Cardiovasc Surg Int 2023;10(1):49-57
http://dx.doi.org/DOI: 10.5606/e-cvsi.2023.1433
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

Is del Nido cardioplegia safe in isolated coronary bypass surgery? It may be possible with this method

Ferhat Borulu[1], Yasin Kılıç[2], Bilgehan Erkut[2], Melih Ürkmez[1], Kaptanıderya Tayfur[1]

[1]Department of Cardiovascular Surgery, Ordu University Faculty of Medicine, Ordu, Türkiye
[2]Department of Cardiovascular Surgery, Atatürk University Faculty of Medicine, Erzurum, Türkiye

Received: October 19, 2022 ***Accepted:*** March 12, 2023 ***Published online:*** March 27, 2023

ABSTRACT

Objectives: This study aimed to share the early results of the del Nido (DN) solution used with a different method in patients who underwent isolated coronary bypass.

Patients and methods: The retrospective study included 150 patients (123 males, 27 females; mean age: 59.8±9.7 years; range, 38 to 84 years) who underwent isolated coronary bypass operation between January 2020 and May 2022. The DN solution was applied differently from the practice in the literature. Seventy-five percent of the dose calculated according to the body weight of the patients was administered at the first moment. The remaining amount was continued to be given through the saphenous veins as distal anastomoses were made. When the cross-clamp was lifted, all grafts were tied to the aorta cannula, and the coronary vascular bed was cleared. Follow-up of patients was done routinely.

Results: The mean preoperative ejection fraction was 49.9±5.6, and the mean postoperative ejection fraction value was 50.3±5.0 (p=0.079). A statistically significant difference was found between the preoperative troponin level and the postoperative troponin level at 6 h (p<0.001). However, there was no significant difference between the postoperative 6 h and the postoperative 24 h. Spontaneous rhythm occurred at the termination of cardiopulmonary bypass in most of the patients (97%). No permanent pacing was required in any patient. An intra-aortic balloon pump was used in nine patients, and extracorporeal membrane oxygenation was used in two patients. Two patients died in the early period.

Conclusion: The use of DN with this method seems to be a reliable alternative to eliminate hesitations in isolated coronary bypass surgery.

Keywords: Cardioplegia, coronary artery bypass surgery, del Nido.

Myocardial protection is crucial in cardiac surgery. Ideal cardiac arrest ensures the immobility of the heart and provides energy to protect the myocardium. There have been attempts to achieve diastolic arrest by administering cardioplegia directly to the coronary vessels. Different suggestions have been made for this purpose.[1,2] Studies were carried out in terms of content, temperature, application method (antegrade or retrograde), and duration. Although del Nido (DN) cardioplegia was first used in pediatric cardiac surgery, studies have shown that it can also be used in adult cardiac surgery.[3,4]

The contents of DN cardioplegia solution are presented in Table 1. This solution differs from classic cardioplegia in that it contains lidocaine, which limits calcium entry into the cell and prolongs the duration of action.[5] It reduces the intracellular accumulation of harmful calcium ions, decreases the energy consumption rate, enables free radical clearance, and causes a major reduction in myocardial edema.[6] It is administered as a single dose. According to a study, the most important benefits include postoperative spontaneous rhythm, less need for defibrillation and inotropic support, and rapid improvement in troponin values.[7]

Studies showing positive results of DN use in adults have increased. However, it is still not widely used in adults. Based on previous studies, we aimed to share the early results of surgeries in which we used the DN solution.

Corresponding author: Ferhat Borulu, MD. Ordu Üniversitesi Tıp Fakültesi Kalp ve Damar Cerrahisi Anabilim Dalı, 52200 Ordu, Türkiye.
E-mail: fborulu@gmail.com

Citation:
Borulu F, Kılıç Y, Erkut B, Ürkmez M, Tayfur K. Is del Nido cardioplegia safe in isolated coronary bypass surgery? It may be possible with this method. Cardiovasc Surg Int 2023;10(1):49-57. doi: 10.5606/e-cvsi.2023.1433.

PATIENTS AND METHODS

The retrospective study was conducted with 150 patients (123 males, 27 females; mean age: 59.8±9.7 years; range, 38 to 84 years) at the Atatürk University Research Hospital between January 2020 and May 2022. At the beginning of 2020, the DN cardioplegia solution was started to be used in the surgeries of coronary artery patients in our clinic. Previously, cold blood cardioplegia was used. The only exclusion criterion was reoperations. The demographic characteristics of all patients, EuroSCORE II data, intraoperative data, postoperative follow-up data, drainage amounts, and postoperative ejection fractions were recorded. The preoperative and postoperative laboratory data were compared and analyzed retrospectively. The primary outcomes of the study were significantly increased troponin levels and decreased lower ejection fraction values, and the secondary endpoint was death.

Surgical procedure and method of cardioplegia delivery

All patients were operated with a median sternotomy. A left anterior thoracic artery (LITA) graft was used in all patients, except for two in whom LITA was dissected. The Trillium Affinity NT (Medtronic, Minneapolis, MN, USA) was used as the oxygenator, and the Terumo Advanced Perfusion System 1 (Terumo Cardiovascular, Ann Arbor, MI, USA) was used as the perfusion system. Standard cannulation was performed from the atrium and aorta in all patients, and the cardioplegia was delivered from the aortic root. In the first stage, 75% of the cardioplegia solution, calculated according to weight, was administered all at once. The remaining amount was continued to be applied at half the rate of the first application from the graft after each distal anastomosis. At the end of the distal anastomoses, the cardioplegia solution was set to run out. After the cross-clamp was lifted, the cardioplegia cannula was connected to the aortic cannula, and the cardioplegia solution was removed from the myocardium by continuously washing it with hot blood. The patient's body temperature was held at 32-34°C. After the cross-clamp was placed, a topical cold application was administered to the myocardium. The cardioplegia solution was delivered as described here: For a 70-kilogram adult patient, a 70×20=1,400 mL solution was prepared as the first dose. Of this amount, 75% (1,050 mL) was initially delivered. The remaining 350 mL was continuously applied from the grafts with a lower flow rate after each of the distal anastomoses was finished. The properties of the cardioplegia solution are presented in Table 1. Proximal anastomoses were performed with a side clamp. Neutralization with protamine was performed after decannulation.

Postoperative follow-up

In our clinic, hemodynamic or neurological follow-ups were performed in accordance with the routine procedure. Vital signs and laboratory values were recorded. Along with routine laboratory follow-ups, troponin I values were monitored in the first 24 h (at postoperative 6 and 24 h). The hemograms and electrolytes of all patients were monitored four times a day during the intensive care follow-up. Blood transfusions and electrolyte replacements were performed based on these results. The drains in the patients were removed if they collected less than 100 mL in the previous 12 h. Patients with stable hemodynamics were discharged from the intensive care unit. Patients who did not have any problems during follow-up were discharged.

Table 1
Contents of the del Nido cardioplegia solution

del Nido plegia solution (1000 mL* Izolex-S, Isolyte) pH: 7.4	%	mL
Potassium chloride	7.5 1 mEq/L	26
Magnesium sulphate	15	14
Sodium bicarbonate	8.4 1 mEq/L	13
Lidocaine	2	6.5
Mannitol	20	17
Blood		200

* After cardiopulmonary bypass, 200 cc of fluid is drained and the same amount of warm autologous blood is added.

Statistical analysis

The Number Cruncher Statistical System 2007 (NCSS LLC., Kaysville, UT, USA) was used for the statistical analysis. When evaluating the study data, descriptive statistical methods were used (mean, standard deviation, median, frequency, ratio, minimum, and maximum), and the distribution of the data was calculated using the Shapiro-Wilk test. The Friedman test was used for quantitative comparisons of three or more periods that did not show normal distributions, and the Wilcoxon test was used for two-term comparisons. Significance was evaluated at $p<0.01$ and $p<0.05$.

RESULTS

The patients' demographic characteristics, EuroSCORE II data, body mass index, and preoperative ejection fractions are presented in Table 2. The mean cross-clamp time was 49.2±16.1 min, and the mean cardiopulmonary bypass time was 100.2±26.6 min. The lowest operational temperature of the patients was 28°C, and the mean was 31.7±0.9°C. The mean number of grafted vessels was 3.1±0.8. All operational and postoperative follow-up data on the patients are given in Table 3. An intra-aortic balloon pump (IABP) was placed in nine of the patients due to chest pain and hemodynamic instability during the preoperative period. Intra-aortic balloon pump support was given to eight patients who did not have IABP in the preoperative period. The mean amount of cardioplegia solution used was 1,591.1±224.5 mL. Extracorporal membrane oxygenation (ECMO) support had to be given in addition to IABP at the termination of cardiopulmonary bypass in two patients. After the removal of the cross-clamp, it was observed that spontaneous rhythm occurred almost uniformly (n=147, 98%). Two of the other three arrhythmic patients were defibrillated because ventricular fibrillation developed. In the remaining patient, intraoperative temporal pacing was achieved. The pacing was disabled when a spontaneous rhythm occurred shortly thereafter. In the postoperative period, 21 patients developed atrial fibrillation. Sinus rhythms were achieved in all of these patients with medical intervention. No other dysrhythmias (supraventricular tachycardia or ventricular fibrillation) that caused hemodynamic effects or required interventions during postoperative rhythm follow-up were observed in any patient.

Table 2
Demographic data and preoperative data

Parameters	n	%	Mean±SD	Median	Min-Max
Age (year)			59.8±9.7	61	33-84
Sex					
Male	123	82			
Female	27	18			
Body mass index (kg/m^2)			27.95±3.35	27.75	20.8-38.6
Body surface area (m^2)			1.95±0.16	1.95	1.59-2.46
Hypertension	51	34.0			
Diabetes mellitus	48	32.0			
Cigarette	44	29.3			
Hyperlipidemia	40	26.7			
COPD	11	7.3			
Peripheral artery disease	5	3.3			
Chronic renal failure	4	2.7			
Cerebrovascular disease	3	2.0			
EuroSCORE II			1.07±0.43	1	0.45-2.69
Emergency operation	4	2.7			

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease.

Table 3
Intraoperative and postoperative data

Parameters	Mean±SD	Median	Min-Max
CPB time (min)	100.17±26.59	98	45-203
Cross clamp time (min)	49.18±16.07	45.5	20-119
Body temperature (°C)	31.65±0.9	32	28-34
Number of vessels (n)	3.11±0.82	3	1-5
Pleji solution amount (mL)	1591.07±224.48	1.580	1120-2320
CPB entry ACT value	129.29±15.53	130	74-165
CPB exit ACT value	135.33±12.32	137	98-191
CPB entry			
pH	7.32±0.06	7.32	7.16-7.51
pO_2	239.65±58.52	221.5	104-405
pCO_2	42.78±6.1	42.45	24.8-58.9
HCO_3	21.8±2.34	21.6	13.3-37.1
BE	3.45±2.09	3.35	0.1-13.6
Saturation	99.04±0.61	99	96.8-100
NaCl	137.47±2.9	138	125-149
KCL	4.52±0.69	4.6	2.4-6.7
Glucose	155.48±41.08	150	86-301
Ca	1.33±0.14	1.32	0.85-2.01
Lactate	1.85±0.94	1.7	0.3-7.8
Hgb	7.16±1.51	7.15	5.1-12.3
Htc	22.4±4.11	22.2	13.8-37
Cross clamp 10^{th} min			
pH	7.35±0.06	7.34	7.2-7.58
pO_2	187.51±46.58	185	73.4-310
pCO_2	38.8±6.64	38.6	25.4-70.2
HCO_3	20.64±1.96	20.4	14.3-27.9
BE	4.16±1.89	4.1	0.1-12
Saturation	98.84±1.13	99.05	90.4-100
NaCl	138.43±2.64	139	131-151
KCL	4.64±0.68	4.7	3-6.5
Glucose	196.38±45.22	195	99-329
Ca	1.27±0.08	1.27	1-1.46
Lactate	2.69±1.7	2.4	0.9-18
Hgb	7.76±1.09	7.7	5.8-12.3
Htc	23.94±3.64	23.9	4.3-37.9
CPB exit			
pH	7.36±0.06	7.35	7.13-7.56
pO_2	189.17±36.1	195	22.4-295
pCO_2	38.37±5	38.7	23.1-52.7
HCO_3	20.99±1.58	20.9	15.1-24.9
BE	3.72±1.52	3.5	0.1-9.4
Saturation	99.03±0.72	99.2	96.3-100
NaCl	139.39±1.83	140	130-145
KCL	4.55±0.48	4.65	3-6.1
Glucose	186.28±43.26	187.5	115-351
Ca	1.30±0.06	1.31	1-1.51
Lactate	2.76±1.22	2.55	1.1-8.8
Hgb	7.93±1	7.9	5.6-11.1
Htc	24.57±2.98	24.1	17.7-39.0
Extubation time (h)	6.07±1.52	6.12	4.2-20.7
ICU stay time (h)	48.63±10.268	49.2	36-142
Hospital stay time (day)	5.94±1.20	6.1	5-12

SD: Standard deviation; CPB: Cardiopulmonary bypass; ACT: Activated clotting time; BE: Base excess; NaCl: Sodium chloride; KCL: Potassium chloride; Ca: Calcium; ICU: Intensive care unit

Table 4
Preoperative and postoperative laboratory data

	Preoperative			Postoperative 6th hour			Postoperative 24th hours			
Parameters	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
BUN (mg/dL)	21.42±7.05	20.75	9.3-56.4				24.58±7.02	23.1	14.4-68.5	0.001*
Creatine (mg/dL)	0.9±0.23	0.87	0.42-2.31				1.01±0.25	0.95	0.69-2.56	0.001*
Hgb (g/dL)	14.53±1.92	14.7	9.5-20				8.7±0.85	8.6	6.4-12.1	
Hct (%)	42.77±5.24	43.1	27.9-59.6				26.09±2.19	6.1	18.8-32.7	
WBC (K/mm^3)	8.37±1.28	8.2	5.5-13.4				14.86±2.69	14.6	8.7-26.9	
PLT (K/mm^3)	262.78±70.14	258.5	102-605				176.28±36.3	171	88-295	
NaCl (mmol/L)	137.85±3.52	138.5	123-158				141.23±5.29	140	126-159	0.175
KCL (mEq/L)	4.21±0.4	4.2	3-5.6				4.29±0.4	4.2	2.7-5.1	0.119
Ca (mg/dL)	9.22±0.72	9.1	7.8-11.7				8.59±0.5	8.65	7.6-10.8	0.001*
CK (U/L)	87.81±56.55	71	13-337				75.79±38.66	68	15-285	0.195
CK-MB (U/L)	34.77±21.8	26	11-149				36.45±19.61	31.5	4-141	0.273
LDH (U/L)	263.31±31.7	261	170-404				257.74±22.8	256	195-329	0.063
Troponin I (ng/L)	76.42±106.57	28.6	0.9-763.5	731.04±374	662.85	112.3-2476.9	444.35±329.32	412.3	12.3-2727.5	0.001**
	Preoperative			Postoperative						
EF (%)	49.86±5.63	50	30-60	50.33±5.00	50	35-60				0.079

SD: Standard deviation; BUN: Blood urea nitrogen; Hgb: Hemoglobin; Hct: Hematocrit; WBC: White blood cell; PLT: Platelet; NaCl: Sodium chloride; KCL: Potassium chloride; Ca: Calcium; CK: Creatine kinase; LDH: Lactate dehydrogenase; EF: Ejection fraction; * Wilcoxon testi; ** Friedman testi.

Table 5
Postoperative complications

Complications	n	%
Atrial fibrillation	21	14
Bleeding revision	5	3.33
Pneumothorax	3	2
Cerebrovascular event (major)	1	0.66
Intra-aortic balloon pump	8	5.33
Extracorporal membrane oxygenation	2	1.33
Exitus*	2	1.33

* One patient died due to postoperative COVID-19.

The mean preoperative ejection fraction of the patients was 49.9±5.6, while the postoperative early-period values were 50.3±5.0. The pre- and postoperative values of troponin I, creatine kinase, creatine phosphokinase, and lactate dehydrogenase are given in Table 4. There were no significant changes from preoperative to postoperative creatine kinase, creatine phosphokinase, or lactate dehydrogenase values. Although troponin I values increased at postoperative 6 h relative to preoperative values, there was no significant difference between the values at the 6 and 24 h.

The mean duration of extubation was 6.1±1.5 h, hospital stay was 5.9±1.2 days, and intensive care follow-up time was 48.6±10.3 h. Important complications (such as renal failure, cerebrovascular accident, severe bleeding, and revision) encountered in postoperative follow-up are given in Table 5.

DISCUSSION

Coronary bypass surgery is the most common form of cardiac surgery. Myocardial protection of the heart during the operation is critical. There is no consensus on the method and content of cardioplegia used for this protection.[6] Reducing cross-clamp and cardiopulmonary bypass times is another important issue in cardiac surgery.[8] Since there is not much variation in the surgical procedure, efforts are continuing to reduce this time through cardioplegia support. Short cross-clamp and cardiopulmonary bypass time (44.2±14.1 min) observed in our study is consistent with the literature.[6] This reduction seems to be a significant contribution to an important issue in cardiac surgery. Although this was not the main point of our study, it is clear that single-dose administration contributes to the reduction of cross-clamp and cardiopulmonary bypass times. It would not be wrong to think that exposure to the unwanted side effects of the heart-lung machine will be decreased accordingly.

There are significant concerns about the use of DN cardioplegia in coronary artery disease, particularly in patients with multiple vessels.[9] Although an effective solution has been provided by administering retrograde cardioplegia to patients who are given conventional blood cardioplegia, there may be confusion in this regard since DN cardioplegia is applied all at once and antegrade. Another important benefit of not requiring retrograde cardioplegia is preventing complications, such as coronary sinus injury or bleeding from the entrance in the atrium. As suggested by our study, appropriate cardiac arrest can be induced with adequate myocardial protection without the need for retrograde cardioplegia. In the application of DN cardioplegia to multivessel patients in our clinic, after the first dose antegrade, one-fourth of the next dose was given from the anastomotic grafts (Figure 1). Thus, the distribution of cardioplegia solution to the whole heart was facilitated. We believe that this contributed to myocardial protection. There is convincing evidence that the DN cardioplegia solution provides strong myocardial protection.[7,10] In a study by Zeng et al.,[11] intermittent washing of metabolites and reoxygenation of blood were demonstrated as an advantage of cold blood cardioplegia. Regarding our method, we

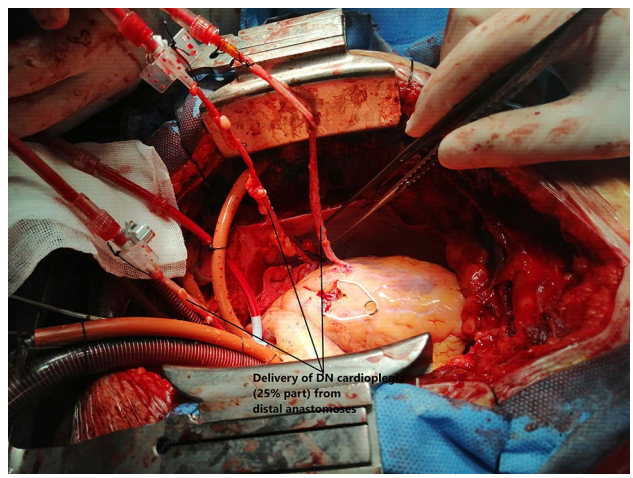

Figure 1. Intraoperative view of the cardioplegia solution being administered from saphenous vein grafts.

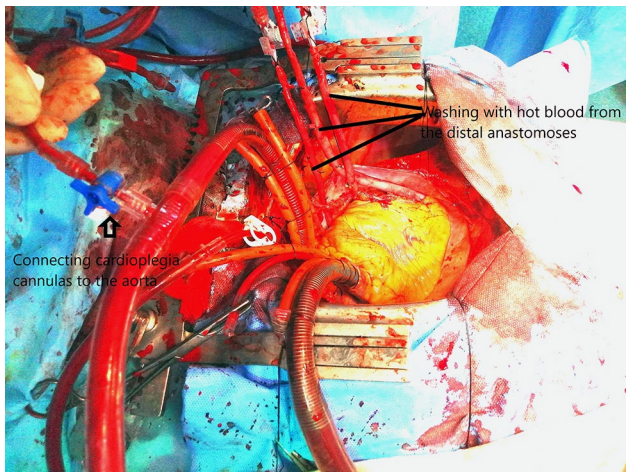

Figure 2. Image demonstrates the connecting of the cardioplegia cannulas to the aortic cannula after the cross-clamp is lifted.

believe that the continuous low dose of cardioplegia solution from the saphenous veins and, ultimately, the cleaning of the entire coronary vascular bed with warm blood from the aorta contributes to the removal of all metabolites, ensuring better protection of the myocardium (Figure 2).

The DN solution was developed to protect immature myocardium against reperfusion injury. However, it has been shown that it also provides functional improvements in elderly hearts.[12] Inspired by these studies, we have used the DN cardioplegia solution in our clinic for the last two years. Although no significant difference was observed in postoperative ejection fraction data in our study, the changes in troponin I values in postoperative follow-up are in accordance with most of the literature. Despite partial elevations, troponin I remained at acceptable levels after coronary artery bypass surgery. It would not be wrong to characterize the preservation of cardiac functions in terms of ejection fraction and troponin I levels. In contrast with this view, some studies have found that troponin I values were not low in groups given DN cardioplegia.[13] Although the main goal of our study was to properly protect cardiac functions through a new application of DN cardioplegia, the need for ventricular defibrillation and temporary pacemakers to address intraoperative arrhythmias was found to be reduced. The rate of spontaneous rhythm was noted to be higher. Since there was no control group in our study, the observational data were compared with the literature.[14] Considering that there were no differences in the intraoperative body temperatures, blood gas data, or electrolyte data of the patients, we believe this finding was an effect of the cardioplegic solution being strengthened. We think that delivering the blood from the aorta to the myocardium through saphenous vein grafts and completely cleaning the cardioplegia solution also contributed to this effect. Many studies have reported a significant decrease in ventricular fibrillation rates after DN use.[8,15] With less need for defibrillation, the possibility of subepicardial necrosis, which may occur through direct contact with the epicardium, is also reduced-contributing, in turn, to a reduction in myocardial damage.[16] Moreover, the components of DN are known to contribute to protection. Due to its hyperosmotic properties, mannitol is effective in clearing out free radicals and reducing edema.[17] Lidocaine acts as a depolarizing agent by inhibiting sodium channels and reducing calcium and sodium entry into cells.[18] Another important component in DN cardioplegia is magnesium. When used as an electrolyte, magnesium has been proven to increase myocardial recovery by blocking calcium channels.[19]

One of the challenges in cardiac surgery is the low cardiac output state. Mechanical support devices (IABP or ECMO) may be needed in patients who have difficulty weaning from a cardiopulmonary bypass and who develop low cardiac output state. The need for IABP ranges from 7 to 17% in different studies.[20,21] The fact that this rate was 6% in our study is seen as a positive outcome. In our study, the need for ECMO support in only two patients (patients with a 35% ejection fraction) was also interpreted positively.

When analyzing arrhythmias in our study, positive effects of the ingredients of the DN (mannitol, lidocaine, and magnesium) were observed. The main benefits were the formation of spontaneous rhythms and reduction in the duration and frequency of arrhythmias, such as atrial fibrillation and ventricular tachycardia. In our study, it was not possible to analyze all the etiological factors that may have caused these rhythm disorders one by one. However, the fact that the frequency of atrial fibrillation in the literature is 45 to 65% suggests that cardioplegia solution is effective at a lower frequency.[20,22] Of course, the findings on this subject will become stronger as studies are conducted with larger prospective patient populations. Another positive finding was that no significant ventricular arrhythmia was experienced in the early postoperative

period by any of the patients treated with DN. As in many studies, no differences were observed in the postoperative follow-up parameters (intubation time, major complications, or discharge time).[23,24] It was observed that observational intensive care follow-up times were shorter compared to our other patients who underwent conventional cardioplegia. We believe that the decreased postoperative arrhythmia contributed to this outcome. Waiting for patients to recover from arrhythmia before being removed from the ICU prolongs this period. No significant difference was observed in terms of the amount of drainage, the number of blood transfusions, the number of patients using inotropic support, or the laboratory data in the postoperative period, which reflects and supports findings that this cardioplegia solution can be used safely in isolated coronary artery bypass grafting.

One of the features of the content of the DN is a lack of glucose, which decreases the need for intraoperative insulin administration. Mick et al.[6] found that glucose levels were lower following the use of DN, and therefore, less insulin was required. In our study, we observed that intraoperative glucose control was easier with low glucose levels.

Although the use of DN cardioplegia for isolated coronary artery bypass grafting was not recommended in a study conducted at the Cleveland Clinic in 2014,[3] more reassuring findings have been reached in other studies.[15,25] Due to the lack of studies with prospective large patient numbers, concerns about this issue cannot be eliminated completely. However, as shown in many studies, DN cardioplegia has become increasingly preferred due to the shortened clamping and operation time and the possibility of performing cardioplegia all at once. In a large-scale study, Guajardo Salinas et al.[15] showed that DN cardioplegia application provides a significant economic advantage as well as other clinical benefits. We found that DN could be used safely in all patients undergoing isolated coronary bypass by following the method presented in our study.

The main limitation of this study is that since a novel application of DN cardioplegia was employed in the study, it could not be compared with the classical DN application. The data were compared instead with the literature. Additionally, only the ejection fraction and troponin I levels were taken as markers of myocardial protection. This restriction prevented a strong assessment from being made for analysis.

In conclusion, although DN cardioplegia solution is more common in pediatric cardiac surgery, it is increasingly used in adult cardiac surgery. However, there are still concerns about its use in isolated coronary bypass surgery. We believe that the method we followed together with a single-dose application will help address these reservations. Studies with more patients are needed for stronger interpretations.

Ethics Committee Approval: The study protocol was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (date: 04.15.2021, no: 3/48). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, literature review, writing the article: F.B.; Data collection and/or processing: Y.K.; Control/supervision, analysis and/or interpretation, final approval of the manuscript: B.E.; Analysis and/or interpretation, final approval of the manuscript: M.Ü., K.T.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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