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Del Nido versus St. Thomas cardioplegia for myocardial protection in pediatric congenital heart surgery: A systematic review and meta-analysis

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ABSTRACT

Background: Congenital heart disease (CHD) is the most common congenital anomaly in newborns and frequently requires open-heart surgery during the neonatal period. This study aimed to determine the most effective cardioplegic solution for pediatric cardiac surgery.

Methods: This study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines. A comprehensive literature search was performed to identify studies comparing Del Nido and St. Thomas cardioplegia in pediatric CHD patients. A total of 53 studies, encompassing 1,099 patients, were included. The primary and secondary outcomes evaluated were postoperative Troponin T/I and CK-MB levels, aortic cross-clamp (ACC) time, cardiopulmonary bypass (CPB) time, intensive care unit (ICU) and hospital length of stay, vasoactive-inotropic score (VIS), and postoperative mortality.

Results: This study included 8 studies. Pooled analyses showed no significant differences between del Nido and St. Thomas for aortic cross-clamp (ACC) time (SMD −0.02; 95% CI −0.24–0.21; p=0.88; I^2=65%), cardiopulmonary bypass (CPB) time (SMD −0.05; 95% CI −0.31–0.21; p=0.71; I^2=73%), ICU/NICU stay (SMD 0.06; 95% CI −0.17–0.28; p=0.63; I^2=66%), hospital stay (SMD −0.68; 95% CI −1.52–0.16; p=0.11; I^2=65%), and postoperative mortality (OR 0.67; 95% CI 0.37–1.20; p=0.17; I^2=0%). In the Tetralogy of Fallot subgroup, St. Thomas showed a borderline shorter ACC time (SMD 0.29; 95% CI −0.01–0.59; p=0.05)

Conclusion: Del Nido and St. Thomas cardioplegia solutions provide comparable long-term surgical outcomes in pediatric CHD patients. However, Del Nido cardioplegia appears to offer superior myocardial protection in the immediate postoperative period.

Keywords: Congenital heart disease, Cardioplegia, Del Nido, Pediatric cardiac surgery, St. Thomas.
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INTRODUCTION

Congenital heart disease (CHD) is the most common structural heart anomaly in neonates and children, with a large global burden that varies across regions.[1] A global analysis from 1990–2021 estimated that in 2021, more than 4.18 million children aged <5 years were living with CHD, with a prevalence of approximately 6.4 per 1,000 live births.[2] Registry-based studies in Europe from 2008 – 2015 reported a total prevalence of non-syndromic CHD of 57.1 per 10,000 births (≈5.7 per 1,000) and a live-birth prevalence of 60.2 per 10,000 (≈6.0 per 1,000), confirming the predominance of CHD among congenital anomalies with heterogeneity across registries.[3,4] Population modeling in the United States demonstrated the magnitude of the affected pediatric cohort and implications for ongoing care needs.[5] In addition to multifactorial factors, genetic comorbidities such as Down syndrome are closely associated with septal lesions and outflow abnormalities, necessitating pediatric-specific perioperative planning.[6] Environmental dynamics, such as prenatal exposures and changing demographic patterns, are also recognized as influencing the pediatric CHD landscape and require adaptation of screening policies and strengthening of registries.[7]

Open surgical correction in the pediatric population, particularly neonates and infants, is often necessary to restore circulation and prevent pathological remodeling. Two crucial intraoperative prerequisites are controlled cardiac arrest and a bloodless surgical field, achieved through aortic clamping, cardiopulmonary bypass, and cardioplegia. However, reperfusion carries the risk of ischemia-reperfusion injury, making myocardial protection strategies that reduce metabolic demand and maintain tissue viability crucial.[8] Pediatric myocardials have different metabolic characteristics and calcium regulation than adults, making them more susceptible to injury and necessitating the selection of cardioplegia regimens that

take into account age, weight, and lesion complexity.[6,8] Randomized controlled trials (RCTs) in pediatric cardiac surgery have evaluated various formulations, with outcomes such as cross-clamp time, bypass duration, injury biomarkers (troponin), inotropic requirements, intensive care unit length of stay, and safety.[8] In parallel, epidemiological trends and environmental changes demand adaptive perioperative management and a robust referral network to optimize pediatric postoperative outcomes.[2,7]

Cardioplegia is a widely employed pharmacologic technique to achieve myocardial protection during cardiac surgery by inducing temporary cardiac arrest.[9] Two commonly used solutions are St. Thomas II and Del Nido. St. Thomas II, an ionic solution containing sodium, potassium, chloride, and bicarbonate, has been traditionally used in adult procedures, but it typically requires repeated dosing, which may interrupt the surgical workflow and increase ischemic risk. Meanwhile, Del Nido cardioplegia was originally developed for neonatal surgery, is a 1:4 blood-to-crystalloid solution containing mannitol, lidocaine, magnesium sulfate, and other ions. Its low calcium content and diluted nature make it suitable for immature myocardium, and its prolonged arrest duration often enables single-dose administration per procedure.[10] Despite its growing use in neonatal surgery, practice varies considerably due to the absence of standardized guidelines. While Kotani et al. reported Del Nido as the most frequently used solution in neonates, many surgeons still employ alternative strategies.[11] This variability reflects ongoing uncertainty regarding optimal myocardial protection in this vulnerable population. Therefore, this study aimed to determine the most effective cardioplegic solution for pediatric cardiac surgery.

METHODS

Search Strategy and Study Design

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched MEDLINE (via PubMed), Embase, and the Cochrane Database from inception to December 5th, 2023. We used iterative combinations of Medical Subject Headings (MeSH) and keywords on PubMed, including "St. Thomas cardioplegia," "del Nido cardioplegia," "del Nido St. Thomas," "del Nido St. Thomas cardioplegia," "STH solution del Nido," and "del Nido St. Thomas comparison."

Eligibility Criteria

Randomized controlled trials (RCTs) and retrospective cohort studies that reported clinical outcomes for both del Nido cardioplegia and St. Thomas cardioplegia in pediatric cardiac surgery were included in this study. Animal/experimental studies, surveys, comparisons focused solely on cardioplegia temperature, case reports, and non-English publications were excluded.

Study Selection

Titles and abstracts were independently screened for eligibility by three reviewers (E.R., S.B., and C.I.). When relevance could not be confirmed from the abstract alone, full texts were retrieved. Any discrepancies were resolved by consensus.

Quality of Evidence and Risk of Bias

As illustrated in Chapter 14th of the Cochrane handbook of reviews to validate the quality of evidence found in our systematic review, GRADEpro was used to evaluate the quality of evidence in the included studies (Table 1). Risk of bias of each study was assessed according to guidelines in Chapter 8th of the Cochrane Handbook of Reviews (Figure 2), and risk of bias plots were generated using RevMan 5 (Figure 2).

Data Extraction and Outcomes

Study characteristics (title, first author, year, design), population details (number of patients and group sample sizes), interventions and comparators, and outcomes (including effect estimates) were independently extracted by one author (E.R.). The primary outcomes were defined as aortic cross-clamp (ACC) time, cardiopulmonary bypass (CBP) time, length of hospital stay, and length of intensive care unit or neonatal intensive care unit stay (ICU/NICU). The secondary outcomes were the vasoactive-inotropic score, troponin I, and mortality.

Statistical Analysis

Comparative meta-analyses (del Nido vs St. Thomas) were conducted in RevMan version 5.4 (Cochrane Collaboration, Oxford, UK). A two-sided p-value ≤0.05 was considered statistically significant. For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated; for continuous outcomes, mean differences (MDs) with 95% CIs were used. Between-study heterogeneity was evaluated with the Cochran Q test and quantified using I^2. Statistical heterogeneity was considered present when the Q-test p <0.05 and I^2 >50%. When heterogeneity was acceptable (p ≥0.10, or p <0.10 with I^2 ≤50%), a fixed-effect model was applied. Otherwise, a random-effects model was used.

RESULTS

The study selection followed PRISMA 2020 guidelines and integrated database and non-database sources (Figure 1). Three major databases, including MEDLINE (via PubMed), Embase, and the Cochrane, were searched. Title and abstract screening were performed independently by three reviewers (E.R., S.B., and C.I.). In total, 325 records were identified. After 84 duplicates had been removed, 241 records remained for title and abstract screening. On the basis of the inclusion criteria, 31 studies were judged potentially eligible and were assessed at the full-text level. Of these, 29 full texts were successfully retrieved, and 8 studies met the inclusion criteria and were included in the final systematic review and meta-analysis. Study characteristics are summarized in Table 1.

Aortic Cross-Clamp (ACC) Time

Across eight studies encompassing 1,099 pediatric CHD patients, ACC time showed substantial heterogeneity (Q-test p=0.006; I^2=65%), so we used a random-effects model with standardized mean difference (SMD). Overall, there was no significant difference between Del Nido and St. Thomas cardioplegia (SMD −0.02; 95% CI −0.24 to 0.21; p=0.88). In the Tetralogy of Fallot (ToF) subgroup, results suggested a borderline shorter ACC time with St. Thomas (SMD 0.29; 95% CI −0.01 to 0.59; p=0.05). Because the confidence interval includes the null, this should

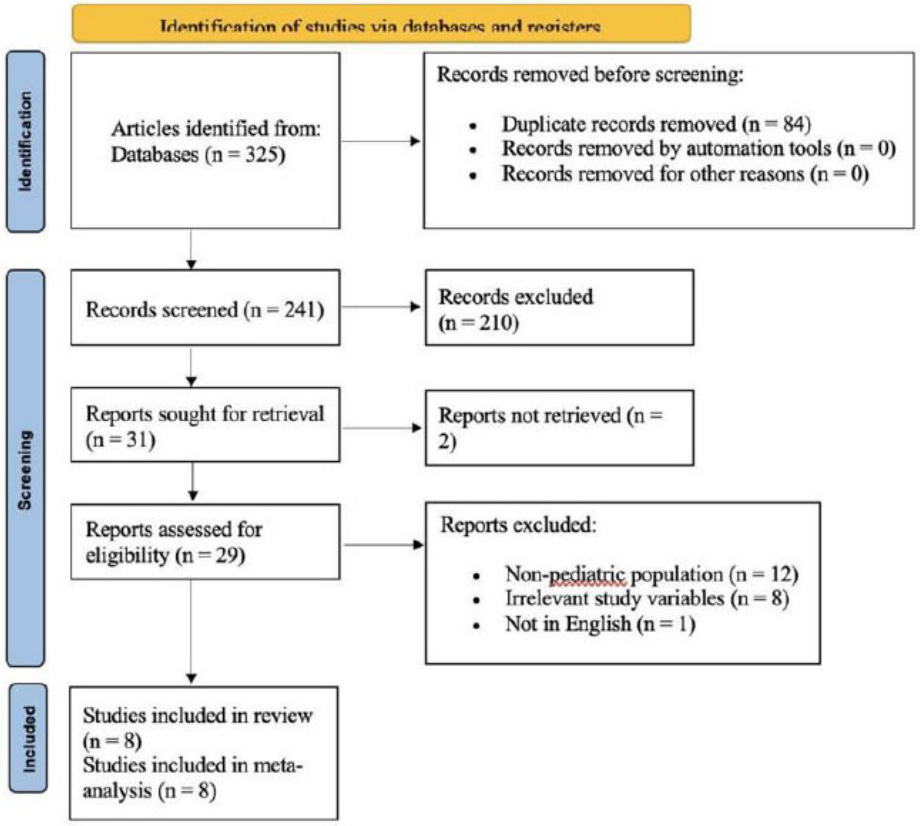

Figure 1. PRISMA schematic of the search strategy.

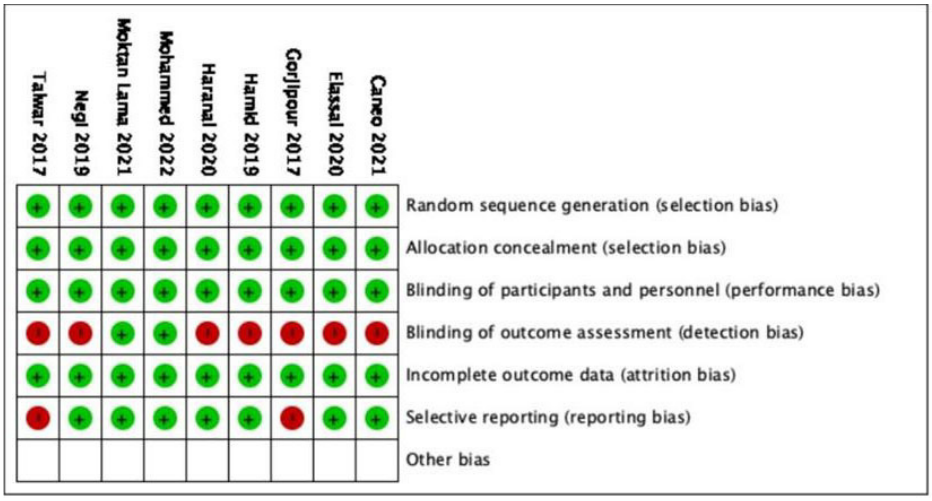

Figure 2. Cochrane Risk of Bias Tools for RCTs.

be interpreted as a trend rather than a definitive effect (Figure 3).

Cardiopulmonary Bypass (CPB) Time

Across eight studies including 1,099 pediatric CHD patients, CPB time showed significant between-study heterogeneity (Q-test p=0.0004; I^2=73%), so we used a random-effects model with SMD. There was no significant difference between del Nido and St. Thomas cardioplegia (SMD −0.05; 95% CI −0.31 to 0.21; p=0.71). St. Thomas in the ToF subgroup tended toward shorter CPB time, but this was not statistically significant (SMD 0.21; 95% CI −0.09 to 0.51; p=0.17) (Figure 4).

Length of Stay in NICU/ICU

Eight studies (n=1,099) assessed ICU/NICU length of stay. Heterogeneity was substantial (p=0.005; I^2=66%), warranting a random-effects SMD model. No significant difference was observed between del Nido and St. Thomas cardioplegia (SMD 0.06; 95% CI −0.17 to 0.28; p=0.63). In the TOF subgroup, St. Thomas was associated with a numerically shorter ICU/NICU stay, but the difference was not significant (SMD 0.22; 95% CI −0.08 to 0.52; p=0.15) (Figure 5).

Length of Stay in Hospital

Five studies (n=820) reported hospital length of stay. Heterogeneity was considerable (p=0.02; I^2=65%), so a random-effects SMD model was applied. There was no significant difference between del Nido and St. Thomas cardioplegia (SMD −0.68; 95% CI −1.52 to 0.16; p=0.11). In the TOF subgroup, no difference was observed (SMD −0.04; 95% CI −1.38 to 1.29; p=0.95) (Figure 6).

Troponin I

Two studies (n=149) assessed postoperative troponin I. Heterogeneity was low (p=0.45; I^2=0%), justifying a fixed-effect SMD model. Del Nido was associated with significantly lower postoperative troponin I compared with St. Thomas (SMD −0.36; 95% CI −0.69 to −0.04; p=0.03) (Figure 7).

Vasoactive-Inotropic Score

Six studies (n=980) evaluated postoperative inotropic support. Heterogeneity was significant (p=0.02; I^2=61%), so we used a random-effects SMD model. Del Nido was associated with a significantly lower postoperative inotropic score than St. Thomas (SMD −0.33; 95% CI −0.56 to −0.10; p=0.005) (Figure 8).

Mortality

Postoperative mortality was reported in seven studies (n=1,040) with very low heterogeneity (p=0.93; I^2=0%), making fixed-effects modeling feasible. Overall, there was no significant difference between del Nido and St. Thomas (OR 0.67; 95% CI 0.37–1.20; p=0.17). The confidence interval included the possibility of a moderate to no benefit, so the data were insufficient to confirm the superiority of one regimen on mortality. In the ToF subgroup, results were similar (OR 0.86; 95% CI 0.05–14.51; p=0.92) with a very wide CI, indicating a rare occurrence of death and low statistical power (Figure 9).

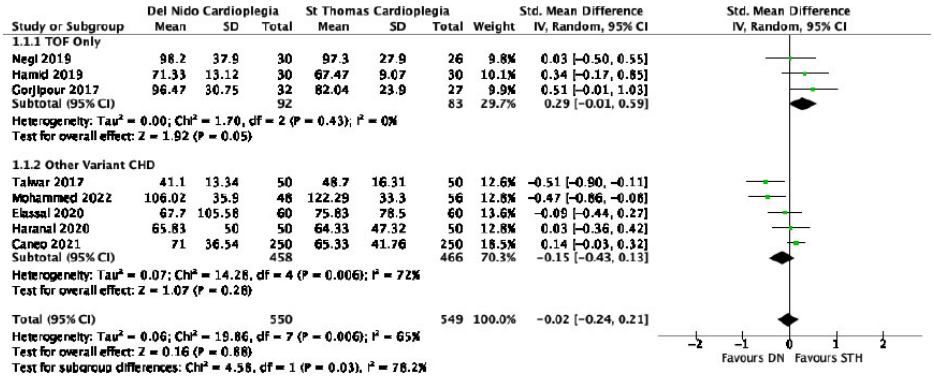

Figure 3. Forest Plot ACC time.

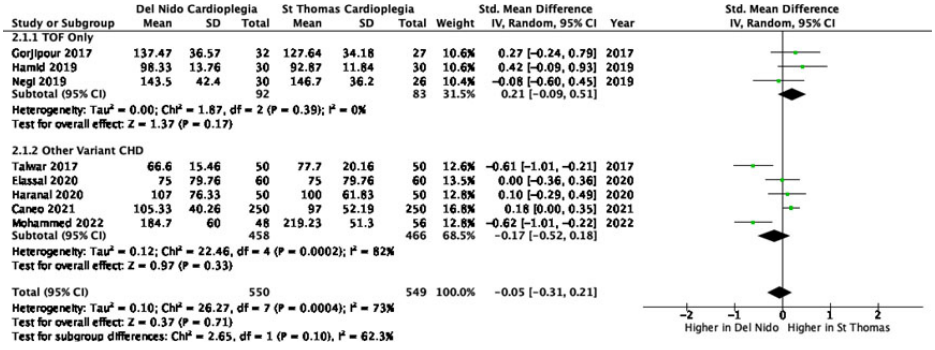

Figure 4. Forest Plot CPB time.

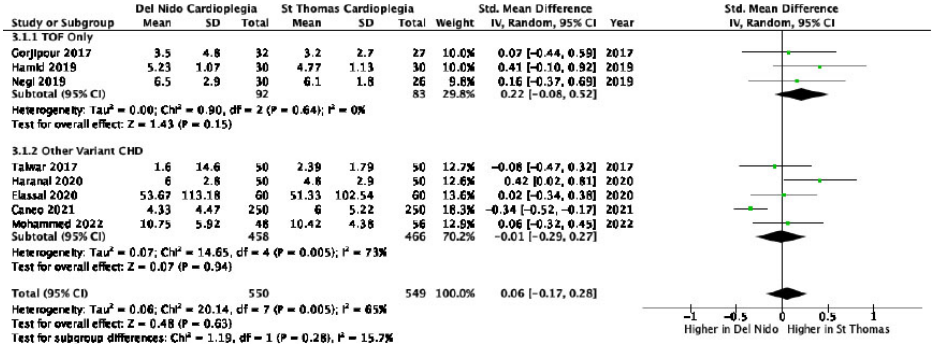

Figure 5. Forest Plot Length of stay NICU/ICU.

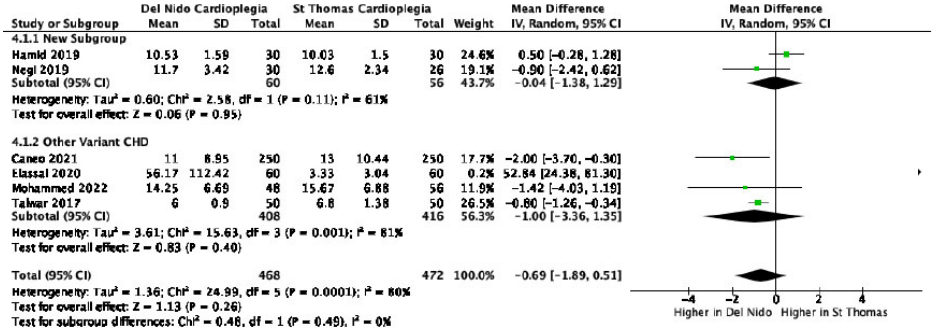

Figure 6. Forest Plot Length of Stay in Hospital.

DISCUSSION

Cardioplegia is a pharmacologic intervention used during cardiac surgery to intentionally and temporarily arrest myocardial activity. The foundational concept of potassium-based cardioplegia dates back to Dr. Melrose in the early 1950s, showing that elevated potassium-citrate levels could induce reversible cardiac arrest.[19] Over time, advances in surgical techniques and cardioplegic solutions have substantially improved the safety of cardiac operations by enabling a bloodless field, myocardial relaxation, and prevention of air embolism.[20] Initially, adult cardioplegic strategies were adapted for neonates and pediatric patients with adjustments in flow, volume, and pressure, and the St. Thomas solution became widely adopted during the 1980s-1990s in this context.[21] Nevertheless, perioperative myocardial injury, often manifesting as reduced cardiac output, remains a leading cause of morbidity and mortality in CHD surgery. Inadequate myocardial protection may result in postoperative myocardial damage, prolonged hospitalization, and later fibrosis with long-term dysfunction. Pediatric myocardium further complicates protection strategies due to its lower responsiveness to inotropic agents compared with adults.[22]

This study compared del Nido versus St. Thomas cardioplegia in pediatric CHD surgery, synthesizing eight eligible studies (six RCTs and two observational cohorts). Findings are discussed across intraoperative, myocardial injury, and postoperative domains. Intraoperatively, ACC time, a key determinant of postoperative outcomes, did not differ overall between groups (SMD -0.02; 95% CI -0.24 to 0.21; p=0.88). Although del Nido is designed for prolonged action with fewer redosing requirements, a subgroup analysis in ToF suggested borderline shorter ACC time with St. Thomas (SMD 0.29; 95% CI -0.01 to 0.59; p=0.05), which may reflect workflow efficiencies during planned redosing of St. Thomas. Similarly, CPB time showed no overall difference (SMD -0.05; 95% CI -0.31 to 0.21; p=0.71), though individual RCTs reported shorter bypass times with del Nido in neonatal populations, plausibly due to fewer procedural interruptions for redosing.[13,14]

Biochemically and physiologically, the finding that del Nido correlated with lower postoperative troponin I (SMD -0.36; p=0.03) is consistent with the pharmacological rationale for this solution: a blood-crystalloid composition with lidocaine (prolongs refractoriness and suppresses oxygen demand), magnesium (a calcium antagonist), mannitol (osmotic/free radical scavenger),

Table 1. Characteristics of studies included

No	Author (Year)	Study Design	Sample Size	Population	Intervention	Comparator	Outcomes	Result	Sample Size (Intervention)	Sample Size (Comparator)
1.	Elassal et al. (2020)[12]	Retrospective Cohort	220	Pediatric and adult cardiac surgery	Del Nido cardioplegia	St. Thomas cardioplegia	Defibrillation rate, mortality, EF, ICU stay	DN comparable or superior for uninterrupted surgery and defibrillation	110	110
2.	Mohammed et al. (2022)[13]	Retrospective Cohort	104	Neonates with congenital heart surgery	Del Nido cardioplegia	St. Thomas II cardioplegia	CPB time, ACC time, VIS, early mortality	DN reduced CPB, ACC, and VIS; no mortality difference	48	56
3.	Talwar et al. (2017)[14]	Prospective Randomized Trial	100	Pediatric patients (≤12y) with VSD and ToF	Del Nido cardioplegia	St. Thomas cardioplegia	Cardiac index, troponin I, ICU/hospital stay	DN better cardiac index, less troponin-I release, shorter ICU/hospital stay	50	50
4.	Bigdelian & Hosseini (2020)[15]	Randomized Controlled Trial	60	Children with ToF	Del Nido cardioplegia	St. Thomas cardioplegia	Heart rhythm recovery time, duration of inotropy	ST better in reducing heart rhythm recovery and inotropy duration	30	30
5.	Gorjipouret al. (2017)[16]	Randomized Controlled Trial	59	Pediatric ToF patients	Del Nido cardioplegia	Modified St. Thomas cardioplegia	Inflammatory cytokines, troponin I levels	MST better IL-10 response; no CTnI difference	32	27
6.	Caneo et al. (2021)[17]	Retrospective cohort	500	Pediatric congenital cardiac surgery	Del Nido cardioplegia	Modified St. Thomas cardioplegia	VIS, ICU LOS, LCOS, mortality	DN associated with lower VIS, LCOS, ICU stay	250	250
7.	Haranal et al. (2020)[9]	Prospective Randomized Controlled Study	100	Congenital heart disease (simple and complex)	Del Nido cardioplegia	Blood-based St. Thomas cardiop legia	Return of spontaneous cardiac activity, troponin T	Both comparable; DN needs less volume and doses	50	50
8.	Negi et al. (2019)[18]	Randomized Controlled Trial	56	TOF patients undergoing intracardiac repair	Del Nido cardioplegia	Blood cardioplegia (St. Thomas)	Inotropic requirement, CK-MB levels, ICU stay	DN reduced inotropic needs, no mortality difference	30	26

and low calcium to minimize "calcium loading" upon reperfusion.[21] Pediatric myocardials have different metabolic profiles, ion channel densities, and calcium homeostasis than adults, making them more susceptible to ischemia-reperfusion injury. Therefore, protective regimens that suppress calcium load and oxidative stress may offer biological benefits.[22] The consistency of this directionality of effect is also supported by small randomized trials showing reductions in markers of injury/inflammation with del Nido,[9,16] and by a systematic review of pediatric RCTs highlighting the role of cardioplegia formulation on perioperative biomarkers and performance.[8] Given the strong association of troponin I with in-hospital mortality (approximately 3.8% increase in risk per 1000 ng/L postoperatively),[23] the troponin reduction in the del Nido group is potentially clinically significant, although a long-term causal relationship cannot be established from the available data. Limited CK-MB data, inadequate for meta-analysis, limit biomarker triangulation, warranting caution in interpretation.[8]

The lack of significant differences in ICU/NICU length of stay and hospital stay in terms of clinical outcomes aligns with the literature showing that postoperative hard outcome indicators in the pediatric population are significantly influenced by lesion complexity, age/weight, anesthesia-perfusion practices, and genetic comorbidities, which necessitate specific perioperative planning.[6,7] However, the lower vasoactive-inotropic score with del Nido (SMD -0.33; p=0.005) is clinically important because the vasoactive-inotropic score has been validated as a predictor of poor outcomes in neonatal/pediatric cardiac surgery.[24] Although in the adult context, associated with mortality in coronary surgery.[25] Operationally, the single-dose/long-acting nature of del Nido has the potential to reduce redosing interruptions, simplifying the surgical workflow in complex cases. Some neonatal RCTs/series have reported a trend toward shorter CPB/ACC with del Nido,[13,14] although this study did not find a significant difference, suggesting this benefit may be contextual due to age, lesion type, or perfusion strategy. Intercenter practice

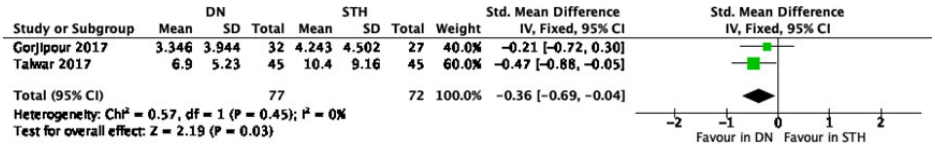

Figure 7. Forest Plot Troponin I.

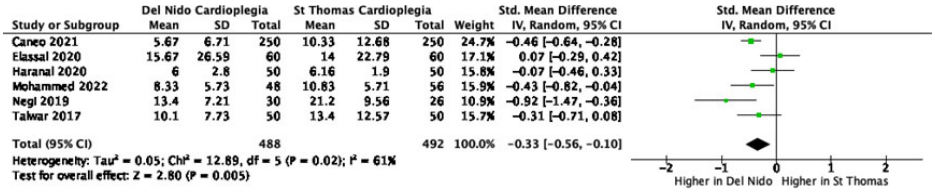

Figure 8. Forest Plot Vasoactive Inotropic Score.

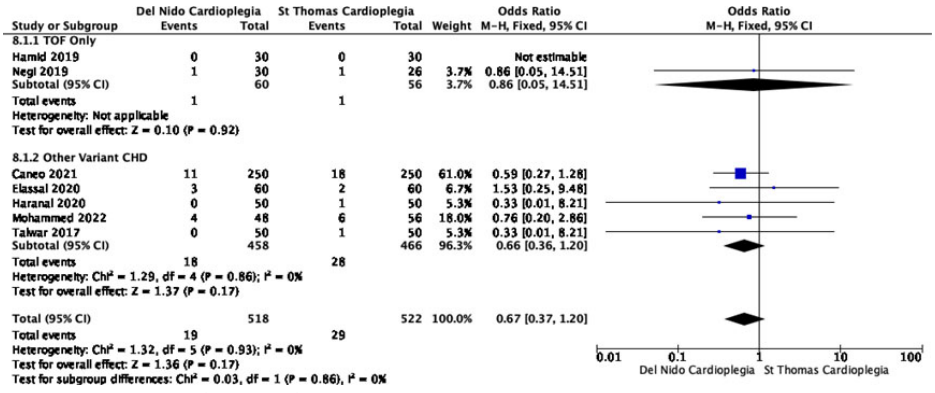

Figure 9. Forest Plot Mortality Post-operative.

variation reflected in a North American multi-institutional survey,[11] and a recent comparative review across ages suggests there is no absolute consensus,[10] while experience from other pediatric programs demonstrates the safety/feasibility of del Nido implementation.[12,15,17,18] Thus, although mortality appears equivalent and low heterogeneity in your analysis supports this conclusion, the need for adequately powered multicenter randomized trials remains urgent to assess long-term effects, at-risk subgroups such as patients with ToF, infants <3 months, genetic syndromes, and interactions with modern perfusion protocols.[2,8]

This study has several strengths. First, it is the most up-to-date synthesis directly comparing del Nido and St. Thomas cardioplegia in pediatric congenital heart surgery, incorporating evidence from both RCTs and observational studies. The inclusion of multiple intraoperative, biochemical, and postoperative outcomes allows for a comprehensive assessment of myocardial protection effectiveness. Moreover, the consistency of results across studies, reflected by the generally low heterogeneity, enhances the reliability of the pooled estimates. However, several limitations should be considered when interpreting these findings. First, the number of RCTs was limited, and they were combined with retrospective studies, so the risk of selection bias and confounding remains. Second, high intercenter heterogeneity, including formulation, dose/redosing interval, cardioplegia temperature, and anesthetic protocol, affected the effect estimates. Third, some outcomes had limited data, and CK-MB was insufficient for meta-analysis. Fourth, outcome definitions and timing of measurements varied. Finally, long-term outcomes were rarely reported, so the implications for long-term survival and ventricular function are uncertain.

CONCLUSION

This meta-analysis demonstrated that, in pediatric CHD surgery, del Nido provides superior myocardial protection (lower postoperative troponin I and vasoactive-inotropic score) without significant differences in ACC/CPB time, ICU/hospital length of stay, or mortality compared with St. Thomas. These findings support the use of del Nido as a practical alternative with potential operational benefits (less frequent redosing). Adequately powered multicenter randomized trials with individual patient data, standardized outcome definitions/measurement times, and subgroup analyses (neonates, ToF, genetic syndromes) are recommended to validate and expand the generalizability of the results.

DISCLOSURES

Funding
None.

Conflict of Interest
None.

Author Contribution
ER and SB were responsible for conceptualization, methodology formulation, and overall project supervision. SB and CI (investigation) conducted the research. ER conducted formal data analysis, which also led to data curation with CI, and developed the visualizations. ER and SB coordinated project administration. All authors contributed to the initial draft and reviewed and edited the final version.

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ETHICAL CONSIDERATION

None declared.

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