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Improving outcomes for infants after cardiopulmonary bypass surgery for congenital heart disease: a commentary on recent randomized controlled trials

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Abstract

The recent NITRIC and STRESS trials demonstrate opportunities to perform pragmatic large randomized trials in congenital heart disease. We discuss lessons learnt from these trials which can inform future trial design and conduct in the field of pediatric heart surgery.

Keywords

cardiopulmonary bypass; congenital heart disease; critical care; infant; surgery; trial

Congenital heart disease (CHD) represents one of the most common congenital malformations, affecting >40,000 births annually in the United States, many of which

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require surgery during the first months of life (1). Furthermore, post-operative mortality is now <2% in many centers for most lesions, and the number of adult survivors of CHD keeps increasing (2) with considerable burden related to neuromotor, cognitive, behavioural, and psychological long-term sequelae (3, 4). In 2010, the NIH-funded Pediatric Heart Network called for randomized clinical trials (RCTs) to enhance the evidence base for novel interventions which could improve outcomes of children with CHD (5).

Paucity of trials for optimum CHD perioperative management

Despite the impressive success in infant heart surgery outcomes, operative and perioperative management remains guided by expert opinion, consensus guidelines, observational studies, and local preference. Since the publication of the Prophylactic Intravenous Use of **Milrinone** After Cardiac Operation in Pediatrics (PRIMACORP) study (6) in 2003, which randomized 238 patients to two doses of milrinone versus placebo and demonstrated superiority of milrinone in reducing low cardiac output syndrome (LCOS), there has been only a handful of well-designed RCTs up to 2018 enrolling over 200 patients (7). The Single Ventricle Reconstruction trial (8), published in 2010, remains unique in randomizing 549 infants with Hypoplastic Left Heart Syndrome to one of two surgical methods for pulmonary blood flow and observed comparable transplant-free 12-month survival. The Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) trial (9) randomized 980 children up to three years to tight-glycemic control versus standard care and reported similar outcomes. In 2023, the TRICC trialists (10) reported the use of triiodothyronine versus placebo in 220 infants and found no difference.

Notably, other fields of pediatric intensive care (11–13) have witnessed considerable growth in RCTs performed over recent years, employing increasingly pragmatic designs, deferred consent, and starting to leverage adaptive methodologies (14, 15). Yet, barriers to the conduct of RCTs in the field of CHD persist. They include firstly the multidisciplinary nature which spans across neonatology, cardiology, surgery, perfusion, anaesthesiology, intensive care, and general pediatrics. This poses challenges on research consortia and consensus process throughout trial design and conduct. Second, individual clinician/surgeon preference for aspects of management may prevail even if there is equipoise for most of the interventions. Third, available cardiac research and data infrastructure was designed for observational cohort and quality improvement studies, and the experience in interventional trials often remains limited. Fourth, contrary to industry-sponsored research using novel devices, investigator-led trials on common interventions are unlikely to attract industry funding yet are costly to perform. Finally, the tremendous heterogeneity of CHD lesions complicates trial design and increases the numbers needed to enrol.

The NITRIC and the STRESS trials – the largest trials performed in CHD

In 2022 the two largest RCTs in the field of CHD surgery were published, providing insights into future opportunities for interventional CHD research (Table 1).

The Nitric Oxide During Cardiopulmonary Bypass to Improve Recovery in Infants With Congenital Heart Defects (16) (NITRIC trial, ACTRN12617000821392]) was investigated

whether the administration of nitric oxide at 20 ppm into the cardiopulmonary bypass (CPB) oxygenator would result in an increase in ventilator-free survival in infants below two years of age undergoing heart surgery. The rationale for the trial was founded in several pre-clinical studies and two pediatric pilot trials indicating potential benefit of nitric oxide to improve postoperative recovery by mitigating CPB associated inflammation and LCOS. The trial was led by the Australia and New Zealand Intensive Care Society Paediatric Study Group (ANZICS PSG) and recruited 1364 infants at major CHD sites in Australia and New Zealand, and one site in the Netherlands. The trial did not observe any difference in the primary outcome (adjusted estimate of absolute difference, −0.01days; 95%-confidence interval −0.25 to 0.22, p-value of 0.92), nor in any of the secondary, safety, and exploratory outcomes. Similarly, additional subgroup and sensitivity analyses did not indicate either benefit or harm associated with nitric oxide. Ancilliary studies including multi-omics investigation of the host response to CPB, and long-term follow-up are in progress.

The Steroids to Reduce Systemic Inflammation after Infant Heart Surgery (STRESS, NCT03229538)(17) trial investigated whether the administration of 30 mg/kg intravenous methylprednisolone into the CPB priming fluid would result in a reduction of a composite hierarchical outcome of several postoperative complications and length of stay. The trial was led by investigators from 24 sites contributing to the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD) and recruited 1200 infants in the United States. The rationale of the trial founded on the ongoing controversy surrounding use of steroids to reduce CPB associated inflammation and the potential of steroids to improve postoperative outcomes in this age group. While the primary outcome did not meet the threshold for significance when comparing methylprednisolone versus placebo (adjusted odds ratio, 0.86; 95%-confidence interval, 0.71 to 1.05; p-value of 0.14), secondary unadjusted analyses indicated potential benefit with a win-ratio of 1.15 (95%-confidence interval, 1.00 to 1.32, p=0.046) in the methylprednisolone group. However, receipt of methylprednisolone was associated with an increased risk of side effects, in particular hyperglycaemia requiring insulin therapy.

When comparing the NITRIC and the STRESS trials, a number of differences, and similarities become apparent (Table 1). Both RCTs recruited a contemporary cohort of infants undergoing CPB surgery characterized by a broad spectrum of high and low risk surgeries (in terms of Aristotle or STS-EACTS [STAT] scores) such as ventricular septal defect, tetralogy of Fallot, atrioventricular canal defects, hypoplastic arches, and transposition of the great arteries. Overall outcomes were excellent, with a mortality of only 1.3% and 2.4% in the NITRIC and the STRESS trials, respectively. While direct comparison of other outcomes such as duration of ventilation, PICU stay, and hospital stay, unfortunately is not possible as the trials did not equally report on those, the studies represent state-of-the-art CHD cohorts likely with high generalizability for current pediatric heart surgery centers and PICUs in high income countries. Both studies investigated immunomodulatory interventions informed by solid pilot data or meta-analyses embedded in pragmatic designs where other interventions and patient care were not prescribed.

Two lessons learnt from the NITRIC and STRESS RCTs and implications for future trial design

First, the NITRIC and the STRESS trials refute the traditional assumption that large-scale RCTs in the field of surgical disciplines are impossible to conduct. In fact, CHD represents an attractive population for RCTs, given the primarily elective nature facilitating prospective consent options, the high frequency, extensive standardization, and the possibility of embedding the study flow in the patient journey spanning from pre-surgical assessment through operating theatres and PICUs to follow-up clinics. Furthermore, prospective capture of high validity minimal datasets for the purpose of quality control and benchmarking has become very common in this patient group, lending itself to cost-effective and efficient trial conduct and data capture. However, in view of the expansion of pediatric cardiac critical care services around the world, such datasets must permit inclusiveness across diverse populations.

Second, given the low mortality associated with CHD in the current era, there is an unmet need to develop standardized end point measures for future trials. For this purpose, international consensus across multidisciplinary healthcare workers, combined with parent and patient involvement in prioritisation of topics, study design and selection of outcomes, would greatly enhance our ability to collate results across trials for ancillary studies and meta-analyses (18). Objective measures such as duration of ventilation, duration of PICU and hospital stay are subject to major site-to-site variation and may be impacted by other context-specific factors such as PICU staffing patterns, availability of fast-track procedures, or discharge bed block. Furthermore, outliers may result from residual defects, cardiac arrest and support using extracorporeal membrane oxygenation. To this end, it will be important for trial designs and analytic plans to consider stratified designs that account for the influence of center, surgeon, and surgeon experience; yet, the variation thereof may still necessitate additional risk-adjustment using validated registry procedures. In addition, novel interventions such as immunomodulation or technical advances may be more suitable to assessment by early proxy measures of efficacy such as markers of host response and specific organ dysfunction, or LCOS. Given the multitude of factors impacting CHD outcomes, a composite of specific, objectively measurable, achievable, relevant, and time-bound end points such as those employed in the STRESS study presents evident advantages. However, these should be complemented by longitudinal assessment of health-related quality of life, and cognitive and behavioural function.

Conclusion

The ongoing burden of CHD for patients, families, and society warrants a stronger focus on interventional trials on perioperative management for this highly vulnerable patient group. Promising strategies based on pre-clinical and clinical Phase 1 and 2 trials should be prioritized and incorporated into trial platforms to enhance the efficiency of research. The availability of high-throughput omics technology carries promise as such may allow to decipher mechanisms underlying individual responses to treatment. Overarchingly, it will

be imperative to build on international research networks which have the capacity and capability to mount RCTs of sufficient power.

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Table 1.

Comparison of design and conduct characteristics of the NITRIC and the STRESS trials.

ASD, atrial septal defect; ASO, arterial switch operation; AVSD, atrioventricular canal defect; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; VSD, ventricular septal defect.

Domain	Feature	NITRIC trial (Schlapbach et al, JAMA 2022)	STRESS trial (Hill et al, NEJM 2022)
Design	*Study type*	Investigator-driven, double-blind	Investigator-driven, double-blind
	Population	1364 infants <24 months undergoing heart surgery on CPB. Most common repair procedures include VSD (32%), Fallot (16%), ASO (12%), ASD (12%), hypoplastic arch (11%), Glenn/Stage II (10%), AVSD (5%), Norwood (4%).	1200 infants <12 months undergoing heart surgery on CPB. Most common repair procedures include VSD (15%), AVSD (12%), Fallot (12%), Hypoplastic Arch (8%), Norwood (8%), Glenn/Stage II (8%), ASO (4%).
	Intervention	Nitric oxide @ 20ppm into CPB oxygenator for entire CPB run; blinded intervention administered by perfusionists	30mg/kg methylprednisolone into CPB priming fluid; blinded intervention administered by perfusionists
	Comparison	CPB without nitric oxide	Placebo
	Outcome	Ventilator-free days @28 days (primary), composite of low cardiac output syndrome, death, ECMO (secondary); several secondary and exploratory outcomes. 1.3% mortality. Median 26.5 days ventilator-free days.	Ranked composite of death, heart transplantation, or any of 13 major complications @90 days (primary); several secondary outcomes contained in the STS database. 2.4% mortality. Prolonged (>7 days) post-op mechanical ventilation: 6.8 vs 8.5% for MP vs placebo.
Conduct	*Countries*	Australia, New Zealand, The Netherlands	United States
	N sites	6	24
	Duration	46 months patient enrolment (July 2017 through April 2021)	54 months patient enrolment (October 2017 through March 2022)
Degree of pragmatism	*Design and protocol adherence*	Protocol mandates use of nitric oxide in intervention, other care up to unit specific procedures. 7.5% protocol deviations, 1.5% with protocol deviations relating to intervention.	Protocol mandates use of methylprednisolone in intervention, other care up to unit specific procedures. Highly pragmatic protocol under which no events met criteria for protocol violations.
	Enrolment	1364 of 2260 (60%) infants meeting inclusion/exclusion criteria enrolled. Parental refusal/withdrawal to consent (23%), and failure to approach parents for consent (10%) as main causes of missed enrolments.	1263 consented and randomized but 63 did not receive study drug, most often because no longer meeting inclusion/exclusion criteria (30%) or pharmacy error preventing drug delivery (21%)
	Data collection	Manual data entry, some fields cross-validated from PICU registry	Registry-based Society of Thoracic Surgeons Congenital Heart Surgery Database (STS)
	Study costs	Approx. 1.5 million US$ (ca. 1100 US$ per patient)	Approx. 3.2 million US$ (ca. 2667 US$ per patient)
Ancillary studies	*biobanking*	PAXgene, serum, EDTA for biomarker and omics studies, cost analysis	Pharmacokinetics/pharmacodynamics on steroids, cost analysis, subgroup analysis
	Follow-up	Questionnaires @ 12, 24, 36, 48 months and face to face neurodevelopmental assessment @ 5 years	None