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Article

Efficacy and Safety of Multidose del Nido Cardioplegia for Optimal Myocardial Protection in Isolated Coronary Artery Bypass Grafting Surgery: A Comparative Retrospective Cohort Study

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Abstract

Background: The perioperative outcomes of del Nido cardioplegia (DNC) as a single-dose solution have been investigated in cardiac surgical procedures. However, the optimal redosing interval for multiple doses of DNC remains an area of ongoing debate. The purpose of this study is to evaluate the safety and efficacy of multidose DNC administered according to our protocol in comparison to intermittent cold blood cardioplegia (BC) in isolated coronary artery bypass grafting (CABG) patients. **Methods**: A retrospective analysis was conducted on 79 consecutive isolated CABG patients between January 2022 and March 2023. The Patients were divided into two groups: the DNC group (n = 35), and the BC group (n = 44). Perioperative clinical characteristics, cardiac enzyme levels, and postoperative complications were compared between the groups. DNC was applied in a 1:4 (crystalloid:blood) ratio, with an initial dose of 20 mL/kg. Maintenance doses of 10 mL/kg were given every 45 to 50 minutes. A half dose was given if the aortic cross-clamp was expected to last less than 60 minutes. Warm blood was applied before releasing the aortic cross-clamp. **Results**: Both groups demonstrated comparable mean aortic cross-clamp and cardiopulmonary bypass times. At 24 hours postoperatively, troponin T levels were significantly lower in the DNC group ($p < 0.001$), while creatine kinase-myocardial band (CK-MB) levels were higher ($p < 0.001$). The DNC group required lower defibrillation rates than the BC group ($p = 0.008$). Multivariate logistic regression analysis revealed that the requirement for defibrillation (odds ratio (OR) = 10.9, 95% confidence interval (CI): 2.9–41.8, $p < 0.001$), cross-clamp time (OR = 1.04, 95% CI: 1.02–1.1, $p = 0.002$) and body mass index (BMI) (OR = 0.8, 95% CI: 0.7–0.9, $p = 0.030$) were independent risk factors for low cardiac output syndrome. DNC and left ventricle ejection fraction >40% were associated with a return to sinus rhythm (OR = 3.6, 95% CI: 1.3–10.1, $p = 0.013$ and OR = 3.1, 95% CI: 1.1–8.7, $p = 0.035$, respectively). No significant differences were found in terms of postoperative adverse events, and in-hospital mortality. **Conclusion**: Multidose DNC in CABG patients provides equivalent clinical outcomes and myocardial protection compared to BC. In addition, the findings suggest that the redosing interval strategy employed in the DNC protocol is acceptable.

Keywords

coronary artery bypass grafting; myocardial protection; del Nido cardioplegia

Introduction

Myocardial protection is critical during cardiac surgeries, as it aims to minimize myocardial injury and optimize patient outcomes. Hence, various myocardial protection techniques and solutions have been developed and applied. However, the optimal myocardial protection for cardiac surgical procedures remains controversial, with no conclusive evidence establishing the definitive superiority of any single cardioplegic solution [1]. This has led to inconsistencies regarding the administration of cardioplegia at different cardiac surgical centers.

Even though del Nido cardioplegia (DNC) was initially designed for pediatric use, it is now more frequently used in adults as it can be safely administered as a single dose and requires less frequent redosing. This has simplified the myocardial protection strategy, potentially resulting in shortened cross-clamp times [2–5]. Despite being labeled as a single-dose technique, surgeons may administer additional doses (as maintenance redosing) based on their preferences or due to intraoperative issues that prolong ischemic time. However, the effect of repeated doses of DNC and a reliable redosing interval, particularly in isolated coronary artery bypass grafting (CABG) procedures, remain areas of ongoing debate and limited investigation in the literature [6–8]. Therefore, this study aimed to evaluate the safety and efficacy of multiple doses of DNC applied according to our dosing interval strategy compared to intermittent cold blood cardioplegia (BC) during isolated CABG procedures.

Materials and Methods

Study Design and Population

This retrospective cohort study was conducted at the Department of Cardiovascular Surgery in Bozok University Hospital. We reviewed the medical records of 243 patients who underwent cardiac procedures at the hospital between January 2022 and March 2023. The study included adult patients who had undergone isolated CABG procedures with multiple doses of cardioplegia solution (two or more, including the initial dose). The exclusion criteria were: patients under 18 years old, those who received single-dose cardioplegia, patients who underwent procedures other than isolated CABG, or required emergency surgery, individuals with prior cardiac surgeries, preoperative hemodynamic instability with cardiogenic shock, preoperative requirement of inotropic support or intra-aortic balloon pump (IABP) insertion, and those with missing data. A total of 79 patients were included in the study. We adopted the DNC in December 2022. The patients were divided into two groups: Group 1 (n = 44) received BC and underwent surgery between January 2022 and November 2022, and Group 2 (n = 35) received multiple doses of DNC and underwent surgery between December 2022 and March 2023 (Fig. 1).

Data were obtained from hospital records, anesthesia and perfusion records, and patient files. Along with demographic data, preoperative comorbidity factors, pre and postoperative laboratory values, cardiac enzymes, echocardiography findings, intraoperative parameters, and postoperative outcomes were collected.

The primary endpoint was the efficacy of myocardial protection, which was assessed by: (1) differences in cardiac biomarker levels between the groups at different postoperative time points; (2) the presence of low cardiac output syndrome (LCOS), which is defined by the need for an intraoperative IABP to facilitate weaning from cardiopulmonary bypass (CPB) or within the first 24 hours in the intensive care unit (ICU) and/or the requirement of inotropic support by at least two of dopamine, dobutamine or epinephrine due to hemodynamic instability. Patients who received single inotropic support were not diagnosed with LCOS; (3) defibrillation requirement after releasing the cross-clamp; (4) cross-clamp and CPB durations, and (5) evaluating the postoperative left ventricular ejection fraction (LVEF) by transthoracic echocardiography within seven days postoperatively without inotropic support. The secondary endpoints included early mortality within 30 days post-surgery and postoperative morbidities.

Surgical Procedures and Myocardial Protection Techniques

All surgeries followed a standard anesthesia protocol with a median sternotomy approach, utilizing ascending aorta and unicaval two-stage venous cannulation. The Sorin c5 (Stockert, Munich, Germany) extracorporeal perfusion system was employed for CPB, with Euroset/Sorin Inspire oxygenator and hardshell reservoir in CPB circuits. Circuit priming consisted of 2000 mL of Isolyte-S (500 mL, Türk Ilaç ve Serum Sanayi, Akkuyu, Ankara), 100 mL of 20% Mannitol (20% 100 mL solution, OSEL, Beykoz, Istanbul), and 1000 IU of Heparin (Koparin 25.000 IU/5 mL, Koçak Farma, Çerkezköy, Tekirdağ). If necessary, one packed red blood cell unit was added during the initial CPB phase to maintain hematocrit (Htc) levels above 22%. Mean arterial pressure was maintained between 60 and 80 mmHg, with a non-pulsatile arterial flow rate between 1.8–2.5 L/min/m^2. Moderate systemic hypothermia (esophageal temperature of 28–30 °C) was applied, and Htc levels were kept at 22–25%. Grafts included the left internal mammary artery and saphenous veins for all patients.

Table 1. Components of cardioplegia solutions.

	Blood cardioplegia	del Nido cardioplegia
Blood: crystalloid ratio	4:1	1:4
Isolyte-S solution	1000 mL	500 mL
Mannitol (20%)	10 cc	17 cc
Potassium chloride (7.5%)	40–50 mL	26 mL
Lidocaine (2%)	0	6.5 mL
Magnesium sulfate (15%)	10 mL	14 mL
Sodium bicarbonate (8.4%)	20 mL	13 mL
Dextrose (10%)	10 mL	0

For myocardial protection, intermittent cold BC was administered at a 4:1 (blood:crystalloid) ratio. The initial dose was 20 mL/kg at 4 °C with a pressure of 180 mmHg administered in 2 minutes, followed by a maintenance dose of 10 mL/kg every 20 minutes. DNC was given at a 1:4 (crystalloid:blood) ratio, with an initial dose of 20 mL/kg (max 1000 mL) at 4–6 °C and a pressure of 100–200 mmHg administered in 1–2 minutes. Maintenance doses of 10 mL/kg (max 500 mL) were administered every 45 to 50 minutes, with a half dose (250 mL) if the aortic cross-clamp was expected to be under 60 minutes. When combined antegrade and retrograde delivery routes were used, 2/3 of the cardioplegia was delivered by the antegrade route, and 1/3 was delivered by the retrograde route as the initial dose for both solutions, with the retrograde route exclusively for maintenance. The severity and location of the coronary artery lesions determined the delivery route. Topical cooling was applied, and 500 mL of warm blood (hotshot; 37 °C) was given before releasing the aortic cross-clamp. The components of both cardioplegia solutions are shown in Table 1. All procedures were performed by the same surgical team, and standard postoperative care was provided to all patients.

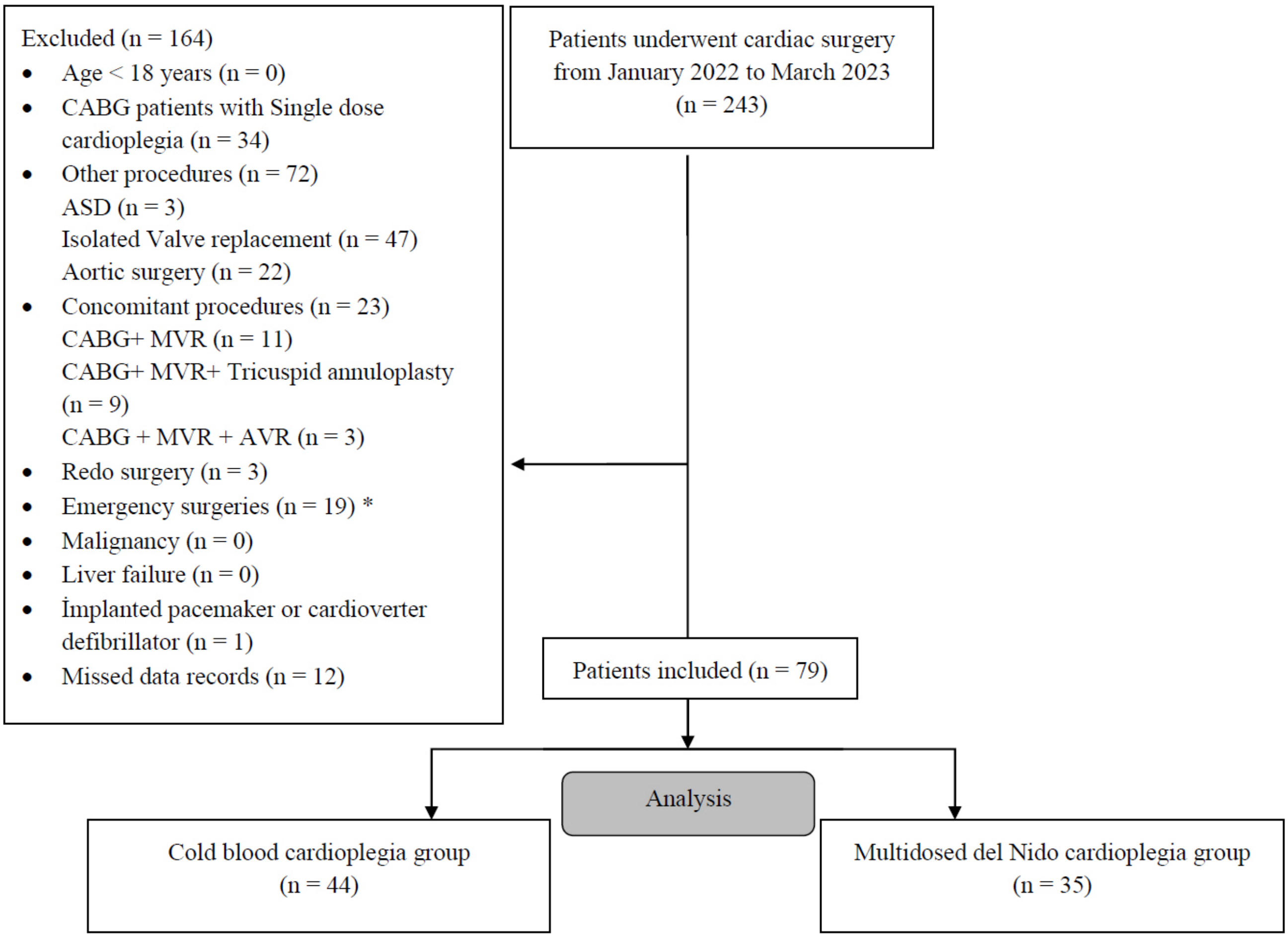

Fig. 1. Flowchart for the study design. ASD, atrial septal defect; CABG, coronary artery bypass graft; MVR, mitral valve replacement; AVR, aortic valve replacement. * Defined as patients with cardiogenic shock or hemodynamic instability with inotropic support or intra-aortic balloon pump support.

Troponin T, Troponin I, and Creatine Kinase-Myocardial Band (CK-MB) Measurements

Cardiac enzyme levels were measured to assess myocardial damage. The baseline values were those available 1–2 days before surgery. As part of our ICU protocol, we routinely assessed these enzyme levels at 1-, 12-, and 24-hours post-CABG surgery. The Roche Cobas 6000 automatic analyzer (Roche Diagnostics, Mannheim, Germany) was utilized for enzyme level measurements.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics include means with standard deviations or medians with interquartile ranges for numerical variables. Categorical variables are represented by frequencies and percentages. Variables distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For analytical statistics, independent sample *t*-tests and the Mann-Whitney test were used to compare numerical variables based on the normality assumptions. For categorical variables, the Pearson Chi-Square test or Fisher's Exact test was used. To identify independent predictors for LCOS and return to sinus rhythm, univariate and multivariate logistic regression analyses were performed, using the 'backward stepwise' elimination method. The factors were selected based on a comprehensive review of relevant literature, clinical expertise, and the availability of data in our study. Model suitability was assessed with the Hosmer-Lemeshow goodness-of-fit test. Statistically significant results were considered for p-values < 0.05.

Results

Baseline Demographics and Preoperative Data

There was no significant difference between the BC and DNC groups in terms of mean age (64 *vs.* 63.9 years, p = 0.951, respectively), EuroSCORE II (1.5 *vs.* 1.4, p = 0.577, respectively), or mean body mass index (BMI) (28.8

Table 2. Baseline preoperative characteristics and comorbidities of both groups.

	Total	BC group	DNC group	p-value
	n = 79	n = 44 (55.7%)	n = 35 (44.3%)	
Age (years), Mean (± SD)	63.9 (8.5)	64 (9.15)	63.9 (7.6)	0.951
Gender, n (%)				
Male	52 (65.8)	29 (65.9)	23 (65.7)	0.986
Female	27 (34.2)	15 (34)	12 (34.2)	
BMI (Kg/m^2), Mean (± SD)	29.2 (4.4)	28.8 (4.1)	29.7 (4.7)	0.367
Euroscore II (%), Median (IQR)	1.17 (0.8)	1.2 (0.9)	1.2 (0.8)	0.399
HT, n (%)	30 (38)	15 (34)	15 (42.9)	0.425
HL, n (%)	12 (15.2)	6 (13.6)	6 (17)	0.666
DM, n (%)	47 (59.5)	23 (52)	24 (68.6)	0.143
COPD, n (%)	12 (15.2)	6 (13.6)	6 (17)	0.666
CKF, n (%)	1 (1.3)	0	1 (2.9)	0.443
Stroke/TIA, n (%)	2 (2.5)	1 (2.3)	1 (2.9)	>0.999
Preoperative MI	11 (14)	5 (11)	6 (17)	0.461
Priority of procedure, n (%)				
Elective	61 (77.2)	31 (70.5)	30 (85.7)	0.108
Urgent	18 (22.8)	13 (29.5)	5 (14)	
Creatinine (mg/dL), Median (IQR)	0.89 (0.3)	0.84 (0.3)	1 (0.2)	**0.006**
Platelet ($\times 10^9$/ L), Mean (± SD)	245.4 (68.4)	237.1 (60.2)	255.7 (77)	0.323
Hemoglobin (gr/dL), Mean (± SD)	13.4 (1.8)	13.4 (1.91)	13.4 (1.69)	0.994
Hematocrit %, Mean (± SD)	39.8 (4.8)	40.1 (5)	39.5 (4.5)	0.542
Troponin T (ng/L), Median (IQR)	53.5 (373.6)	45 (376.6)	96 (372.8)	0.534
Troponin I (ng/mL), Median (IQR)	1.9 (2.7)	2.06 (2.1)	1.5 (3)	0.132
CK-MB (ng/mL), Median (IQR)	2.6 (4.1)	2.31 (2)	2.8 (15)	0.560
Echocardiography features				
LVEF (%), Mean (± SD)	48.3 (9.3)	47.6 (9.9)	49.3 (8.5)	0.419
SPAP (mmHg), Mean (± SD)	25.9 (7.7)	23.9 (5.8)	28.6 (9)	**0.009**
EDD (cm), Mean (± SD)	47.3 (6.6)	47.9 (6.9)	46.5 (6.1)	0.326
ESD (cm), Mean (± SD)	31.5 (5.2)	30 (3.8)	33 (6)	**0.005**

BC, blood Cardioplegia; DNC, del Nido cardioplegia; CI, confidence interval; BMI, body mass index; EuroSCORE, European system for cardiac operative risk evaluation; TIA, transient ischemic attack; MI, myocardial infarction; HT, hypertension; HL, hyperlipidemia; DM, diabetes milletus; COPD, chronic obstructive pulmonary disease; CKF, chronic kidney failure; LVEF, left ventricular ejection fraction; SPAP, systolic pulmonary artery pressure; EDD, end-diastolic diameter; ESD, end-systolic diameter; CK-MB, creatine kinase-myocardial band isotype. Bold p-values indicate statistical significance.

vs. 29.7 kg/m^2, p = 0.367, respectively). The gender distribution was comparable between the groups. Comorbidities including preoperative myocardial infarction (MI) were comparable between both groups. There were no significant differences in preoperative LVEF between the groups (47.6% *vs.* 49.3%, p = 0.419, respectively). The mean platelet count, hemoglobin (Hgb) level, and Htc percentage, as well as troponin T, CK-MB, and troponin I levels were not statistically different between the BC and DNC groups (Table 2).

Intraoperative Outcomes

The intraoperative data are summarized in Table 3. There were no significant differences between both groups in terms of CPB and cross-clamp times (p = 0.480 and 0.310, respectively). The antegrade route was used more frequently in the DNC group (14 patients), while both antegrade and retrograde delivery routes were used more frequently in the BC group (33 patients). However, this was not statistically significant (p = 0.154). There were also no significant differences between the BC and DNC groups regarding cardioplegia volume (mean volume = 1842 mL *vs.* 1807 mL, p = 0.671, respectively) or cardioplegia doses (median = 3 doses *vs.* 2 doses, p = 0.965, respectively).

The DNC group demonstrated a significantly higher rate of sinus rhythm recovery compared to the BC group (77% *vs.* 47.7%, p = 0.008, respectively). No significant differences were observed between the groups regarding inotropic support, IABP support, lactate and glucose levels, or the occurrence of LCOS.

Table 3. Intraoperative data of both groups.

	Total	BC group	DNC group	*p*-value
	n = 79	n = 44 (55.7%)	n = 35 (44.3%)	
Number of distal anastomoses, Mean (± SD)	3.2 (0.95)	3.23 (0.96)	3 (0.95)	0.363
CPB time (minute), Mean (± SD)	126 (44.8)	130 (50.6)	122.9 (39.9)	0.480
Cross clamp time (minute), Mean (± SD)	83.2 (28.1)	86.8 (31.4)	80.3 (25.2)	0.310
LBT (°C), Mean (± SD)	28.5 (1.3)	28.55 (1.2)	28.51 (1.3)	0.913
Delivery route of cardioplegia, n (%)				
Antegrade	25 (31.6)	11 (25)	14 (40)	0.154
Antegrade + retrograde	54 (68.4)	33 (75)	21 (60)	
Cardioplegia volume (mL), Mean (± SD)	1822.8 (358.4)	1842 (416.06)	1807 (309.85)	0.671
Number of doses, Median (IQR), (min-max)	3 (1)	3 (1), (2–4)	2 (1), (2–4)	0.965
İnflow lactate (mmol/L), Mean (± SD)	2.5 (0.8)	2.5 (0.89)	2.42 (0.74)	0.638
Outflow lactate (mmol/L), Mean (± SD)	4.1 (1.4)	4.2 (1.38)	4 (1.42)	0.466
Inflow glucose (mg/dL), Mean (± SD)	179.8 (40.3)	172.9 (33.76)	188.57 (46.39)	0.087
Outflow glucose (mg/dL), Mean (± SD)	222 (43.2)	223.43 (45.92)	222.26 (40.28)	0.905
Return to sinus rhythm, n (%)	48 (60.8)	21 (47.7)	27 (77)	**0.008**
Requirement for defibrillation, n (%)	31 (39)	23 (52)	8 (23)	
Inotrope support, n (%)	48 (60.8)	30 (68.2)	18 (51.4)	0.130
IABP support, n (%)	7 (8.8)	5 (11.4)	2 (6)	0.408
LCOS, n (%)	38 (48)	23 (52)	15 (42.9)	0.405

CPB, cardiopulmonary bypass; IABP, intra aortic balloon pump; LCOS, low cardiac output syndrome; LBT, lowest body temperature. Bold *p*-values indicate statistical significance.

Postoperative Outcomes

Postoperative outcomes revealed no significant differences between the groups regarding adverse events, including new-onset atrial fibrillation, hemodialysis requirement, reopening for bleeding, and neurologic complications. However, the DNC group had a slightly longer mechanical ventilation time than the BC group (median = 11 hours *vs.* 10 hours $p = 0.027$, respectively). There were no significant differences between the two groups regarding blood product transfusion requirements, ICU length of stay, and 30-day mortality. Predischarge echocardiography indicated comparable LVEF between the BC and DNC groups (mean = 49% *vs*. 50.7%, $p = 0.384$, respectively) (Table 4).

Troponin T, Troponin I, and CK-MB Levels

Table 4 compares cardiac enzyme levels at different time points between both groups. Postsurgical troponin T and troponin I levels in the DNC group did not increase as much as in the BC group. For troponin I, there were no statistically significant differences between the groups at the postoperative time points of 1 hour, 12 hours, and 24 hours (p = 0.054, 0.133, 0.524, respectively) (Fig. 2). For troponin T, there were no statistically significant differences at 1 hour and 12 hours. However, 24 hours post-surgery, the median troponin T level reached 1755 ng/mL in the BC group, whereas it was 447.5 ng/mL in the DNC group ($p < 0.001$) (Fig. 3). CK-MB levels in the DNC group were higher than those in the BC group, but there were no significant differences at 1 hour and 12 hours. By 24 hours, CK-MB levels decreased to 9.7 ng/mL in the DNC group, while in the BC group, the levels were 3.9 ng/mL ($p < 0.001$) (Fig. 4).

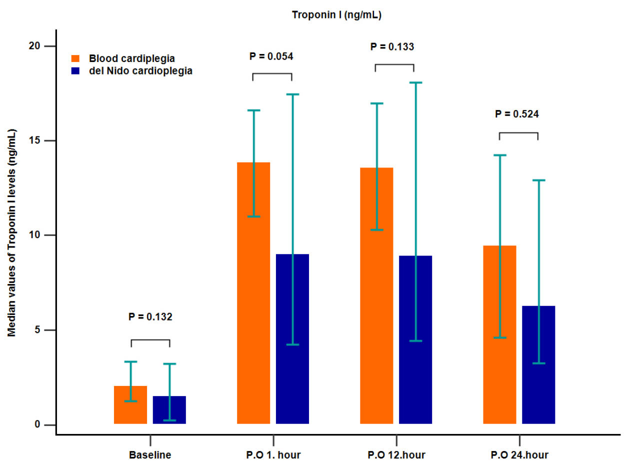

Fig. 2. Perioperative comparison serum levels of Troponin I between the BC group and DNC group. Error bars represent 25–75 percentiles.

Subanalysis of Redosing Interval Strategy

A subanalysis was performed to evaluate the redosing strategy of DNC. The patients were divided into two groups based on aortic cross-clamp time (ACC) (subgroup

Table 4. Postoperative outcomes of both groups.

	Total	BC group	DNC group	*p*-value
	n = 79	n = 44 (55.7%)	n = 35 (44.3%)	
New onset A. Fib, n (%)	27 (34.2)	17 (38.6)	10 (28.6)	0.349
Stroke/TIA, n (%)	6 (7.5)	4 (9.1)	2 (5.7)	0.574
Reopening for bleeding, n (%)	5 (6.3)	1 (2.3)	4 (11.4)	0.165
Mechanical ventilation time (hour), Median (IQR)	10 (4)	10 (4)	11 (6)	**0.027**
Requirement for hemodialysis, n (%)	2 (2.5)	1 (2.3)	1 (2.9)	>0.999
Blood products transfusion (unit), Mean (± SD)				
PRBC	2.8 (0.9)	2.7 (1)	2.8 (0.9)	0.844
FFP	4 (1.1)	4.2 (1.2)	3.8 (1)	0.106
Platelets	0.3 (0.9)	0.2 (0.8)	0.5 (1.2)	0.137
Creatinine (mg/dL) (P.O 1 hour), Median (IQR)	1 (0.4)	0.9 (0.5)	1 (0.5)	0.540
Platelet ($\times 10^9$/L), (P.O 1 hour), Mean (± SD)	143.6 (63.3)	191.9 (53.4)	145.6 (74.5)	0.796
Hemoglobin (gr/dL), (P.O 1 hour), Mean (± SD)	9.9 (1.5)	10.2 (1.6)	9.6 (1.2)	0.052
Hematocrit %, (P.O 1 hour), Mean (± SD)	28.7 (4.2)	29.5 (4.6)	27.6 (3.3)	0.056
Troponin T (ng/mL), Median (IQR)				
P.O 1 hour	874 (1337.2)	1016.6 (1363.5)	528.4 (1225)	0.189
P.O 12 hours	1052 (1724.5)	1460 (1711.5)	484.9 (1500.7)	0.199
P.O 24 hours	741 (1765)	1755 (1527.6)	447.5 (422.3)	**<0.001**
Troponin I (ng/mL), Median (IQR)				
P.O 1 hour	12.4 (10)	13.9 (5.7)	9 (14)	0.054
P.O 12 hours	12.8 (12)	13.6 (6.9)	8.9 (13.7)	0.133
P.O 24 hours	7.8 (9.8)	9.5 (9.8)	6.3 (9.8)	0.524
CK-MB (ng/mL), Median (IQR)				
P.O 1 hour	30 (45)	31 (57.6)	28.6 (46.3)	0.992
P.O 12 hours	16.5 (39.5)	15.6 (19.5)	30.8 (51.6)	0.126
P.O 24 hours	5 (9.8)	3.9 (3.8)	9.7 (21)	**<0.001**
LVEF (%), Mean (± SD)	48.8 (8)	49 (8.9)	50.7 (6.8)	0.384
ICU LOS (days), Median (IQR)	4 (3)	4 (3)	4 (4)	0.292
P.O hospital LOS (days), Median (IQR)	10 (5)	10 (5)	10 (6)	0.248
30-day mortality, n (%)	3 (3.8)	1 (2.3)	2 (5.7)	0.581

TIA, transient ischemic attack; A. Fib, atrial fibrillation; PRBC, packed red blood cells; FFP, fresh frozen plasma; CK-MB, creatine kinase-myocardial band isotype; LVEF, left ventricular ejection fraction; ICU, intensive care unit; LOS, length of stay; P.O, postoperative. Bold *p*-values indicate statistical significance.

1: ACC $\leq$60 minutes, subgroup 2: ACC >60 minutes). In subgroup 1, there were 30 patients in the BC group and 23 patients in the DNC group. Defibrillation was required in 4 patients (1.4%) in the DNC group and 16 patients (53%) in the BC group (p = 0.007). Postoperative inotropic support was needed in 8 patients (34.8%) in the DNC group and 20 patients (22.6%) in the BC group (p = 0.021). In subgroup 2 there were 14 patients in the BC group and 12 patients in the DNC group. No significant difference was found in the defibrillation requirement (p = 0.391), or the need for inotropic support (p = 0.652). However, postoperative Htc and Hgb levels were significantly lower in the DNC group compared to the BC group (Htc: 26% $\pm$ 3.2 *vs.* 30% $\pm$ 5.1, p = 0.027, and Hgb: 9 $\pm$ 1.2 *vs.* 10 $\pm$ 1.5, p = 0.031, respectively). In-hospital mortality did not significantly differ between the groups in either subgroup.

In subgroup 1, there were no statistically significant differences in troponin T levels at 1 hour and 12 hours. However, at 24 hours, the median troponin T level reached 1531 ng/mL in the BC group, while the DNC group showed a significantly lower level of 447.5 ng/mL (p = 0.004). In subgroup 2, troponin T levels were consistently lower in the DNC group, reaching statistical significance at 24 hours (2018.5 ng/mL *vs.* 434 ng/mL, p = 0.011).

Troponin I levels were lower in the DNC in both subgroups with a trend to higher levels in subgroup 2. However, there were no statistically significant differences between the groups at different time points.

In subgroup 1, CK-MB levels were higher in the DNC group, but no significant differences were observed at 1 hour and 12 hours. By 24 hours, CK-MB levels decreased to 8.2 ng/mL in the DNC group, compared to 3.9 ng/mL in the BC group (p = 0.007). In subgroup 2, CK-MB levels in the DNC group demonstrated a trend to higher levels compared to subgroup 1. However, at 1 hour and 12 hours, no significant differences were observed. By 24 hours, CK-

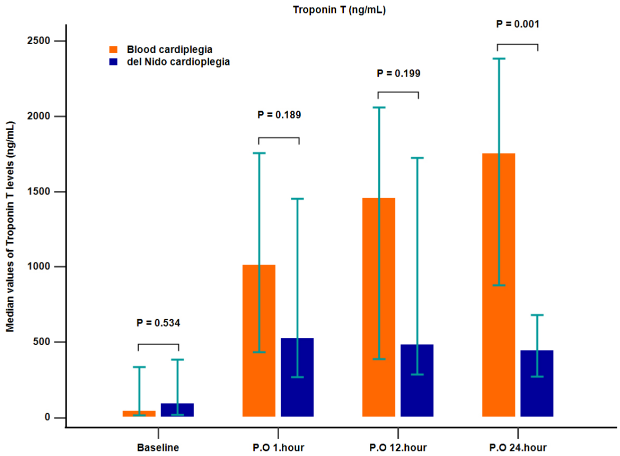

Fig. 3. Perioperative comparison serum levels of Troponin T between the BC group and DNC group. Error bars represent 25-75 percentiles.

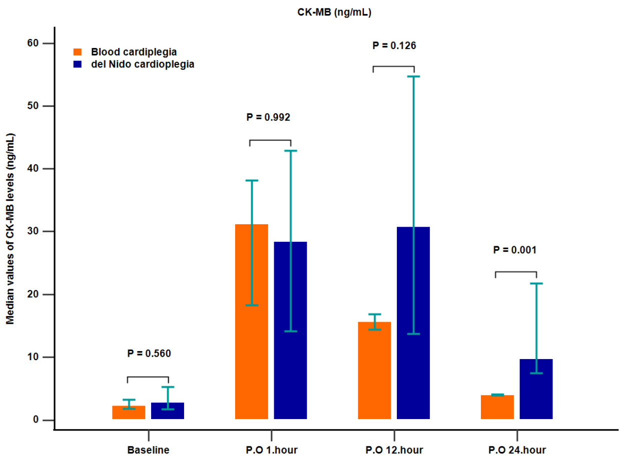

Fig. 4. Perioperative comparison serum levels of CK-MB between the BC group and DNC group. Error bars represent 25–75 percentiles.

MB levels decreased to 23.6 ng/mL in the DNC group, while the BC group recorded levels of 4 ng/mL ($p < 0.001$) (Table 5).

Predictors of Low Cardiac Output Syndrome

In the multivariate analysis, after adjusting for other variables, independent risk factors for LCOS were identified: the requirement for defibrillation (OR = 10.9, 95% CI: 2.9–41.8, $p < 0.001$), cross-clamp time (OR = 1.04, 95% CI: 1.02–1.1, $p = 0.002$) and BMI (OR = 0.8, 95% CI: 0.7–0.9, $p = 0.030$). The type of cardioplegia solution did not show a significant association with LCOS in either analysis (Table 6).

Predictors of Return to Sinus Rhythm

In the multivariate analysis, LVEF >40% (OR = 3.1, 95% CI: 1.1–8.7, $p = 0.035$) and the use of DNC (OR = 3.6, 95% CI: 1.3–10.1, $p = 0.013$) emerged as significant predictors of return to sinus rhythm (Table 7).

Discussion

In this study, we evaluated our initial experience with the recurrent administration of DNC doses. We assessed the efficacy and safety of our redosing interval strategy in the context of myocardial protection compared to multidose cold BC during isolated CABG procedures. Our findings indicate that the two solutions yielded comparable levels of myocardial injury biomarkers, particularly within the initial 12 hours postoperatively, even with prolonged ischemic time, and similar intraoperative and early postoperative outcomes in terms of morbidity and mortality. However, DNC showed a higher rate of sinus rhythm recovery and reduced need for defibrillation after releasing the aortic cross-clamp.

To evaluate myocardial protection, various parameters were examined, including the need for defibrillation, inotropic support requirements, perioperative MI, regional wall abnormalities, low cardiac output, and cardiac biomarker levels [9]. While previous studies have reported mixed results [5,9–11], our study found that postoperative troponin T and I levels were lower in the DNC group, although there was no statistically significant difference between the groups. Notably, troponin T levels in the BC group failed to reach a real peak during the 24-hour postoperative interval, while the DNC group showed a significant reduction in biomarker release. However, we observed a nonsignificant tendency toward higher CK-MB levels in the DNC group at 12 hours with significantly higher levels at 24 hours. Similar to our findings, Ad *et al.* [12] compared DNC to whole BC in patients with CABG and/or valve surgery in a prospective randomized trial. The DNC group had lower troponin levels, suggesting superior myocardial protection. Nevertheless, other studies have failed to identify differences in the release of CK-MB or troponin I between DNC and BC [12–14]. This effect of DNC on myocardial enzyme release can be attributed to its components, including its lower viscosity [15] and the presence of Lidocaine [16] which may promote nitric oxide release and coronary vasodilation and subsequent better distribution. Nevertheless, lidocaine was associated with increased postoperative CK-MB levels in other studies using modified DNC delivered at a blood-to-crystalloid ratio of 8:1 [17,18]. Although we used traditional DNC administered at a crystalloid-to-blood ratio of 1:4, the repeated doses of the del Nido solution in our cohort may have affected the observed findings regarding elevated CK-MB levels. It is important to note that these findings should be interpreted

Table 5. Subgroup analysis of clinical outcomes based on ACC time.

	Subgroup 1: ACC ≤60 minutes		*p*-value	Subgroup 2: ACC >60 minutes		*p*-value
	BC group	DNC group		BC group	DNC group	
	n = 30 (56.6%)	n = 23 (43.4%)		n = 14 (53.8%)	n = 12 (46%)	
Cardioplegia volume (mL), Mean (± SD)	1716.6 (284.1)	1608.7 (210.9)	0.119	2291 (334.3)	2000 (277)	**0.023**
Number of doses, Median (IQR), (min-max)	2 (1), (2–4)	2 (0), (2–3)	0.148	4 (1), (2–4)	3 (0), (2–4)	**0.031**
Requirement for defibrillation, n (%)	16 (53.3)	4 (17.4)	**0.007**	7 (50)	4 (33.3)	0.391
İnflow lactate (mmol/L), Mean (± SD)	2.4 (0.7)	2.6 (0.9)	0.209	2.4 (0.78)	2.2 (0.73)	0.367
Outflow lactate (mmol/L), Mean (± SD)	3.9 (1.3)	3.7 (1.06)	0.815	5.1 (1.5)	4.1 (1.6)	0.134
Inflow glucose (mg/dL), Mean (± SD)	173 (34.6)	182 (49.9)	0.815	200 (38)	171 (32)	**0.049**
Outflow glucose (mg/dL), Mean (± SD)	220 (48.2)	215 (40.5)	0.647	236 (37)	230 (41)	0.727
Inotrope support, n (%)	20 (66.7)	8 (34.8)	**0.021**	10 (71.4)	10 (83.3)	0.652
IABP support, n (%)	3 (10)	1 (4.3)	0.878	2 (14.3)	1 (8.3)	0.903
LCOS, n (%)	13 (43.3)	6 (26)	0.194	10 (71.4)	9 (75)	>0.999
New onset A. Fib, n (%)	14 (46.7)	6 (26)	0.126	3 (21.4)	4 (33.3)	0.665
Stroke/TIA, n (%)	2 (6.7)	1 (4.3)	>0.999	2 (14.3)	1 (8.3)	0.903
Hemoglobin (gr/dL), (P.O 1 hour), Mean (± SD)	10.2 (1.7)	9.9 (1)	0.879	10.3 (1.5)	9 (1.2)	**0.031**
Hematocrit %, (P.O 1 hour), Mean (± SD)	29.2 (4.4)	28.5 (3.1)	0.767	30 (5.1)	26 (3.2)	**0.027**
Troponin T (ng/mL), Median (IQR)						
P.O 1 hour	1016.6 (1392.6)	753.6 (1421.3)	0.484	1009 (1506)	402 (779)	0.297
P.O 12 hours	1397.5 (1599.8)	612 (1940.5)	0.641	1705.3 (2025)	365.5 (348.5)	0.131
P.O 24 hours	1531 (2177.4)	447.5 (387.3)	**0.004**	2018.5 (1395.5)	434 (402)	**0.011**
Troponin I (ng/mL), Median (IQR)						
P.O 1 hour	13.9 (6.8)	9 (14.7)	0.129	13.8 (5)	9.4 (14)	0.252
P.O 12 hours	13.5 (8.1)	6.4 (12.2)	0.088	13.7 (5.7)	12.8 (19.8)	0.860
P.O 24 hours	6.6 (10.6)	5.4 (7.2)	0.490	10.3 (6.6)	112 (10.7)	0.781
CK-MB (ng/mL), Median (IQR)						
P.O 1 hour	35.5 (69.9)	20 (72.4)	0.473	23.5 (35.8)	34 (28)	0.297
P.O 12 hours	15.9 (25)	30 (40)	0.641	15 (8.4)	58 (63)	0.060
P.O 24 hours	3.9 (5.3)	8.2 (17.4)	**0.007**	4 (0.68)	23.6 (27.5)	**<0.001**
LVEF (%), Mean (± SD)	49.2 (9.1)	52.1 (6.4)	0.196	48.8 (8.7)	47.9 (6.8)	0.767
ICU LOS (days), Median (IQR)	4 (2)	4 (1)	0.715	6 (6)	4 (4)	0.053
Postoperative hospital LOS (days), Median (IQR)	10 (5)	10 (4)	0.731	12 (5)	11 (7)	0.231
30-day mortality, n (%)	1 (3.3)	1 (4.3)	>0.999	0	1 (8.3)	0.462

ACC, aortic cross-clamp; IABP, intra aortic balloon pump; LCOS, low cardiac output syndrome; A. Fib, atrial fibrillation; TIA, transient ischemic attack; ICU, intensive care unit; LVEF, left ventricular ejection fraction; LOS, length of stay; P.O, postoperative. Bold *p*-values indicate statistical significance.

in conjunction with a clinical assessment, electrocardiography, and echocardiography findings [19]. In addition, the specific thresholds for clinically significant biomarker elevations may also vary depending on the assay used. Despite optimal myocardial protection methods, some degree of cardiac damage may still occur in CABG patients due to a variety of factors, including surgical technique, suture insertion or manipulation of the heart and coronary dissection, and aortic cross-clamping and CPB times [20]. Lenoir *et al.* [21] in their study on adult aortic root surgery, reported increased levels of CK-MB and troponin T in patients who received DNC with ischemic times longer than 180 minutes. In the present study, the reduced levels of postoperative troponin T were unrelated to the duration of aortic cross-clamp time based on our subgroup analysis. However, we observed a trend toward higher troponin I and CK-MB levels in patients who received DNC with extended myocardial ischemic times exceeding 60 minutes. This discrepancy prompts further investigation into the specific mechanisms underlying myocardial protection afforded by DNC, as well as considerations for its optimal application in cases with extended ischemic times.

Based on our literature review, previous studies have reported that DNC had no significant impact on the incidence of postoperative LCOS [3,9]. In the current study, patients in the DNC group had a lower incidence of LCOS than those in the BC group, although the difference was not significant. Multivariate logistic regression analysis revealed that LCOS was independently associated with the need for defibrillation, increased aortic cross-clamp time, and low BMI, while the type of cardioplegia did not predict LCOS. Consistent with our findings, Elassal *et al.* [14] re-

Table 6. Predictors of low cardiac output syndrome.

Risk factor	Univariate		Multivariate	
	OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age (years)	1 (0.96–1.07)	0.473		
Female	1 (0.39–2.54)	0.995	2.9 (0.8–10.9)	0.103
BMI (kg/m^2)	0.9 (0.8–1.01)	0.074	0.8 (0.7–0.9)	**0.030**
Hypertension	1.4 (0.6–3.5)	0.467	3.2 (0.8–12.7)	0.092
DM	1.6 (0.7–4.1)	0.274		
Preoperative MI	3.3 (0.8–13.8)	0.091		
LVEF ≤40%	2.3 (0.9–6.2)	0.094		
SPAP (mmHg)	1 (0.97–1.1)	0.245		
EDD (cm)	1.1 (0.98–1.1)	0.108		
ESD (cm)	1 (0.93–1.1)	0.799		
Cross clamp time (minute)	1.03 (1.01–1.1)	**0.001**	1.04 (1.02–1.1)	**0.002**
CPB (minute)	1.02 (1.01–1.03)	**0.004**		
Temperature (°C)	0.7 (0.48–1.02)	0.068		
del Nido cardioplegia	0.7 (0.28–1.67)	0.406		
Total cardioplegia volume (mL)	1 (1–1.003)	**0.045**		
Antegrade + retrograde delivery route	2.6 (0.98–7.2)	0.055		
Requirement of defibrillation	6.3 (2.3–17.3)	<**0.001**	10.9 (2.9–41.8)	<**0.001**
Inflow lactate (mmol/L)	0.8 (0.5–1.4)	0.431		
Outflow lactate (mmol/L)	1.3 (0.9–1.8)	0.155		
Inflow glucose (mg/dL)	1.005 (0.99–1.02)	0.378	1.01 (0.99–1.03)	0.096
Outflow Glucose (mg/dL)	1.006 (0.99–1.02)	0.293		

MI, myocardial infarction; LVEF, left ventricle ejection fraction; DM, diabetes milletus; SPAP, systolic pulmonary arterial pressure; EDD, end-diastolic diameter; ESD, end-systolic diameter; CPB, cardiopulmonary bypass. 'Backward stepwise' method was used to identify predictive variables in the multivariate model. *p*-value of Hosmer and Lemeshow Test for multivariate model = 0.875. Bold *p*-values indicate statistical significance.

Table 7. Predictors of return to sinus rhythm.

Predictive variables	Univariate		Multivariate	
	OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Cross clamp time (minute)	0.99 (0.98–1)	0.381		
Temperature (°C)	1.1 (0.8–1.6)	0.519		
Total cardioplegia volume (mL)	1 (0.99–1.001)	0.521		
Inflow lactate (mmoL/L)	1.04 (0.6–1.8)	0.900		
Inflow glucose (mg/dL)	1 (0.99–1.02)	0.422		
LVEF >40%	1.1 (1.03–1.14)	**0.003**	3.1 (1.1–8.7)	**0.035**
del Nido cardioplegia	3.7 (1.38–9.9)	**0.009**	3.6 (1.3–10.1)	**0.013**
Antegrade + Retrograde route	0.6 (0.23–1.72)	0.372		

LVEF; left ventricle ejection fraction. 'Backward stepwise' method was used to identify predictive variables in the multivariate model. *p*-value of Hosmer and Lemeshow Test for multivariate model = 0.256. Bold *p*-values indicate statistical significance.

ported that the need for defibrillation was a significant risk factor for postoperative LCOS, whereas the type of cardioplegia was not. Similarly, Yerebakan *et al.* [3] found that DNC was not a predictor of postoperative LCOS in CABG patients with acute MI. Previous studies have shown additional benefits of DNC, such as a reduced need for defibrillation and higher rates of spontaneous resumption of normal sinus rhythm, indicating better myocardial protection [11,18,22]. Our results are in line with these findings. We also found that a LVEF higher than 40% and DNC were independent factors associated with the return to sinus rhythm. DNC was associated with a 3.6-fold increase in the rate of sinus rhythm resumption. Buel *et al.* [23] observed a 6-fold reduction in the rate of required defibrillation while using DNC compared with the St. Thomas solution. The decreased requirement for defibrillation reduces myocardial injury caused by electrical current [24], potentially benefiting the recovery of the myocardium [5].

This might also explain the reduction in cardiac enzyme release observed in this and other studies. Furthermore, DNC has been shown to reduce the need for inotropic support in adult cardiac surgery [11,12,17]. While we observed a lower rate of patients who needed inotropic and mechanical support in the DNC group compared to the BC group, this difference did not reach statistical significance. The lower frequency of defibrillation and inotropic support required in DNC might be due to its low calcium and high lidocaine concentration, which may prevent intracellular calcium accumulation during ischemia, minimizing myocardial damage after reperfusion [2]. Furthermore, similar to a recently published study [25], we included a terminal warm blood 'hot shot' before cross-clamp removal to our DNC delivery protocol, which may have contributed to these findings. It is noteworthy to mention that patients who received DNC with prolonged ischemic time tended higher rates of inotropic support and LCOS, although statistical significance was not reached. This suggests that the benefits of DNC over BC may be more pronounced in cases with shorter aortic cross-clamp durations. In cases with prolonged ischemic times, the choice of cardioplegia might have a limited impact on these outcomes.

DNC has been associated with shorter cross-clamp and CPB times [3–5]. Furthermore, the use of DNC was previously demonstrated to reduce postoperative atrial fibrillation [4] as well as durations of ICU and hospital stays [11]. Even though patients in the current study received multiple doses of DNC (as opposed to previous studies in which patients received a single dose), our findings revealed comparable perioperative outcomes in terms of aortic cross-clamp and CPB times, cardioplegia volume, atrial fibrillation, stroke, postoperative LVEF, hospital and ICU length of stay, and mortality rates. Although the intubation period was longer in the DNC group, it was not considered clinically relevant. Consistent with our results, previous studies have shown comparable outcomes between DNC and control cardioplegia solutions [8,12,14]. Nevertheless, Timek *et al*. [8] reported higher stroke rates in patients receiving DNC requiring more than one dose in an unmatched analysis, and atrial fibrillation was more frequent in the propensity-matched groups.

One of the benefits of DNC, particularly for patients with diabetes mellitus, is that it is a glucose-free solution. While intraoperative glucose levels were lower in DNC patients in a prior study [10], our results did not show any differences between the groups in terms of intraoperative glucose levels, which is consistent with other studies [26].

Previous studies have highlighted the lower total volume of DNC when given as a single dose compared to other solutions, which reduces hemodilution and blood transfusion requirements [27]. Despite redosing DNC in our patients, we observed no differences in postoperative Hgb, Htc, and platelet levels or blood transfusion rates between the DNC and BC groups. However, with increased cross-clamp time over 60 minutes, the Hgb and Htc levels were significantly lower in the DNC. Recent studies have demonstrated higher levels of Htc and Hgb with DNC, although blood transfusion rates were similar between DNC and other solutions [14,26].

The use of DNC in CABG procedures has raised concerns regarding inadequate distribution with an entirely antegrade delivery [28]. We used both antegrade and retrograde delivery in most patients in the DNC group, and the outcomes were similar to those in the BC group. In addition, the delivery route was not associated with LCOS or a spontaneous return to sinus rhythm, which reflects the efficacy of myocardial protection. Most of the studies in the literature embrace the fact that antegrade-only delivery is sufficient with DNC [5,9,10]. While this might be reliable in non-CABG patients, we believe that in patients with multivessel coronary artery disease, the cardioplegia delivery route should be determined according to coronary artery lesion severity and location rather than the type of cardioplegia solution.

DNC raises potential concerns about dosing frequency. While a single, initial dose with supplemental doses delivered every 60 to 90 minutes is commonly used in adult cardiac surgery [3,10], multidose cardioplegia allows intermittent elimination of accumulated toxic metabolites, which is imperative for optimal myocardial protection, particularly in ischemic hearts with coronary artery disease [29]. Therefore, single-dose cardioplegia may not be as effective as the traditional Buckberg protocol due to its non-homogeneous distribution and the accumulation of toxic metabolites [28]. Nevertheless, Govindapillai *et al*. [30] reported that a single dose of DNC resulted in better myocardial function recovery than multiple doses in rat hearts subjected to 60-minute cardioplegic arrest, possibly due to a dose-dependent, lidocaine-induced, negative inotropic effect. However, they reported that multi-dosed hearts had less myocardial cell swelling due to the mannitol in DNC. Since there is no consensus on the timing of DNC redosing, we adopted a more conservative approach, reassessing the need for additional doses every 45 minutes. Smigla *et al*. [24] used the same redosing intervals in their adult congenital cardiac surgery observational study. Despite the lack of a control group, they observed no change in ejection fraction, while roughly half of the patients required inotropic support, and 91% experienced spontaneous resumption of cardiac rhythm. Timek *et al*. [8] and Koda *et al*. [6] redosed every 60 minutes in their studies on CABG patients and other cardiac procedures, respectively. While the cross-clamp time, cardioplegia volume, and the number of doses were significantly lower in patients who received DNC, they concluded that DNC provided non-inferior myocardial protection and clinical outcomes. In the present study, both groups received 2–4 doses of cardioplegia (not including the terminal hot shot) with comparable cross-clamp times, cardioplegia volumes, and postoperative outcomes.

Strengths and Limitations

The limitations of this study include its single-center retrospective and observational design with a relatively small sample size, potentially limiting the generalizability of the findings. Furthermore, using different cardioplegia solutions during different periods could have introduced confounding factors related to changes in surgical techniques or other aspects of patient care over time. However, since the same team performed all procedures, we minimized the potential confounding effect of variations in myocardial protection strategies, such as the route of cardioplegia delivery, systemic hypothermia, and the use of topical cooling, which were comparable between the groups. Furthermore, the population was well-defined, the inclusion and exclusion criteria were clearly stated, and the patient's baseline clinical characteristics were well-matched between the two groups, which enhanced the internal validity of the findings and minimized potential bias. The study also considered various perioperative observations to assess the safety and efficacy of DNC redosing.

Conclusion

The literature includes substantial variations in the use of DNC and administration strategies, making reliable conclusions difficult due to diverse patients and procedures. Therefore, it is difficult to conclusively demonstrate that one strategy is superior to another. As a result, choosing between strategies remains surgeon-dependent. This study adds to the existing knowledge regarding DNC, demonstrating its efficacy and safety when administered in multiple doses during CABG procedures. Our findings suggest that DNC, even with repeated doses, provides comparable myocardial protection and perioperative outcomes to traditional BC. Furthermore, the redosing interval of the DNC protocol appears appropriate. The consideration of randomized controlled trials in future studies, along with larger samples and different procedures are needed to validate these results and can contribute additional robust evidence to the evolving field of myocardial protection strategies in cardiac surgery.

Abbreviations

DNC, del Nido cardioplegia; BC, blood cardioplegia; IABP, intra aortic balloon pump; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; LCOS, low cardiac output syndrome; CK-MB, creatine kinase-myocardial band isotype; MI, myocardial infarction; BMI, body mass index; EuroSCORE, European system for cardiac operative risk evaluation; TIA, transient ischemic attack; HT, hypertension; HL, hyperlipidemia; DM, diabetes milletus; COPD, chronic obstructive pulmonary disease; CKF, chronic kidney failure; LVEF, left ventricular ejection fraction; SPAP, systolic pulmonary artery pressure; EDD, end-diastolic diameter; ESD, end-systolic diameter; A. Fib, atrial fibrillation; PRBC, packed red blood cells; FFP, fresh frozen plasma; ICU, intensive care unit; LOS, length of stay; LBT, lowest body temperature; ACC, aortic cross-clamp; HTC, hematocrit; Hgb, hemoglobin.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author Contributions

SA designed the study and collected and analyzed the data. SA and FÇ wrote the original draft. FÇ interpreted the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved by the local ethics committee of Bozok University and performed in accordance with the Declaration of Helsinki. (No: 2017-KAEK-189_2023.05.11_2. Date: May 11, 2023). Patient consent was waived due to the retrospective nature of the analysis.

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Conflict of Interest

The authors declare no conflict of interest.

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