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Original Article

Impact of Reducing Intervals Between Two Cardioplegia Injections on Clinical Outcomes Among Pediatrics Undergoing Cardiopulmonary Bypass: A Randomized Clinical Trial

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ABSTRACT

Background: The use of a cardiopulmonary bypass machine during heart surgery can increase the risk of myocardial damage, as indicated by elevated levels of troponin I and creatine phosphokinase markers. Therefore, there is a need to reduce ischemia-reperfusion injury following pediatric cardiopulmonary bypass surgery. It appears that myocardial damage may be mitigated by shortening the intervals between cardioplegia injections.

Methods: This randomized controlled trial was conducted on pediatric patients undergoing surgery for Tetralogy of Fallot. Participants were randomly assigned to either an intervention group or a control group using the block randomization method. In the intervention group, the interval between 2 doses of Del Nido cardioplegia was reduced to 40 minutes, while patients in the control group received Del Nido cardioplegia every 60 minutes. Data for the trial were collected using checklists prepared by the researcher.

Results: The study findings indicated that, although the mean levels of troponin and phosphokinase were significantly lower in the trial group compared with the control group, the changes in both markers across different measurement times were similar in both groups. Most other clinical outcome parameters of heart surgeries, such as left ventricular ejection fraction, the time required for the heart rhythm to return to normal after aortic declamping, and the type of arrhythmia, did not show significant differences between the trial groups.

Conclusions: The findings of our trial demonstrated that, although there were no statistically significant changes in hemodynamic status, left ventricular ejection fraction, blood urea nitrogen, creatinine levels, inotropic score, time for heart rhythm resumption, and frequency of arrhythmia, reducing the interval between 2 Del Nido injections had positive effects on myocardial protection in pediatric heart surgeries. ***(Iranian Heart Journal 2025; 26(2): 6-14)***

KEYWORDS: Cardioplegia, Clinical outcome, Pediatric patients, Tetralogy of Fallot

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Cardiac operations with cardiopulmonary bypass are widely recommended as therapeutic procedures for congenital cardiac abnormalities. [1] Nonetheless, ischemia-reperfusion injury is one of the cardiac lesions that can occur during these operations. [2] Despite advancements in cardioprotective strategies, elevated troponin I levels resulting from myocardial damage remain independent predictors of unfavorable postoperative clinical outcomes in pediatric patients, including left ventricular systolic dysfunction, cardiac heart failure, and even mortality. [2,3]

Cardioplegia is crucial in cardioprotective strategies during operations, particularly with cardiopulmonary bypass, by reducing cardiac function and energy expenditure. Cardioplegia solutions are available in 2 forms: intracellular (low sodium and potassium) and extracellular (high sodium and potassium with magnesium). [4] Various modifications have been made to the composition of cardioplegia solutions, including increasing the osmotic pressure, adding buffers to control acidosis, and adding supplements to trap free radicals. All these alterations seek to improve the mechanisms for removing ischemia-reperfusion lesions in patients. [4]

The Del Nido cardioplegia solution, composed of crystalloid and whole blood components in a 4-to-1 ratio, is administered as a single dose and does not require multiple injections. The unique formulation of the Del Nido cardioplegia solution reduces energy consumption, blocks calcium entry into the intracellular space, and collects hydrogen ions, thereby improving anaerobic glycolysis during cardiac arrest. [5] For instance, hyperosmotic mannitol in the Del Nido cardioplegia solution helps scavenge free radicals and reduce cell inflammation in adults and children. [6] The advantages of using the Del Nido cardioplegia solution in cardiac operations include decreased injection times and increased intraoperative time for surgeons and perfusionists. [7]

Given the high prevalence of congenital cardiovascular defects and associated complications among pediatric patients in surgery, it is crucial to explore procedures and innovations aimed at reducing operation-related complications. It is hypothesized that reducing the interval between cardioplegia injections could improve operation-related outcomes by reducing arrhythmias and the need for defibrillation.

Therefore, this study aimed to assess the impact of reducing the injection interval of the Del Nido cardioplegia solution from 60 minutes to 40 minutes among pediatric patients undergoing tetralogy of Fallot repair.

METHODS

Trial Design: The present randomized clinical trial with a parallel design was performed on pediatric patients who were candidates for tetralogy of Fallot surgery in 2021 at the Rajaie Cardiovascular Institute, Tehran, Iran. The study protocol received approval from the Research Ethics Committee of the Rajaie Cardiovascular Institute, and all study participants signed informed consent (IR.RHC.REC.1400.080). The trial protocol was registered in the Iranian Randomized Clinical Trial Registration System (IRCT20220424054638N1).

Participants: Trial participants were pediatric patients who were candidates for tetralogy of Fallot surgery. Inclusion criteria were pediatric patients weighing < 10 kg, parental informed consent, an aortic cross-clamping period between 60 and 180 minutes, and sternotomy. Among these, patients who experienced cardiac arrest and return to the pump, or severe hypothermia (< 25 °C) were excluded.

Intervention: Included patients were randomly allocated to the intervention (n=20) and control (n=21) group according to the block randomization method. Anesthesia conditions, operation type, age, body surface area, priming type, perfusion type, and temperature management were similar between the 2 groups. The first dose of the Del Nido cardioplegia injection for patients in both groups was 20 mL/kg, and the second was half of the first dosage. In the intervention group, the interval between 2 Del Nido cardioplegia solution injections was reduced to 40 minutes. The control group received the del Nido cardioplegia dosage every 60 minutes as previously described. [8] The cardioplegia solution was injected into the aortic root after clamping between 8 °C and 12 °C. Heart rate, blood pressure, and pulse oximetry data were recorded for patients in the operating room. Oxygenation (2 L/min) was initiated for patients upon entering the operating room, and 10 mL/kg of the crystalloid Ringer solution was injected before the operation. The routine monitoring included ECG, pulse oximetry, invasive blood pressure, central venous pressure, capnography, and the Bispectral index. [9,10] After anesthesia induction, a central vein catheter was inserted, and antipain and muscle relaxant drugs were injected. Following intubation, anesthesia was continued with a maintenance dosage of intravenous agents. Ventilation was controlled mechanically. A blood sample was collected every hour for arterial blood gases and hemoglobin, hematocrit, and lactate levels. Cardiopulmonary bypass was primed with ringer lactate, albumin, and packed cells and managed with 2.5 to 3.2 L/m² BSA with a roller pump according to the patient's blood pressure. Anticoagulation status was assessed with an active coagulation time > 480 seconds. [11] Subsequently, heparin (300 units/kg) was administered. The cooling phase was conducted for the included patients until a temperature of 28 °C was reached. Following the declamping of the aorta, the rewarming phase was initiated and continued until a temperature of 37 °C was achieved.

Outcomes: Heart rate; systolic, diastolic, and mean arterial blood pressure values; coronary sinus lactate; troponin; creatine phosphokinase; and arrhythmia type were measured as trial outcomes in the preoperative and postoperative phases, as well as at ICU entrance and 12 and 24 hours afterward. One sample was collected from the entrance of the coronary sinus into the right atrium at the time of aortic declamping to measure coronary sinus lactate levels. Troponin and creatine phosphokinase were measured before and 24 hours after the intervention. The mean left ventricular ejection fraction (LVEF), resumption of normal sinus rhythm after aortic declamping, and arrhythmia type were recorded. Whole blood was added to the prime solution according to the formula by Gravlee [4] for patients with low preoperative hemoglobin and hematocrit levels, aiming to maintain the hematocrit between 25% and 30%.

Sample Size: Based on the sample size formula from reference 12 and the study characteristics ($\alpha = 0.05$, $\beta = 0.8$, dropout rate = 20%, case/control ratio = 1), a minimum of 46 samples were required for the trial.

Randomization and Allocation: Randomization of included patients was performed according to the block randomization method. Study participants were randomly allocated to the intervention (n=20) and control (n=21) groups.

Blinding: This study is a double-blind clinical trial, and patients and cardiac surgeons were unaware of the trial groups.

Statistical Analysis

Study data were entered into the SPSS, version 24.0, for statistical analysis. Mean, standard deviation, frequency, and percentage were used to describe quantitative and qualitative variables. Two-way ANOVA with repeated measure analysis and the χ^2 test were employed to analyze quantitative and qualitative variables. A *P*-value < 0.05 was considered significant.

RESULTS

This trial was performed on 41 pediatric patients hospitalized for tetralogy of Fallot surgery. Study participants were randomly allocated into the intervention (n=21) and control (n=20) groups. The basic characters of the study participants and the flow diagram are presented in Table 1 and Figure 1.

Table 1. The frequency distribution of the basic characteristics of the study participants in the intervention and control groups

Basic Characteristics	Intervention (n=21) Mean±(SD)	Control (n=20) Mean±SD	*P*
Age, mon	9 (16.25)	8.5 (19.16)	0.85
Weight, kg	5 (2.6)	6 (3.9)	0.71
Height, cm	75 (26)	70.5 (32)	0.98
Body surface area, cm^2	0.32 (0.11)	0.34 (0.25)	0.73
Flow (L/min)	900 (240)	920 (523)	0.69

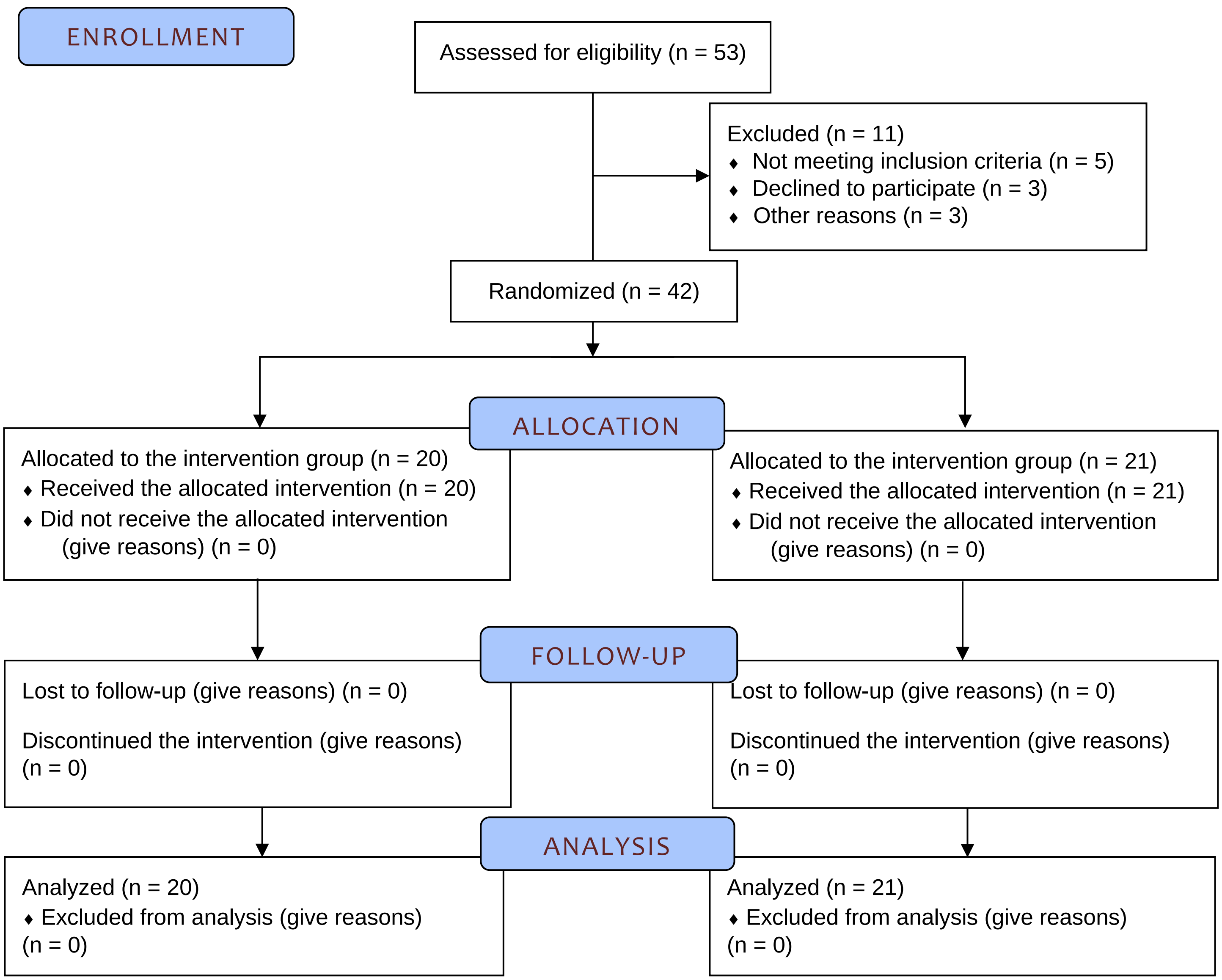

Figure 1. The image presents the flow diagram of the present study.

The mean systolic, diastolic, and mean arterial blood pressure values had no significant differences between the intervention and control groups at different measurement times. On the other hand, the reduction in the time of the Del Nido cardioplegia solution injection as an intervention in this trial had no significant impact on systolic, diastolic, and mean arterial blood pressure values between the 2 groups. The mean heart rate was significantly higher in the intervention group than in the control group. Table 2 presents details of the above comparisons.

Table 2. The mean and standard deviation (SD) of systolic, diastolic, and mean arterial blood pressure values among the trial participants

	Groups Time	Intervention (n=21) Mean±(SD)	Control (n=20) Mean±(SD)	*P*
Systolic blood pressure, mm Hg	Preoperative	92.38±10.70	91.40±15.78	00.97
	Postoperative	92.38±10.70	92.38±10.70	00.87
	ICU entrance	92.38±10.70	92.38±10.70	00.95
	6 hours after ICU entrance	92.38±10.70	92.38±10.70	00.76
	12 hours after ICU entrance	92.38±10.70	92.38±10.70	00.69
	18 hours after ICU entrance	92.38±10.70	92.38±10.70	00.71
	24 hours after ICU entrance	92.38±10.70	92.38±10.70	00.80
Diastolic blood pressure, mm Hg	Preoperative	46.62±12.50	41.30±10.15	00.81
	Postoperative	47.86±10.80	40.70±8.27	00.89
	ICU entrance	47.52±10.10	41.05±7.52	00.74
	6 hours after ICU entrance	48.05±9.98	42.60±6.98	00.71
	12 hours after ICU entrance	49.14±10.69	43.01±6.72	00.68
	18 hours after ICU entrance	49.05±10.60	44.05±7.22	00.90
	24 hours after ICU entrance	49.24±10.66	43.25±7.55	00.70
Mean arterial blood pressure, mm Hg	Preoperative	58.71±12.54	52.95±11.75	00.60
	Postoperative	59.14±11.46	51.95±8.68	00.63
	ICU entrance	58.86±10.80	52.25±8.60	00.59
	6 hours after ICU entrance	59.57±10.98	54.25±8.25	00.10
	12 hours after ICU entrance	60.67±11.83	54.60±8.48	00.50
	18 hours after ICU entrance	61.01±11.89	55.45±8.33	00.71
	24 hours after ICU entrance	61.33±12.72	54.65±8.74	00.09
Heart rate	Preoperative	136.95±14.82	136.85±31.19	00.98
	Postoperative	138.86±16.91	130.95±22.49	00.78
	ICU entrance	138.90±15.32	131.40±22.35	00.50
	6 hours after ICU entrance	138.38±13.51	130.60±23.12	00.41
	12 hours after ICU entrance	138.24±12.70	128.90±22.28	00.23
	18 hours after ICU entrance	137.95±12.34	129.01±21.38	00.12
	24 hours after ICU entrance	137.71±11.64	127.85±21.40	00.09

The mean preoperative LVEF had no significant differences between the intervention and control groups (51.67 ± 4.28 vs 49.50 ± 4.26; P = 0.11). The mean postoperative LVEF exhibited no significant differences between the 2 groups (54.05 ± 2.01 vs 53.01 ± 2.99; P = 0.19). The mean time for returning to normal heart rhythm after aortic cross-clamp removal was similar between pediatric patients in both groups (74.29 ± 55.66 vs 60.01 ± 42.18; P = 0.36). Only 1 patient in the intervention group and 2 patients in the control group had arrhythmias (ventricular tachycardia and ventricular fibrillation, respectively). Thus, arrhythmia distribution was similar between the 2 groups (P = 0.36). The mean of inotropic usage did not significantly differ between the intervention and control groups (11.36 ± 2.13 vs 11.28 ± 5.94; P = 0.95). The mean coronary sinus lactate level after aortic declamping was similar between the 2 groups (5.10 ± 0.86 vs 5.81 ± 1.75; P = 0.11).

The serum level of nitrogen in the intervention group was significantly higher than that in the control group (P < 0.001). The shortened Del Nido injection interval significantly impacted the serum blood nitrogen urea level in pediatric patients.

There were significant differences in the mean values of blood urea and creatinine between the intervention and control groups at the ICU entrance and 24 hours afterward (P < 0.05). The decrease in the Del Nido injection time significantly affected the serum level of creatinine, with the serum level of creatinine being significantly lower at all 3 measurement points in the intervention group than in the control group. Table 3 presents details of the above comparisons.

The mean troponin and creatine phosphokinase levels in the intervention group were significantly lower than those in the control group. Additionally, troponin and creatine phosphokinase levels showed a significant initial increase followed by a decrease across the intervention measurement points (P < 0.05). A decrease in the Del Nido injection time as the trial intervention significantly reduced the serum levels of troponin and creatine phosphokinase in the intervention group. Table 4 offers details of the above comparisons.

Table 3. The frequency distribution of the serum levels of blood urea and creatinine in the intervention and control groups

	Groups Time	Intervention (n=21) Mean±(SD)	Control (n=20) Mean±(SD)	P*
Blood urea, mg/dL	Preoperative	13.05±5.19	10.13±3.96	0.015*
	ICU entrance	17 ± 4	10.5 ± 4	<0.001**
	24 hours after ICUentrance	17±14	11±5	<0.001**
Creatinine, mg/dL	Preoperative	0.59±0.4	0.65±0.6	0.08
	ICU entrance	0.6±0.7	0.75±0.7	<0.001**
	24 hours after ICUentrance	0.7±0.4	0.7±0.6	<0.001**

* Independent sample t-test ** Mann-Whitney U test

Table 4. The frequency distribution of the serum levels of troponin and creatine phosphokinase in the intervention and control groups

	Groups Time	Intervention (n=21) Mean±(SD)	Control (n=20) Mean±(SD)	*P**
Troponin, ng/mL	Preoperative	18.15±12.95	22.91±17.82	00.053
	ICU entrance	28.85±24.56	72.23±53.04	00.001
	24 hours after ICU entrance	30.71±21.96	48.46±38.44	00.01
Creatine phosphokinase, ng/mL	Preoperative	187.34±48.63	212.44±279.86	00.01
	ICU entrance	136.33±54.44	312.99±527.55	<0.001
	24 hours after ICU entrance	143.56±29.93	165.02±252.94	0.05

DISCUSSION

This trial was conducted to assess the impact of reduced Del Nido cardioplegia injection intervals on the clinical outcomes of pediatric patients undergoing tetralogy of Fallot surgery. Our findings demonstrated that the demographic and hemodynamic parameters of pediatric patients were similar between both groups, consistent with the results reported by Gorjipour et al. [13] The serum levels of cardiac enzymes rose immediately after the operation due to tissue impermeability and subsequently decreased postoperatively one day after the operation. In the study by Gorjipour et al, [13] although the postoperative serum level of troponin I in a single injection of the Del Nido cardioplegia solution increased, there was no significant difference in troponin I levels between the 2 patient groups receiving different cardioplegia solutions. The trends in creatine phosphokinase levels during our trial differed between the intervention and control groups, contrary to the findings of Panigrahi et al, [14] where similar changes were observed between the groups.

In our study, the mean preoperative and postoperative LVEF showed no significant differences between the intervention and control groups, consistent with the findings reported by D'Angelo et al. [15] In our study, the mean renal function parameters (blood urea nitrogen and creatinine) were dissimilar between the pediatric patients in the 2 groups. This contrasts with the findings of Gorjipour et al, [13] where blood urea nitrogen and creatinine changes were similar between the intervention and control groups.

Our findings suggest that the renal function of pediatric patients appears to be independent of the type of cardioplegia solution used.

The mean inotropic usage was similar between patients in the intervention and control groups, which aligns with the findings of Koda et al. [16] In contrast, Ucak et al [17] reported a significantly higher mean inotropic score among patients receiving the St Thomas cardioplegia solution compared to the Del Nido cardioplegia solution, and Caneo et al [18] also found significantly higher inotropic scores in patients receiving the San Thomas cardioplegia solution compared to the Del Nido cardioplegia solution.

We believe that the postoperative use of inotropic agents may be related to various factors such as preoperative patient health, disease severity, and surgical complexity, and not specifically tied to the type of cardioplegia solution used.

The mean time for resumption of sinus rhythm after removing aortic cross-clamping was similar between the intervention and control groups in our study. This finding differs from other studies, such as the one conducted by Luo et al, which reported a longer time to return to normal rhythm in patients receiving the St Thomas cardioplegia solution compared to those in the Del Nido group.

Our study indicates that reducing the cardioplegia injection interval may have a positive impact on myocardial protection and reduce markers of cardiac muscle damage.

It is important to exercise caution when interpreting the findings of the current study due to the limited study population.

CONCLUSIONS

The findings of our study showed that all postoperative outcome parameters were similar between the intervention and control groups. On the other hand, a decline in the injection interval of the Del Nido cardioplegia solution had a significant impact on myocardial protection markers.

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