# COMPARATIVE EFFECTIVENESS OF A LOCALLY ADAPTED SALINE-BASED DEL NIDO CARDIOPLEGIA IN PEDIATRIC SEPTAL DEFECT REPAIR

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***Abstract. Background:*** *In pediatric cardiac surgery, the prevention of ischemic myocardial injury remains a key factor in ensuring favorable outcomes. The cardioplegia technique selected during surgery plays a decisive role in protecting the immature myocardium in infants and toddlers undergoing correction of congenital heart defects (CHDs).*

***Aim:*** *To evaluate and compare the incidence of early postoperative myocardial injury in children aged 12 to 36 months who underwent open surgical repair of septal congenital heart defects, depending on the type of cardioplegic solution applied-crystalloid versus a locally adapted blood-based del Nido cardioplegia.*

***Study Design and Methods:***

*This single-center, prospective, comparative clinical study was carried out at the National Children's Medical Center (Uzbekistan) from February 2021 to December 2024. Ninety-one pediatric patients with atrial or ventricular septal defects were assigned to two treatment arms: 44 children received traditional cold crystalloid cardioplegia, while 57 were treated using a modified del Nido solution containing oxygenated blood in a 4:1 ratio. The main outcome measure was a persistent >10-fold elevation in plasma troponin I within 6 hours postoperatively and at the 24-hour mark. Additional parameters included left ventricular ejection fraction (LVEF) changes and need for inotropic support.*

***Findings:****The rate of significant troponin I elevation was considerably lower in the del Nido group (31.3%) than in the crystalloid group (62.5%; $p < 0.001$). Although both groups demonstrated a postoperative decline in LVEF, the reduction was markedly less in the del Nido group (18% vs. 30.7%), suggesting more efficient myocardial protection.*

***Conclusions:****The use of a blood-enhanced del Nido cardioplegia formulation demonstrated clear clinical advantages over crystalloid cardioplegia in pediatric patients undergoing septal defect repair, resulting in reduced biochemical markers of myocardial injury and better preservation of ventricular contractility in the early postoperative period.*

***Keywords:*** *Myocardial protection, pediatric heart surgery, del Nido cardioplegia, ischemia-reperfusion injury, congenital heart disease.*

**Introduction.** Myocardial protection during pediatric cardiac surgery remains one of the most critically discussed challenges in contemporary cardiac practice. The diversity of cardioplegic strategies and the continuous development of modified solutions reflect the ongoing search for optimal methods to minimize ischemia-reperfusion injury during procedures requiring cardiopulmonary bypass (CPB). As the complexity and duration of congenital heart defect (CHD) repairs increase, so does the need for cardioplegic formulations capable of maintaining myocardial integrity during prolonged periods of asystole and ischemia [3].

Effective intraoperative myocardial protection significantly impacts not only perioperative stability but also the long-term cardiac function and survival of pediatric patients undergoing open-heart surgery [1,2]. Current global trends show that approximately 84% of pediatric cardiac surgeons perform procedures under cardioplegic arrest, while only 16% operate on a fibrillating heart. Among those using cardioplegia, blood-based techniques remain predominant (83.5%) over crystalloid-based methods (16.5%) [7]. A previous survey by Jacob S. (2008) also revealed that 56% of surgeons preferred cold blood cardioplegia, 14% used normothermic blood cardioplegia, 14% used crystalloid

cardioplegia, 21% employed retrograde perfusion, and 16% performed surgery without any cardioplegic strategy [6].

In response to the unique metabolic characteristics of immature myocardium, researchers at the University of Pittsburgh introduced a specialized cardioplegic solution in the early 1990s, targeting intracellular calcium control, energy preservation, lactate minimization, and enhanced buffering capacity. This formula, later refined by Dr. Pedro del Nido, became widely used in pediatric settings. However, its base component—Plasma-Lyte A—is not consistently available in several Asian healthcare systems, including Uzbekistan.

To address this limitation, we developed a modified version of the del Nido solution, substituting Plasma-Lyte A with 0.9% normal saline and tailoring the composition using locally available pharmacological agents. Despite the growing clinical use of del Nido cardioplegia worldwide, there is still limited evidence linking postoperative biomarker levels, such as high-sensitivity troponin I, with echocardiographic parameters of myocardial function in young children [2-3].

This study, therefore, was designed to evaluate the clinical efficacy of our adapted del Nido formulation by analyzing a comprehensive set of metabolic and functional indicators, including serum troponin and CK-MB levels, lactate and glucose trends, CPB and aortic cross-clamp times, incidence of arrhythmias, duration of mechanical ventilation, ICU stay, and the need for inotropic support.

**Objective.** To assess the incidence and severity of myocardial ischemic injury in children aged 1 to 3 years undergoing open-heart surgery for septal congenital heart defects, comparing the outcomes of blood-based modified del Nido cardioplegia versus conventional crystalloid cardioplegia.

**Materials and Methods.** A prospective, comparative clinical study was conducted at the National Children's Medical Center in Tashkent, Republic of Uzbekistan, from February 2021 to December 2024. The objective was to assess the effectiveness of intraoperative myocardial protection in children undergoing open-heart surgery for congenital heart defects (CHDs), using either cold crystalloid cardioplegia or a modified blood-based del Nido solution.

**Study Population:**

The study enrolled 106 pediatric patients aged 1 to 3 years with isolated septal defects—atrial septal defect (ASD) or ventricular septal defect (VSD). All patients underwent elective surgical correction under cardiopulmonary bypass (CPB) with cardioplegic arrest.

**Group Allocation:**

- **Control Group (n = 45):** Received standard cold crystalloid cardioplegia.
- **Intervention Group (n = 61):** Received a modified del Nido cardioplegia composed of pharmacological agents and oxygenated blood in a 4:1 ratio.

**Inclusion Criteria:**

- Age between 12 and 36 months;
- Diagnosis of isolated ASD or VSD indicated for primary radical repair;
- Preoperative high-sensitivity troponin I (hs-TnI) ≤ 0.034 ng/mL;
- Absence of ischemic changes on preoperative electrocardiogram (ECG);
- No associated genetic or comorbid systemic pathology;
- Signed informed consent obtained from parents or legal guardians.

**Exclusion Criteria:**

- History of prior palliative CHD surgery;
- Presence of complex or non-septal congenital heart anomalies;
- Lack of parental/legal consent for study participation.

**Surgical Protocol:**

All procedures were performed under standardized general anesthesia. The operative technique included a median sternotomy, harvesting and tailoring of an autologous pericardial patch, and initiation of CPB through arterial cannulation of the ascending aorta and bicaval venous cannulation (superior and inferior vena cava).

Myocardial arrest was induced via antegrade administration of the cardioplegic solution through a cannula placed in the aortic root after application of the aortic cross-clamp. The target systemic temperature was maintained between 32°C and 33°C. Cardioplegic solutions were prepared by trained nursing personnel according to a standardized digital calculator protocol, maintaining strict aseptic conditions. Solutions were cooled to 2–4°C prior to administration. In the intervention group, oxygenated blood was added to the base solution following the initiation of CPB.

**Post-Bypass Management:**

After restoration of spontaneous cardiac rhythm and successful weaning from CPB, all patients underwent modified ultrafiltration to optimize fluid balance and hemodynamics.

The detailed composition and formulation of the cardioplegic solutions utilized in each group are provided in Tables 1 and 2.

**Table 1.**

**Original Del Nido Cardioplegia Formulation**

| Ingredient | Volume (mL) | Function |
|---|---|---|
| Plasma-Lyte A | 1000.0 | Base solution: Na 140 mEq/L; K 5 mEq/L; Mg 3 mEq/L; pH 7.4 |
| Potassium chloride (KCl) | 13.0 | Myocardial depolarization |
| Sodium bicarbonate 8.4% ($NaHCO_3$) | 13.0 | pH buffer |
| Magnesium sulfate 50% ($MgSO_4$) | 4.0 | Calcium channel blocker, enhances myocardial recovery |
| Lidocaine 1% | 13.0 | Sodium channel blocker, hyperpolarizing agent |
| Mannitol 20% | 16.3 | Osmotic agent, scavenger of free radicals |

**Table 2.**

**Composition of Cardioplegic Solutions Used in the Study**

| Ingredient | Crystalloid Cardioplegia (CC) | Modified del Nido Solution | Function |
|---|---|---|---|
| Sodium chloride 0.9% (NaCl) | 500.0 mL | 500.0 mL | Base solution |
| Potassium chloride 4% (KCl) | 32.5 mL | 32.6 mL | Myocardial depolarization |
| Sodium bicarbonate 4% ($NaHCO_3$) | 13.8 mL | 14.4 mL | pH buffer |
| Magnesium sulfate 25% | 4.0 mL | 4.2 mL | Calcium channel blocker |
| Lidocaine 2% | 3.25 mL | 3.4 mL | Sodium channel blocker, stabilizes membrane potential |
| Mannitol 15% | 11.5 mL | 11.5 mL | Osmotic diuretic, free radical scavenger |
| Glucose 40% | 2.5 mL | — | Energy substrate (present only in CC solution) |
| Oxygenated autologous blood | — | 142.0 mL | Oxygen carrier, added in a 1:4 ratio (blood:solution) |

We also developed a custom electronic calculator for cardioplegic solution formulation, which enables rapid and precise computation of the required drug volumes. This tool minimizes reagent overuse and allows for individualized volume adjustment based on the patient's body weight.

**Table 3.**

**Electronic Calculator for Modified Del Nido Cardioplegia Composition**

| Component | Concentration (mg/mL) | Volume (mL) |
|---|---|---|
| Sodium chloride 0.9% | 7.947 | **200.0** |
| Mannitol 15% (150 mg/mL) | 3.044 | 4.6 |
| Lidocaine 2% (20 mg/mL) | 0.122 | 1.4 |
| Magnesium sulfate 25% (250 mg/mL) | 1.867 | 1.7 |
| Sodium bicarbonate 4% (40 mg/mL) | 1.020 | 5.8 |
| Potassium chloride 4% | 2.304 | 13.0 |
| Mix the prepared volume by shaking 3 times | 4 parts | 226.5 |
| Add oxygenated blood (mL) | 1 part | 57.0 |
| Administer cold (6–8°C) at a dosage of 20 mL/kg, not exceeding 100 mmHg | Total: 5 parts | 283.0 |

Specify volume of NaCl 0.9% for final solution preparation

**Endpoints and Outcome Measurements**

**Primary Endpoint:**

The primary clinical endpoint was defined as a >10-fold increase in serum troponin I concentration at 6 hours following surgery that persisted through the 24-hour mark. This biochemical finding was interpreted in conjunction with the diagnosis of **myocardial injury syndrome**, which was established based on the following criteria:

- Sustained elevation of troponin I (>10× upper reference limit) at both 6 and 24 hours postoperatively;
- Emergence of pathological Q waves or complete left bundle branch block (LBBB) on the postoperative electrocardiogram;
- At least a 50% reduction in global longitudinal strain (GLS) of the left ventricle, as assessed via transthoracic echocardiography (TTE), relative to baseline preoperative values.

**Biomarker Assessment:**

Cardiac-specific biomarkers—including high-sensitivity troponin I and creatine kinase–MB (CK-MB)—were quantified using immunofluorescence-based assays (NT-proBNP, Finecare) processed on the WONDFO Finecare III Plus analyzer. Measurements were obtained at four time points: preoperatively, and at 6 hours, 24 hours, and 72 hours (day 3) following surgery.

**Reference Ranges:**

- Troponin I: 0.00–0.10 ng/mL
- CK-MB: 0.00–5.00 ng/mL

**Echocardiographic Monitoring:**

Transthoracic echocardiography was performed using a Vivid T8 ultrasound system (General Electric Healthcare, USA). Examinations were conducted at baseline (preoperatively), and postoperatively at 6 hours, 24 hours, and on postoperative day 10. Left ventricular function was assessed, with specific focus on global longitudinal strain (GLS) and ejection fraction.

**Statistical Analysis**

All tabulated data are presented as mean ± standard deviation (M ± σ), where *M* represents the arithmetic mean and *σ*denotes the standard deviation. The analysis of differences between groups was conducted using **nonparametric statistical methods**, considering the non-normal distribution of several variables.

Group comparisons for independent samples were performed using the **Mann–Whitney U-test**. The Wilcoxon–Mann–Whitney *W*-statistic was calculated according to the formula:

$W=\min(\sum Ri,\sum Si)$

where:

• Ri- denotes the ranks of the sample with the lower rank sum,
• Si- denotes the ranks of the sample with the higher rank sum.

Statistical significance was determined by comparing the smaller rank sum to critical *W*-values from standard reference tables. A *p*-value < 0.05 was considered statistically significant.

Correlation between independent variables was assessed using the **Spearman rank-order correlation coefficient ($r_s$)**, calculated as follows:

rs=1−6∑(r1−r2)2n(n2−1)rs=1−n(n2−1)6∑(r1−r2)2

where ∑(r1−r2)2∑(r1−r2)2 is the sum of squared differences between paired ranks.

The strength of association was interpreted as follows:

• r>0.7r>0.7: strong correlation,
• 0.3<r≤0.70.3<r≤0.7: moderate correlation,
• r≤0.3r≤0.3: weak correlation.

All statistical computations were performed using **Microsoft Excel 2019** and **IBM SPSS Statistics version 26**. The methodology and interpretation principles were guided by Rebrova O.Yu., *Statistical Analysis of Medical Data*, 3rd ed., Moscow: Media Sfera, 2006

**Table 4.**

**Preoperative Clinical and Demographic Characteristics of Patients (M ± SD)**

| Parameter | Crystalloid Group (n=45) | Del Nido Group (n=61) | p-value |
|---|---|---|---|
| Length of hospital stay, days | 25.8 ± 11.5 | 13.3 ± 5.1 *** | < 0.001 |
| Mechanical ventilation time (hrs) | 26.8 ± 10.7 | 20.3 ± 8.3 *** | < 0.001 |
| Age, years | 2.2 ± 0.9 | 1.69 ± 0.69 *** | < 0.001 |
| Height, cm | 86.3 ± 8.5 | 81.6 ± 7.1 *** | < 0.001 |
| Weight, kg | 11.7 ± 2.5 | 10.6 ± 3.3 ** | < 0.01 |
| Body surface area (BSA), m² | 0.53 ± 0.08 | 0.49 ± 0.08 ** | < 0.01 |
| Body mass index (BMI), kg/m² | 23.8 ± 6.9 | 25.9 ± 8.0 | n.s. |

**Table 5.**

**Intraoperative Parameters in Study Groups (M ± SD)**

| Parameter | Crystalloid Group (n=45) | Del Nido Group (n=61) | p-value |
|---|---|---|---|
| Total anesthesia time, hours:min | 3:50 ± 0:53 | 3:02 ± 0:32 *** | < 0.001 |
| Surgical time, hours:min | 2:56 ± 0:44 | 2:09 ± 0:29 *** | < 0.001 |
| Cardiopulmonary bypass duration (CPB), minutes (t IK) | 67.9 ± 32.5 | 50.1 ± 18.6 *** | < 0.001 |
| Aortic cross-clamp time, minutes (t Ao SS) | 43.1 ± 24.4 | 31.8 ± 15.5 ** | < 0.01 |
| CPB duration after aortic unclamping, minutes | 13.5 ± 5.1 | 9.53 ± 4.19 *** | < 0.001 |

**Table 6.**

**Cardioplegia Delivery Parameters in Study Groups (M ± SD)**

| Parameter | Crystalloid Group (n=45) | Del Nido Group (n=61) | p-value |
|---|---|---|---|
| Volume of first cardioplegia dose, mL ($V_1$) | 251.9 ± 60.7 | 229.1 ± 58.1 * | < 0.05 |

| | | | |
|---|---|---|---|
| Volume of second (repeat) dose, mL ($V_2$) | 114.4 ± 24.1 | 101.0 ± 26.1 | n.s. |
| Total volume of solution administered, mL (*V_total*) | 295.1 ± 79.9 | 235.7 ± 61.5 *** | < 0.001 |
| Volume per kilogram of body weight, mL/kg (*V/weight*) | 25.6 ± 6.1 | 23.0 ± 5.5 * | < 0.05 |
| Volume per minute of CPB duration, mL/min (*V/t_CPB*) | 5.1 ± 2.37 | 5.3 ± 2.3 | n.s. |
| Volume per kg and CPB time, mL/kg·min (*V/(weight × t_CPB)*) | 0.44 ± 0.18 | 0.51 ± 0.20 ** | < 0.01 |
| Frequency of cardioplegia administration (*number of doses*) | 1.43 ± 0.64 | 1.07 ± 0.25 *** | < 0.001 |

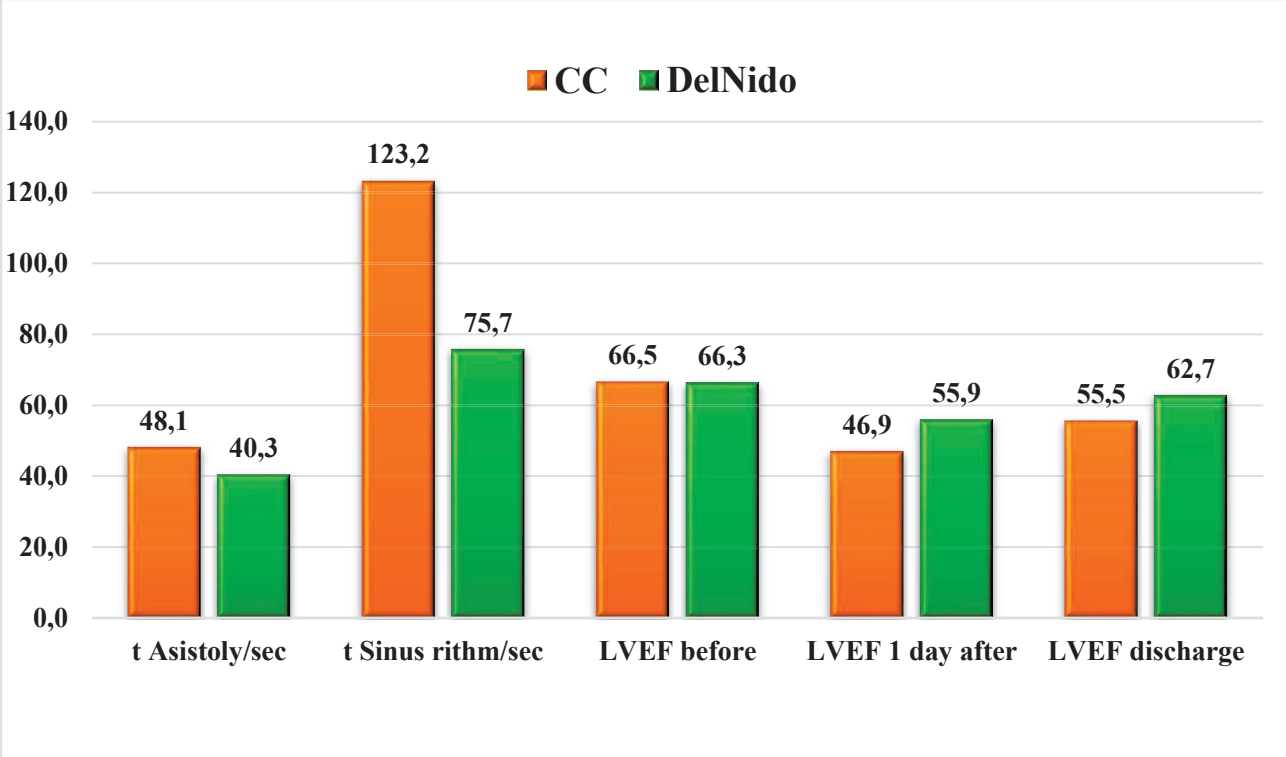


**Fig. 1.** Comparison of results in the CC and Del Nido Groups

**Results.** Baseline preoperative plasma troponin I concentrations were within the normal reference range in both the crystalloid cardioplegia (CC) and modified del Nido groups. Preoperative transthoracic echocardiography demonstrated no statistically significant differences between the groups in terms of left ventricular longitudinal mechanics or overall cardiac function.

Likewise, no significant intergroup differences were observed in intraoperative parameters such as cardiopulmonary bypass (CPB) duration, aortic cross-clamp time (myocardial ischemia period), duration of postoperative mechanical ventilation, or length of stay in the intensive care unit (ICU).

Importantly, no in-hospital mortality occurred in either group.

**Troponin I Kinetics:**Postoperative monitoring revealed a significant elevation in serum troponin I at 6 hours in all patients. However, the magnitude of increase was significantly greater in the CC group compared to the del Nido group (9.03 ± 1.02 ng/mL vs. 7.09 ± 0.01 ng/mL, $p < 0.001$). Notably:

- In the del Nido group, 16 patients (28%) exhibited a >10-fold elevation in troponin I at 6 hours, which persisted through 24 hours.
- In the CC group, this pattern was observed in 25 patients (56.8%).

Thus, the **primary endpoint**—defined as sustained troponin I elevation >10× upper reference limit at both 6 and 24 hours—was reached significantly more frequently in the CC group ($p < 0.001$).

By postoperative day 3, troponin I levels declined in both cohorts, with no statistically significant difference in the **rate of decline** between the groups.

**Left Ventricular Function (LVEF):** Postoperative echocardiographic assessment revealed marked differences in LVEF preservation:

- At 24 hours post-surgery, LVEF declined by **30.7%** from baseline in the crystalloid group.
- In contrast, LVEF in the del Nido group declined by only **18%**, indicating superior myocardial functional preservation ($p < 0.01$).

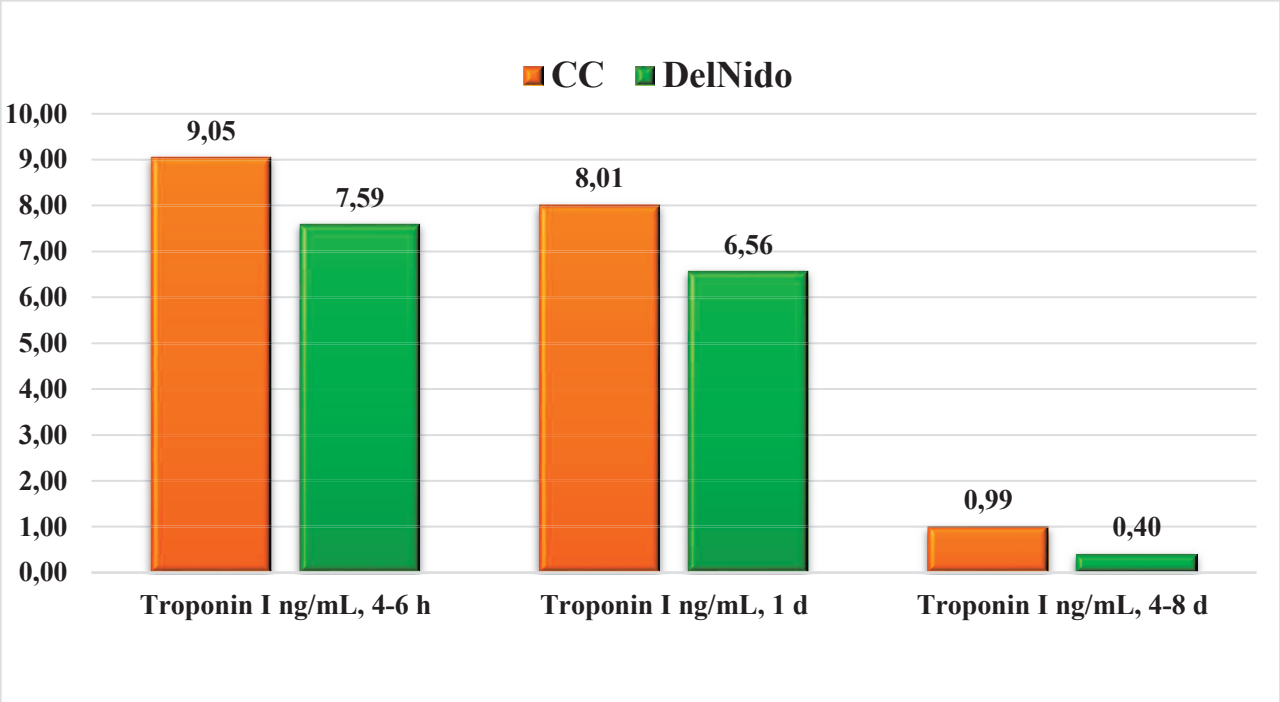


**Fig. 2.** Postoperative Troponin I Dynamics in the CC and Del Nido Groups

**Additional Observations.** No statistically significant differences were noted between the study groups in terms of postoperative serum lactate and glucose dynamics. Both groups exhibited similar metabolic responses across all monitored time points. Furthermore, no instances of new-onset complete left bundle branch block (LBBB) or clinically significant arrhythmias were observed during the postoperative period in any patient.

**Discussion.** This prospective clinical study compared two widely utilized cardioplegic strategies in pediatric patients undergoing surgical correction of atrial and ventricular septal defects: conventional cold crystalloid cardioplegia and a locally modified, blood-enriched del Nido solution.

Children in the del Nido group demonstrated:

- significantly lower postoperative elevations in cardiac-specific troponin I,
- more favorable preservation of left ventricular longitudinal function (assessed by echocardiography),
- and a reduced need for postoperative inotropic support compared to those who received crystalloid cardioplegia.

These findings suggest superior myocardial protection conferred by the del Nido solution in this pediatric cohort.

Although cardioplegia is a routine component of pediatric open-heart surgery, the literature continues to reflect a lack of consensus regarding the optimal formulation for young patients [11,12]. Among the proposed intraoperative markers of myocardial injury, **dynamic changes in troponin I**

have emerged as a sensitive and reliable indicator, even in pediatric populations [11]. However, pediatric-specific thresholds for prognostic interpretation remain undefined.

A study by J.A. Su et al. (2019) found that 93% of infants under one year of age exhibited elevated troponin I levels at 8 hours following CHD repair. Interestingly, only 14% of these children had persistent or rising troponin levels thereafter. This subgroup experienced a disproportionately high incidence of postoperative complications such as low cardiac output syndrome, ischemic stroke, and acute kidney injury. Although a troponin I concentration of 8.44 ng/mL at 12 hours post-surgery showed a trend toward prognostic significance ($p = 0.1$; AUC = 0.53), no definitive cutoff value was established [10].

In the present study, **21 patients (23.1%)** exhibited sustained elevation of troponin I at 24 hours, which was accompanied by pathological ECG findings and increased inotropic requirements—criteria consistent with **postoperative myocardial injury syndrome**. These outcomes are likely multifactorial, reflecting the cumulative effects of direct surgical trauma, ischemia–reperfusion injury, and systemic inflammatory responses induced by cardiopulmonary bypass (CPB).

**Conclusion:**

1. **Myocardial injury syndrome** was observed in **26% of pediatric patients** during the early postoperative period following surgical repair of atrial and ventricular septal defects. This syndrome was characterized by sustained elevation of troponin I levels beyond 24 hours, ischemic electrocardiographic changes, and the need for increased inotropic support, reflecting significant perioperative myocardial stress.

2. The application of **blood-based del Nido cardioplegia** in young children was associated with a **lower incidence and reduced severity of myocardial injury** when compared to conventional cold crystalloid cardioplegia. These findings suggest that the modified del Nido protocol may offer superior myocardial protection and should be considered a favorable strategy in the surgical management of congenital septal heart defects in early childhood.

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