regression methods to determine the relationship between regional oxygen saturation and organ injury.
- The study includes detailed monitoring of cerebral and renal oxygen

saturation using near-infrared spectroscopy throughout the perioperative period, including desaturation and oversaturation events.

- Multiple prognostic indicators, such as quality-of-life scores, length of hospital stay, and hospitalization costs, are incorporated into the analysis.
- The study is limited by its single-center design, which may affect the generalizability of the findings.
- Data collection relies on continuous NIRS monitoring, which may be subject to technical limitations such as sensor detachment or signal interference.

Background

The intraoperative monitoring of oxygen delivery and consumption in pediatric vital organs faces unique challenges due to developmental factors, including age-dependent physiological variability, body size limitations, and hemodynamic instability. Conventional perioperative indicators, such as lactic acidosis, hypothermia, bradycardia, hypotension, and oliguria, though routinely monitored perioperatively, provide only indirect and nonspecific warnings of incipient organ dysfunction. Near-infrared spectroscopy (NIRS) has emerged as a noninvasive modality for real-time monitoring of regional tissue oxygen saturation (rSO_2) in both surgical and critical care settings. Accumulating evidence delineates its clinical applications across multiple organ systems.[1 2] There are studies on

brain tissue oxygen saturation, abdominal oxygen saturation, and renal oxygen saturation. Some studies have described trends in normal values of rSO_2 in the brain and internal organs of preterm infants, and changes in rSO_2 indices over time may be indicative of the maturation of physiologic oxygen balance in this tissue.[3 4] In children, cerebral rSO_2 below a certain level from baseline during noncardiac surgery can lead to adverse behavioral changes or delirium in the postoperative period.[5 6] It has been suggested that reduced renal rSO_2 in preterm infants is associated with AKI, which is an independent risk factor for mortality and morbidity in hospitalized patients and can lead to chronic kidney disease and adverse long-term health problems. Notably, cerebral and renal functional integrity constitutes pivotal prognostic determinants in pediatric postoperative outcomes.

Altering the state of organ perfusion, oxygen delivery, and energy expenditure can prevent or promote cellular damage (from oxidative stress and inflammation) and recovery, a state that occurs during cardiac surgery under cardiopulmonary bypass (CPB). Brain regional oxygen saturation, which is characterized by high constant blood flow and high oxygen uptake, and renal tissue oxygen saturation, which is characterized by high blood flow variability and relatively low oxygen uptake, have the potential to be disrupted during cardiopulmonary bypass. In the present study,

cerebral/renal rSO_2 monitoring will be continuously performed during surgery for CHD in children and an attempt will be made to investigate its relationship with brain injury and AKI. To evaluate the association between rSO_2 and quality of life after surgery and anesthesia, the Pediatric Quality-of-Life (PedsQL) survey will be given to caregivers on the day of surgery (baseline), and 30 days after surgery.[7]

Methods

Study design

This is a prospective, observational, cohort study. This study has been approved by the ethics committee of Beijing Children's Hospital ([2024]-Y-093-D, protocol amendment number:4.0, issue date: 27 Mar 2024) and is registered in the Chinese clinical trial registry (ChiCTR2400083225). We will strictly adhere to clinical practice guidelines and the Declaration of Helsinki throughout the trial. Participants will include pediatric patients (age≤18 years) undergoing CHD surgery requiring CPB. Written informed consent will be obtained from legal guardians prior to enrollment.

Objectives

The primary objective is to determine the relationship of cerebral and renal oxygen saturation to brain injury and kidney injury. The secondary objectives are to determine the perioperative factors associated with brain

injury and kidney injury and to explore the effects of brain injury and kidney injury on patients' quality of life.

Sample size

The sample size calculation is based on the primary objective of evaluating the relationship between cerebral rSO_2 changes and brain injury. Ten clinically relevant covariates will be included in the multivariate regression model: age, sex, weight, Risk Adjustment for Congenital Heart Surgery-2 (RACHS-2) category, preoperative cyanosis status, baseline hematocrit, left ventricular ejection fraction (LVEF), CPB duration, and mean arterial pressure during CPB. Using the Multiple Regression module in PASS 15.0, the calculation assumes a target coefficient of determination (R^2) of 0.25 with an anticipated effect size of $R^2=0.5$. With $\alpha=0.05$ and 90% power, the minimum required sample size is determined to be 117 participants after accounting for 20% attrition (attributable to withdrawal or data collection errors).

Eligibility criteria

Inclusion criteria: (1) Age$\leqslant$18 years old. (2) To be operated under CPB for corrective surgery of congenital heart disease. (3) Parental or guardian's permission (signed informed consent). Exclusion criteria: (1) Post-menstrual age $\leqslant$38 weeks. (2) Renal disease or renal insufficiency. (3)

Neuropsychiatric disorders (autism, developmental delay, cognitive impairment). (4) Heart transplantation, preoperative dialysis, infection, sepsis, preoperative extracorporeal life support, use of contrast media within 7 days before surgery.

Study Procedures

The flow of the study is shown in Figure 1. A baseline PedsQL will be administered to caregivers on the day of surgery. A repeat assessment will be conducted at postoperative day 30. All patients will receive standard anesthetic protocols as determined by the attending anesthesiologist. Continuous rSO_2 measurements will be acquired from operating room admission until transfer to the cardiac intensive care unit (CICU). The SenSmart™ Model X-100 Universal Oximetry System (Nonin Medical, Plymouth, MN, USA) will be utilized to record cerebral and renal rSO_2 values at 4-second intervals. Fraction of inspired oxygen will be maintained at 100% throughout the surgery. The forehead and right kidney regions will be inspected for lesions or abrasions prior to electrode application. Under ultrasound guidance, one NIRS sensor electrode will be positioned on the right paravertebral region (T10-L2 vertebral levels), and the other sensor electrode is placed over the forehead and connected to the monitor to start recording rSO_2 data. To avoid electrode detachment, the

renal region electrode can be covered with a 3M film and the forehead electrode can be wrapped with an elastic bandage.

Measurement of cerebral rSO_2(C-rSO_2) and renal rSO_2(R-rSO_2)

Real-time rSO_2 values will not be accessible to the anesthesia or perfusion teams to prevent intervention bias. Three distinct perioperative phases will be analyzed: Phase 1: pre-induction baseline. Phase 2: CPB duration. Phase 3: post-CPB period. All 4-second interval measurements within each phase will be averaged to compute mean C-rSO_2/R-rSO_2. We also will evaluate cumulative time spent during CPB at or below a rSO_2 value 10% less than baseline (desaturation) and cumulative time spent at or above a rSO_2 value 10% more than baseline (oversaturation). The 10% threshold for cerebral rSO_2 desaturation is based on established evidence in pediatric populations. While adult studies suggest that a 20% decrease from baseline cerebral rSO_2 is associated with postoperative cognitive dysfunction,[8] pediatric brains exhibit greater sensitivity to hypoxia. Therefore, we adopted a more conservative threshold of 10%, consistent with Holmgaard et al.'s methods in children undergoing cardiac surgery.[9]

Definition of brain and kidney injury

To recognize brain injury, one method is to assess the concentration of

specific markers in plasma, among which the most studied in the pediatric population is S100 calcium-binding protein B (S100B), which is the most abundant calcium-binding protein in neural tissues (especially astrocytes) and is one of the injury-associated molecules released early in brain injury or after primary brain injury, which can lead to secondary injury.[10] S100B is considered a biomarker of traumatic brain injury and has been shown to correlate with the extent of injury, survival, and neurological prognosis.[11] Serum levels of S100B protein are elevated in patients with brain injuries induced by trauma, hemorrhage, and ischemia, and therefore S100B is often used as a biomarker to assess the severity and prognosis of brain injuries.[12] Three-time points are selected for S100B measurement: pre-CPB (baseline), immediate postoperative, and on the first postoperative day.

Acute kidney injury after congenital heart surgery (pediatric cardiac surgery-associated acute kidney injury, PCS-AKI) is a common complication in children, with reported incidence ranging from 40% to 60%.[13-15] PCS-AKI is an independent risk factor for mortality and morbidity in hospitalized patients[16-18] and can lead to chronic kidney disease and adverse long-term health problems. [19 20]The diagnostic criteria for AKI in children in present study used the pRIFLE system (the pediatric Risk for renal dysfunction, Injury to the kidney, Failure of kidney function,

Loss of kidney function, and End-stage renal disease), which is a classification based on estimated creatinine clearance and urine output as criteria and has been validated in pediatric cardiac surgery patients. pRIFLE system is the most sensitive indicator for detecting AKI, and it is particularly suitable for the early recognition of AKI in infants, young children and low-risk patients. [21]AKI is categorized as stage I (risk), stage II (injury) and stage III (failure). These stages correspond to a decrease in glomerular filtration rate of 25%, 50% or 75%, respectively. Baseline serum creatinine (SCr) will be measured within 48 hours preoperatively. The postoperative maximum level of SCr will be obtained within 4 days after surgery.

Study duration and safety

Participation in the study begins with submission of the baseline PedsQL questionnaire and ends with completion of the follow-up PedsQL questionnaire. The patient's caregivers are free to withdraw the child from the study at any time. As this is a very low-risk observational study, there are no guidelines for ending the study early, and the safety data (if applicable) will be summarized.

Definitions of study objectives and other terms

Primary study objective

To comprehensively evaluate the association between intraoperative rSO_2 fluctuations and organ injuries, five quantitative metrics will be analyzed. (a) Occurrence of brain and kidney injuries; (b) A mean rSO_2 for before, during, and after CPB periods (c) Total duration of all desaturation or oversaturation; (d) Percentage of total desaturation or oversaturation time over total CPB time; and (e) Area-under-the-curve (AUC) for rSO_2 deviations from baseline, calculated separately for each phase and the entire surgical period.

Secondary study objectives

Identify perioperative factors associated with injury to the brain and kidney. Such factors include patient, anesthetic, surgical, and physiological factors as mentioned in Section variables for analyses. Also, determine whether the brain and kidney injuries are associated with postoperative changes in quality-of-life scores.

Definition of study periods

NIRS monitoring will be performed continuously from anesthesia induction until surgery completion. For analytical purposes, the following phases are defined: Pre-CPB: from anesthesia induction to the onset of CPB; CPB: from the onset to the end of CPB; Post-CPB: from the end of CPB to completion of the surgery.

Variables for analyses

Patient factors

- Gender (M/F)
- Age at study (months)
- Height (cm)
- Weight (kg)
- American Society of Anesthesiologists (ASA) physical status
- Preoperative hemoglobin and hematocrit level
- Preoperative SCr
- Preoperative left ventricular ejection fraction
- Cyanotic lesions (yes/no)

Surgical factors

- Type of surgery: ventricular septal defect repair, patch or primary closure; atrial septal defect repair; tetralogy of Fallot repair, with or without ventriculostomy; total anomalous pulmonary venous connection repair; double outlet right ventricle repair; others.
- RACHS-2, is a new approach to identifying and risk-stratifying pediatric cardiac surgery using ICD-10 administrative data.
- CPB and aortic cross-clamp time
- Number of attempts to end CPB
- Ventricular fibrillation during weaning
- Extubation time

Anaesthetic factors

Standard anesthetic medications, including propofol, midazolam, opioids, and end-tidal sevoflurane concentrations, will be recorded and adjusted for as covariates in the analysis.

Physiological factors

Oxyhemoglobin saturation (SpO_2), mean arterial pressure, temperature, urine output, hemoglobin, and hematocrit during CPB.

PedsQL quality-of-life survey

An age-appropriate pediatric quality-of-life questionnaire will be given to caregivers on the day of surgery and 30 days after surgery. Each question will be scored on a 5-point scale, with the lower the score, the better the "quality of life".

- Survey for 1-12 months: 36 questions divided into physical functioning (6), physical symptoms (10), emotional functioning (12), social functioning (4), and cognitive functioning (4).
- Survey for 13-24 months: 45 questions divided into physical functioning (9), physical symptoms (10), emotional functioning (12), social functioning (5), and cognitive functioning (9).
- Survey for 24+ months: 27 questions divided into physical functioning (8), emotional functioning (5), social functioning (5), school functioning, if applicable (3), and cognitive functioning (6).

Prognostic indicators

- Length of postoperative hospital stay
- Hospitalization expenditures

Statistical analysis

Description of baseline data

Basic and population demographic characteristics are summarized using standard descriptive statistics (e.g., mean [SD] or median [IQR] for continuous variables such as age, and percentages for categorical variables such as sex).

Analysis of the primary objective

All subjects who meet the inclusion and exclusion criteria and complete the study will be included in the primary analysis. Descriptive statistics will be used to analyze the primary endpoints throughout anesthesia and for each surgical stage.

(1) Occurrence (%) of brain and kidney injuries.

(2) A mean rSO_2 (IQR) for before, during, and after CPB periods.

(3) Total duration (IQR) of all desaturation or oversaturation.

(4) Percentage (IQR) of total desaturation or oversaturation time over total CPB time.

(5) The AUC of desaturation or oversaturation (IQR).

Analysis of secondary study objectives

A continuous variable will be created for change in S100B protein and a

binary outcome variable will be created for the presence or absence of an acute kidney injury event (yes/no) based on the criteria defined in the primary objective. To identify perioperative factors associated with the change in S100B protein and acute kidney injury, we will use the chi-square test or Fisher's exact test for categorical variables and the two-tailed independent samples t-test or the Wilcoxon rank sum test for continuous variables, as appropriate. We will accept a Type I error rate (α) of no more than 0.05.

We will then select variables with p-values less than 0.1 from the univariate analyses to build multivariate linear regression models and logistic models, respectively, to adjust for confounders. In order to test the association between changes in cerebral/renal oxygen during CPB and the results of the PedsQL (quality of life) survey, a multilevel analysis will be performed. In addition to the main predictor, AUC of desaturation or oversaturation, quality of life scores may be influenced by other factors. These factors include, but are not limited to, general medical condition, type of surgery, postoperative extubation time, and ICU length of stay, all of which may be confounders. Therefore, we will assess the relationship between baseline (day of surgery) quality of life scores and these factors using two-sample t-tests, analysis of variance, Pearson's correlation coefficient, or nonparametric alternatives (e.g., Wilcoxon's rank sum,

Kruskal-Wallis ANOVA, or Spearman's rank correlation), as appropriate. If the p-value of the test was less than 0.1, the factor was added to the model as a covariate.

A sensitivity analysis will be performed to test the robustness of the results in order to account for loss to follow-up, using patients with complete PedsQL follow-up measures.

Selection bias

To evaluate potential selection bias, we will conduct a retrospective comparison of baseline characteristics, including age, RACHS-2 score, preoperative LVEF, and orther relevant variables, between enrolled patients and non-participants from the same surgical cohort.

Patient and public involvement

Participants in this study are given the opportunity to provide feedback on the study visit (i.e., the visit is too long, too many question entries). In addition, at the end of the baseline visit, we will conduct a survey asking study participants about their current quality of life. We will continue to share study results and updates with participants both online and in person. The purpose of the interviews is twofold: to disseminate study results and to provide participants with the opportunity to ask about their research interests and priorities.

Ethics and dissemination

This study has been approved by the Institutional Review Board of Beijing Children's Hospital (approval number: [2024]-Y-093-D), and strictly adheres to the Declaration of Helsinki. Prior to enrollment, written informed consent will be obtained from all participants after detailed disclosure of study objectives, potential risks, and benefits. Participant confidentiality will be ensured through restricted access to anonymized data by authorized investigators only. Participants retain the right to withdraw from the study at any time without penalty. As an investigator-initiated academic trial, the financial compensation is not feasible due to funding limitations. However, participants experiencing treatment-emergent adverse events will receive free medical management at our institution. The results of this research will be presented at academic conferences and published in peer-reviewed journals. The International Committee of Medical Journal Editors guidelines on authorship criteria will be followed, and the manuscript will be drafted and edited by the authors, not by any professional writers.

Discussion

Organ injuries, particularly neurological and renal complications, remain a significant concern in pediatric cardiac surgery, contributing to increased morbidity, mortality, and healthcare resource utilization.[22-24] It is known that intraoperative cerebral hypoperfusion and ischemia are recognized as

potential contributors to long-term cognitive impairment in infants. Despite the widespread use of NIRS for cerebral oxygenation monitoring, its ability to predict perfusion deficits and subsequent cognitive dysfunction remains controversial. One pediatric study demonstrated that lower mean intraoperative cerebral rSO_2 values were associated with unfavorable neurological outcomes.[25] Nevertheless, A large international multicenter study suggested that cerebral desaturation is unlikely to fully explain postoperative cognitive dysfunction.[24] Similarly, the relationship between intraoperative renal oxygenation and postoperative AKI is similarly inconsistent. Higher average renal rSO_2 during CPB has been linked to an increased risk of PCS-AKI.[26] Conversely, another study reported that decreased intraoperative renal saturation was associated with higher odds of AKI in infants.[27] In summary, organ functional status is influenced by multifactorial determinants, including the delicate balance between oxygen supply and demand. The predictive utility of intraoperative NIRS monitoring for organ outcomes requires further validation through well-designed prospective studies. The identification of reliable NIRS thresholds for organ protection could significantly improve perioperative management strategies in pediatric cardiac surgery.

Reporting of study results

Please see Tables 1 – 3. The results for cerebral rSO_2 and renal rSO_2 are reported separately, according to the table above.

Trial status

The protocol version number is 3.0, and the protocol date is March 7, 2024. The date recruitment began on April 22, 2024, with an approximate date of July 2025 for completion of recruitment.

List of abbreviations

NIRS: Near-infrared spectroscopy

rSO_2: Regional oxygen saturation

CPB: Cardiopulmonary bypass

PedsQL: Pediatric Quality-of-Life

RACHS-2: Risk Stratification for Congenital Heart Surgery

S100B: S100 calcium-binding protein B

LVEF: Left ventricular ejection fraction

PCS-AKI: Pediatric cardiac surgery-associated acute kidney injury

pRIFLE: The pediatric Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease

SCr: Serum creatinine

AUC: The area under the curve

ASA: American Society of Anesthesiologists

Declarations

Ethics approval and consent to participate

This prospective observational study was approved by the local ethics committee (Beijing Children's Hospital Institutional Review Board, China, March 28, 2024, IRB [2024]-Y-093-D). The trial was registered with http://www.chictr.org.cn (ChiCTR2400083225; date of registration, April 18, 2024). Our methodology will follow the international guidelines for observational studies. Written informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets collected and/or analyzed during the current study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

ZZ. G: Study design, data collection, and manuscript write-up; JM. Z: Study design, analysis, and interpretation of data; LJ. L and F.W: Study design, data analysis, and critical manuscript revision; ZK. G: Study design,

data collection. XX.W and L.H: Data collection and analysis, write up of the manuscript. All authors read and approved the final manuscript. ZZ.G is the guarantor.

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Table 1. Demographic and clinic characteristics of the participants

Patient characteristics	All patients	rSO_2 desaturation	rSO_2 oversaturation	P value
Male				
Female				
Age (months)				
Height (cm)				
Weight (kg)				
ASA physical status				
1				
2				
3				

Desaturation: below a rSO_2 value 10% less than baseline; Oversaturation, above a rSO_2 value 10% more than baseline. Abbreviation: ASA, American Society of Anesthesiologists.

Table 2. Perioperative variables and outcomes

	All patients	rSO_2 desaturation	rSO_2 oversaturation	P value
Outcomes				
Changes in S100B				
PCS-AKI				
Preoperative variables				
Pre-hemoglobin				
Pre-hematocrit				
Pre-SCr				
Pre-LVEF				
Pre-Cyanotic lesions (yes/no)				
Pre-S100B				
Type of surgery				
VSD				
ASD				
TOF				
TAPVC				
DORV				
others				
RACHS-2				
Pre-PedsQL score				
Anaesthetic durgs				
Propofol				
Midazolam				
Opioid				
End-tidal of sevoflurane				
Intraoperative variables				
CPB and aortic cross clamp time				
Aortic cross clamp time				
Number of attempts to end CPB				
Ventricular fibrillation during weaning				
SPO_2 during CPB				
MAP during CPB				
Temperature during CPB				
Urine output during CPB				
Hemoglobin during CPB				
Hematocrit during CPB				
Postoperative variables				
Post-SCr				
Post-S100B				
Extubation time (hour)				
Hospitalization costs				
Post-PedsQL score				

Desaturation: below a rSO_2 value 10% less than baseline; Oversaturation, above a rSO_2 value 10% more than baseline. Abbreviation: S100B, S100 calcium-binding protein B; PCS-AKI, pediatric cardiac surgery-associated acute kidney injury; SCr, serum creatinine; LVEF, left ventricular ejection fraction; VSD, ventricular septal defect repair; ASD, atrial septal defect repair; TOF, tetralogy of Fallot repair; TAPVC, total anomalous pulmonary venous connection repair; DORV, double outlet right ventricle repair; RACHS-2, Risk Stratification for Congenital Heart Surgery for ICD-10 Administrative Data; PedsQL, Pediatric Quality-of-Life; CPB, cardiopulmonary bypass; MAP, mean arterial pressure.

Table3. rSO_2 measurement during surgery

	All	Baseline	Pre-CPB	CPB	Post-CPB
Mean of rSO2					
Desaturation rSO_2 events					
Minimum level					
Total duration					
Percentage of desaturation/total time					
Desaturation AUC					
Oversaturation rSO2 events					
Maximum level					
Total duration					
Percentage of oversaturation/total time					
Oversaturation AUC					

Desaturation: below a rSO_2 value 10% less than baseline; Oversaturation, above a rSO_2 value 10% more than baseline. Abbreviation: AUC, area-under-the-curve

Figure Legends

Figure 1. Flow diagram of the patients in the study.