Pediatric cardiology: In search for evidence

Evidence-based medicine is considered the cornerstone of modern medicine. Practice-changing research in pediatric cardiology is limited due to the various challenges. In the current *Annals of Pediatric Cardiology* issue, Littman *et al.*[1] have highlighted the paucity of high-level evidence in pediatric cardiology. Out of the 731 articles related to pediatric cardiology published in 2021, only 21 randomized controlled trials (RCT) were identified. Only 5.8% of the studies could qualify as high-level evidence, and RCTs in pediatric cardiology are 20 times less than their adult counterpart. Not only are the numbers low, but the quality is also poor, as more than half of RCTs are classified as having low levels of evidence. Primary endpoints were frequently based on surrogate factors, whereas longer-term and patient-centered outcomes were rarely used and reported. The situation is even worse for low- and middle-income countries such as India, contributing to only ~3% of total RCTs in the field. Most high-quality evidence in pediatric cardiology is from the US, UK, and Canada only.

PEDIATRIC CARDIOLOGY AND EVIDENCE-BASED MEDICINE

The first identifiable RCT in children and adolescents evaluated the treatment strategies for acute rheumatic fever and was published in 1955.[2] An RCT evaluating the utility of epsilon aminocaproic acid during cardiopulmonary bypass, published in 1974, maybe the first RCT in children with congenital heart disease (CHD).[3] The single ventricle reconstruction trial[4] is the first multicenter pediatric cardiac surgical RCT published in 2000 in the *New England Journal of Medicine*. It compared the shunt types in the Norwood procedure for single ventricle physiology. It was a multicentric trial but included most patients from two centers only because some surgeons/centers refused to participate, and some withdrew due to small case volume or because they thought using different techniques was unsuitable for technical proficiency.

Despite the lack of perceived evidence, the field of pediatric cardiology has made rapid and giant strides in improving the outcomes for children with most CHD. This paradox is explained by the fact that most improvements are related to surgical or interventional procedures, and the outcome improvements are often so undeniable.[5,6] For instance, balloon atrial septostomy improving saturation and outcomes in transposition of great arteries (TGA), arterial switch operation for TGA, and pulmonary valve balloon dilatation in a patient with valvular pulmonary stenosis became established procedures without an RCT to document improvement in outcomes. As Gidding[5] pointed out, in the "craft era" of surgical and technological innovation, long-term outcomes improved tremendously with visionary pioneers offering a cure or successful palliation to most children born with CHD. Developments in interventions, imaging, anesthesia, intensive care, medications, surgical techniques, and hybrid approaches to management contributed immensely to this journey. High-skill and complex procedures are readily accepted, and RCT was considered impractical, inappropriate, and maybe unethical in some instances.[5] More physiological repair, expected to result in long-term normal adulthood, even at the cost of higher initial mortality, usually has become an acceptable standard of care for most conditions.

For the above reasons, historically, the decision-making in pediatric cardiology is not often based on evidence. It is usually based on a curious mix of factors, including the understanding of physiology and hemodynamics, the natural history of the lesions, procedural outcomes in the institution, expert opinion, experimental evidence derived from adults, and individual experiences.[6] Various guidelines in pediatric cardiology[7,8] are also primarily based on expert consensus or using "hand-me-down" paradigms derived from adult cardiology studies with limited pediatric data. Recent innovations such as ductal stenting and right ventricular outflow tract stenting have been accepted rather quickly without RCTs. However, most recent innovations provide more minor incremental benefits; hence, we need rigorous evidence.

QUANTITY AND QUALITY OF RANDOMIZED CONTROLLED TRIALS IN PEDIATRIC CARDIOLOGY

For this editorial comment, we looked at the number of RCTs published in 2022 among the three major journals [Table 1], which showed an unsatisfactory picture. Various reviews looked at the quality and quantity of RCTs in pediatric cardiology over the years.[6,9-12] In an analysis of 933 pediatric cardiology RCTs done till 2018,[9] the yearly average improved to 46 RCTs/year between 2010 and 2020. Another study of 83 RCTs in pediatric cardiology[11] also confirmed a significant increase in the numbers over time. Despite the rise in the number of RCTs, impactful RCTs are limited in pediatric cardiology. The majority are not well-recognized and have not yielded a significant influence on patient care. Most published trials are small, single-center, phase II

trials of uncertain quality, usually not prospectively registered, recruiting small numbers of patients without independent oversight, not conforming to current international standards, and providing only a limited evidence base for contemporary practice.[5,6]

Over half of RCTs in pediatric cardiology are inadequately powered; more than 50% of the RCTs had <50 patients, and only 19% had >100 participants.[6,9] Over the years, 72,416 children were studied in 933 pediatric cardiology RCTs, yet the numbers are fewer than three large adult RCTs.[6] Worryingly, there is no meaningful increase in the number of patients randomized per trial over time in pediatric cardiology. Only a third had explicitly reported a defined primary endpoint, and most have used surrogate endpoints of uncertain significance.[6,9,10] Only one out of 333 studies reported mortality benefits.[10] Even the major practice-changing trials had significant issues. The PRIMACORP trial established the safety and efficacy of milrinone after cardiac surgery, with the risk of death or low cardiac output syndrome decreasing from 26.7% to 9.6%.[13] However, in the initial planning stages, the authors estimated that a 20% reduction in mortality with a baseline mortality rate of 5% would require 14,000 participants.[14] In the clopidogrel study, despite recruiting from 134 sites in 31 countries, the estimated treatment effects had large confidence intervals.[15] The underpowered pediatric carvedilol study[16] combined groups of patients with ventricular dysfunction who had etiological heterogeneity. Carvedilol is also more rapidly metabolized in children. These highlight the challenges in conducting an RCT in children.[6] However, specific trials in the 1980s and 1990s answered some key questions,[5] including pharmacological therapies for closure of neonatal patent ductus arteriosus, treatment options for Kawasaki disease, and cerebral protection during cardiopulmonary bypass in infants.

CHALLENGES IN CONDUCTING QUALITY RANDOMIZED CONTROLLED TRIALS IN PEDIATRIC CARDIOLOGY

The various challenges in conducting a high-quality RCT are summarized in Table 2. Most of the difficulties stem from recruiting an adequate number of subjects, randomizing to defined interventions, and choosing reliable endpoints. Most pediatric cardiology RCTs are underpowered[11] and have low generalizability, often related to the rarity of specific anatomy and pathobiology and the low occurrence of hard endpoints. Hence, a meaningful RCT usually requires extensive collaboration between the units. The timing and nature of the surgery, the ability to diagnose prenatally, expertise in pediatric cardiology, imaging, anesthesia, and intensive care, and attitudes to therapy are vastly different in different countries. In adult cardiology trials, delaying an endpoint is considered a successful outcome in areas such as heart failure or recurrent myocardial infarction. However, the goals are different for pediatric cardiology RCTs. Often, the goal is to treat children with CHD effectively to ensure they experience decades of near normal quality and quantity of life.

Table 1: Number of randomized controlled trials published as a proportion of original articles

Journal title	Total original articles published (2022)	Total RCTs published (2022) (%)
Cardiology in young	211	9 (4.3)
Pediatric cardiology	190	3 (1.6)
Annals of pediatric cardiology	24	0

RCTs: Randomized controlled trials

Table 2: Reasons for the lack of high-quality randomized controlled trials in the field of pediatric cardiology[5,6]

Recruiting subjects
Relative rarity of individual cardiac malformations
Varied age of presentations with different challenges
Specific circulatory physiologies even rarer
Heterogeneity of presentation - patient, disease, economic, societal, etc.
Complex anatomical and physiological challenges
Difficulties in subject recruitment
Parental concerns
Greater scrutiny from regulators and ethics committees
Interventions
Heterogeneity in the delivery of the intervention
Nonpharmacological interventions challenging to define
Pharmacological RCTs
Varied PK/PD of medications over a wide range of patient factors, including age, body surface area, and physiological states
Multiple study groups to establish PK/PD before moving to efficacy trials
Safety assessment in every individual situation
Smaller effect sizes necessitate larger trials to ensure adequate power
Designing interventions that are engaging and appropriate for children across different age categories
Adherence to intervention
Increased complexity if it involves child and parent or family members
Masking/blinding - can be difficult to impossible
Defining meaningful outcomes
Need for tangible long-term outcomes to show a meaningful difference
Defining clinically meaningful endpoints
Mortality and significant functional impairment in pediatric cardiology are low
Variations in practice and outcomes
Individual physician skill to outcome
Interaction between institution and outcome
Across countries and populations
Others
Rapid changes in technology
Unanticipated crossover
Higher costs and complex logistics
Perceived lack of willingness of surgeons and parents
Lack of funding priority
Lack of infrastructure and culture
Lack of large collaborating agencies compared to other fields

RCTs: Randomized controlled trials, PK/PD: Pharmacokinetics and pharmacodynamics

IMPROVING THE QUALITY AND QUANTITY OF PEDIATRIC CARDIOLOGY RANDOMIZED CONTROLLED TRIALS

As a specialty, we need to move from empiricism to evidence-based decision-making. Scientific societies, academic institutions, and industry must collaborate and provide scientific leadership. We need multicenter clinical trials that are well-designed and rigorously conducted, with clinically relevant endpoints answering key questions. As a community, we need to learn and adapt the ways of other pediatric subspecialties such as oncology. A recent estimate suggested that approximately <1% of children undergoing cardiac surgery in the National Health Service system are enrolled in any RCT.[10] In contrast, the corresponding number is 70% for children diagnosed with cancer.[17] The suggested framework for setting up high-quality RCTs in pediatric cardiology is summarized in Table 3.

We must take advantage of three vital developments, including regulatory mandates, the setting up of national-level collaborative networks, and the standardization of trial methodology in children. The US Food and Drug Administration requires pediatric studies, if the new drug or device is expected to be used in many children following the implementation of the Pediatric Research Equity Act.[18] The European Union also implemented a similar act.[19] Regulatory requirements paved the way for more scientific evaluation of newer-generation therapies like PICOLO device and sacubitril/valsartan for children with heart failure. In 2001, the National Heart, Lung, and Blood Institute launched the Pediatric Heart Network (PHN).[20] The single ventricle reconstruction trial remains the greatest accomplishment of the PHN.[4] Despite the promising initiative, several further studies did not result in practice-changing conclusions.[21] The Canadian Pediatric Cardiology Research Network[22] is a national-level data-sharing organization that facilitates research on pediatric heart diseases. Developing specific guidelines in children, including SPIRIT-Children and CONSORT-Children, is essential for the smooth conduct of pediatric trials.[23] The International Consortium for Health Outcome Measurements, in 2020, released a standard set of defined outcome measures for pediatric and adults with CHD.[24]

On the broader front, we need to move to qualitative studies and a Bayesian approach to design and analysis. The frequentist statistical approach poses severe limitations, and hence, a Bayesian approach may be preferable in pediatric cardiology RCTs. Adaptive platform trials and stepped wedge design are further innovative methods that should find a place in pediatric cardiology.[6] Further, we must innovate to disseminate and effectively incorporate RCT findings in daily practice.

Table 3: Suggested framework for setting up high-quality pediatric cardiology randomized controlled trials [10]

Identify essential research questions
Genuine clinical equipoise
Important to all stakeholders
Preliminary data from observational studies
Disease-specific registries
Country-specific datasets
Assess feasibility and identify potential outcome measures
Primary endpoint
Standardized, validated, and clinically relevant
Acceptable widely to facilitate meta-analyses of pooled data
Ensure an adequate sample size
Inclusive
Collaborative approach
Multicenter/multicounty
Make it more generalizable
Ensure timely recruitment
Identify a priori subgroups
Setup or utilize clinical trial units and clinical research network infrastructure
Conduct and report the trial rigorously to international standards
Oversight by independent data safety monitoring committee
Facilitate ancillary studies and public data sharing
Engage and educate the wider community

Table 4: Selected vital questions to be answered by Indian Pediatric Cardiology randomized controlled trials

Surgery
Acyanotic CHD (ASD, VSD, and PDA) with elevated pulmonary artery pressure: When (not) to operate?
Timing of surgery in VSD with a chest infection
Single stage versus Staged Fontan in unoperated adults with single ventricle physiology
Types of right ventricle to pulmonary artery conduit
Regurgitant valvular heart disease (mitral or aortic regurgitation)
Early valve repair in asymptomatic children
Long-term outcomes after valve repair and replacement strategy
Ebstein's anomaly: Type and timing of surgery
Interventions versus surgery
Ideal treatment strategy for coarctation of aorta
RVOT/ductal stenting versus surgical shunts
Surgical valvotomy versus balloon valvuloplasty for aortic stenosis
Device versus surgery in selected situations
Interventions
Follow-up after repair of tetralogy of Fallot
Importance of chronic pulmonary regurgitation
Timing of pulmonary valve replacement
Catheter closure of VSD - indications and long-term follow-up data
Epicardial versus endocardial pacing in children
Drugs
Utility of IV immunoglobin in pediatric myocarditis
Treatment opportunities in Eisenmenger syndrome
Drug therapy for pediatric heart failure
Drugs for failing Fontan
Anesthesia/ICU
Anesthesia and ICU strategies in late presenters, pulmonary hypertension, and sepsis

VSD: Ventricular septal defect, ICU: Intensive care unit, PDA: Patent ductus arteriosus, CHD: Congenital heart disease, RVOT: Right ventricular outflow tract, IV: Intravenous

PEDIATRIC CARDIOLOGY RANDOMIZED CONTROLLED TRIALS – OPPORTUNITIES FOR INDIA

Considering the expertise and patient load, India can lead in multicentric pediatric cardiology RCTs. India cannot only answer some of the common questions facing the field but also generate high-quality evidence for some of the problems peculiar to its population [Table 4].[25] However, India's contribution is limited to a few multicentric case series,[26-28] moderate-quality single-center RCTs,[29,30] and a few clinical practice guidelines.[7,8] Even long-term natural history and outcome studies are limited from India. We need to link the major academic institutions across the country, and a few efforts are ongoing. We must further build on other US, European, and Canadian networks. We must develop a core group of experts forming strong teams, identify specific questions and core outcomes, and use state-of-the-art methods to develop RCTs addressing national priorities. We must also focus on social issues, health-care equity, accessibility, and affordability.[25,31] During the COVID-19 pandemic, the Pediatric Cardiac Society of India organized and reported a few retrospective multicenter studies.[32,33] It is the time for us to plan futuristic RCTs.

CONCLUSIONS

RCTs remain a gold standard only when appropriately designed, conducted, and reported. However, the evidence base of pediatric cardiology remains suboptimal in quality and quantity. It is often said that children are not simply little adults. Hence, we must conduct well-designed contemporary trials in pediatric cardiology and move toward evidence-based decision-making even in children with heart disease.

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