

Effects of Del Nido and Terminal Warm Blood Cardioplegia on Myocardial Protection and Rhythm in Isolated CABG Patients

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ABSTRACT

Objective: To investigate the effect of using del Nido cardioplegia+terminal hot-shot blood cardioplegia on myocardial protection and rhythm in isolated coronary bypass patients.

Material and methods: A total of 122 patients were given cold (+4-8C) del Nido cardioplegia antegrade and evaluated. Del Nido+terminal warm blood cardioplegia (TWBCP) was applied to 63 patients out of 122 patients, while del Nido cardioplegia alone was applied to the other 59 patients. The preoperative and postoperative data of the patients were recorded and compared.

Results: There was a significant statistical difference between the groups, in terms of volume with more cardioplegia in the del Nido+terminal warm blood cardioplegia group. Although there was no significant difference between cardiac arrest times in both groups, a statistically significant difference was found in the del Nido+terminal warm blood cardioplegia group in the starting to work time of the heart. No difference found between the groups regarding myocardial preservation.

Conclusions: We can add a return to spontaneous sinus rhythm to the advantages of terminal warm blood cardioplegia and del Nido cardioplegia in literature. We think it would be a good strategy to extend the safe ischemic time limit of del Nido to 120 minutes with a terminal warm blood cardioplegia. It seems that cardioplegia techniques that will be developed by adding the successful and superior results of crystalloid cardioplegia applications, such as single dose del Nido in various open heart surgery operations and the superior myocardial return effects of terminal warm blood cardioplegia, will be used routinely in the future.

INTRODUCTION

Bigelow's hypothermia and Melrose's potassium-based diastolic arrest form the basis of myocardial protection in open heart surgery [Bigelow 1950; Melrose 1955]. Many studies related to applied cardioplegia for myocardial protection were made. In line with the results of these studies, various cardioplegia techniques applied with different contents, different temperatures, and different application methods have been developed [Scott 2009]. Blood cardioplegia given as cold induction at +4 degrees, followed by multiple maintenance doses at 20-minute intervals has become the most commonly used cardioplegia technique [Buckberg 2016]. With the development of minimally invasive cardiac surgery, surgeons have begun to search for alternatives to traditional blood and crystalloid cardioplegia. Hyperpolarizing cardioplegic solutions, such as modern Bretschneider solutions (Custodiol®, Essential Pharmaceuticals, LLC, Ewing, NJ, USA), have begun to be used with the assumption that more effective solutions will emerge for myocardial protection by reducing aortic clamp time with a single dose of cardioplegia and continuing uninterrupted surgery [Siddiqi 2018]. However, the high cost of Custodiol-HK has enabled some surgeons to develop cardioplegia with similar content and effect [Cagdas 2020]. In 1995, Dr. Del Nido cardioplegia defined by Pedro del Nido is the most popular of these [Cagdas 2020]. Originally developed for use in pediatric cardiac surgery, it was later used for adults as well [Matte 2012; Yerebakan 2014; Teoh 1986; Ad 2018]. There are studies showing the superiority of del Nido cardioplegia in myocardial protection in adults [Yerebakan 2014]. As it has been known for a long time, it is possible to increase metabolic repair and minimize reperfusion injury by minimizing oxygen demand in the ischemic myocardium with warm terminal blood cardioplegia [Teoh 1986]. Clinical studies are insufficient, except for animal studies on the association of del Nido cardioplegia and terminal warm blood cardioplegia. There is no study examining the effect of terminal warm blood cardioplegia after del Nido cardioplegia, especially on intraoperative rhythm. When studies with del Nido cardioplegia are evaluated in the literature, some centers additionally apply terminal warm blood (hot shot; 37 C) cardioplegia, and some centers do not apply terminal warm blood cardioplegia [Cagdas 2020; Kim 2014]. In our study, we evaluated the effects on myocardial protection and intraoperative cardiac rhythm by giving terminal warm blood cardioplegia to patients who underwent coronary artery bypass surgery using del Nido cardioplegia. We compared our results

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with patients who underwent coronary artery bypass surgery using del Nido cardioplegia and did not use terminal warm blood cardioplegia.

MATERIAL AND METHOD

This retrospective observational clinical trial was conducted on patients, who underwent on-pump isolated CABG at the Cardiovascular Surgery Department in Izmir Tepecik Education and Research Hospital between June 2019 and February 2021. The study was approved by the Clinical Research Ethical Committee of Tepecik Training and Research Hospital. All procedures were performed, in accordance with the Declaration of Helsinki. We evaluated 308 patients, who underwent coronary artery bypass surgery in our clinic between June 2019 and February 2021. While cold blood cardioplegia was applied in the past years, we recently started using del Nido cardioplegia routinely. Patients ages 30 to more than 80 years, and those with kidney disease, hematological dysfunction, and preoperative atrial fibrillation were not included in the evaluation. Patients using preoperative anticoagulant and thrombolytic drugs and those requiring additional cardiac surgery were excluded from the evaluation. (Table 1) Patients who had no acute myocardial infarction and had normal preoperative cardiac marker (troponin

and CK-MB) values were evaluated. (Table 2) Among these patients, those who developed neurological dysfunction or other systemic complications in the postoperative period were excluded from the study. Patients who underwent reoperation due to bleeding in the postoperative period also were excluded (Table 1). As a result, 122 patients who were given cold (+4-8°C) del Nido cardioplegia antegrade were evaluated. Del-Nido+terminal warm blood cardioplegia (TWBCP) was applied to 63 patients out of 122 patients, while del Nido cardioplegia alone was applied to the other 59 patients. The preoperative and postoperative data of the patients were recorded and compared. To evaluate myocardial damage, cardiac markers and echocardiography data were evaluated 4 hours after the postoperative cross-clamp removal. How long the heart was stopped and the time it worked was evaluated. Patients who needed defibrillation were recorded.

Surgical and myocardial protection procedure: All operations were performed by the same surgical and perfusion team via median sternotomy. On CPB, a cross-clamp was put on the ascending aorta, and diastolic arrest was achieved by del Nido cardioplegia solution in both groups. All patients were given del Nido as antegrade cardioplegia by calculating a dose of 20cc/kg, while terminal warm blood cardioplegia was given to 63 people before the cross-clamp was lifted. The compositions of cardioplegia solutions are shown in Table 3. (Table 3) An additional 500 cc dose of del Nido cardioplegia was given to patients with cross-clamps that exceeded 60 minutes. Conventional coronary artery bypass surgery was performed on all patients. Additional terminal warm blood cardioplegia approximately 500-700 cc was given to the patients on 63 patients before the cross-clamp was lifted. LIMA-LAD bypass was applied to all patients. The saphenous vein was used as a graft in other coronary artery anastomoses. After coronary artery distal bypass procedures, patients were warmed, and the cross-clamp was lifted at 34 degrees. Proximal anastomoses of the distal bypasses performed with vein graft with side clamp were performed to the ascending aorta.

Statistical analysis: The analysis was performed using IBM SPSS Statistics for Mac Version 20 (IBM Corp. Released 2011, Armonk, NY, USA). Numeric variables were summarized as mean \pm SD values. Categorical variables were evaluated with cross-table analysis. Comparison of various subgroups was made using chi-square test. Chi-square test was used in the comparison of the groups for nominal variables. In case the minimum expected count was < 5 , Fisher's exact test was used. A $P < 0.05$ was considered statistically significant.

Table 1. Preoperative and postoperative exclusion criteria

1. Patient age lower than 30 and higher than 80
2. Existence of preoperative medically treated renal disease
3. Existence of preoperative haematological dysfunction
4. Preoperative warfarine and/or fibrinolytic agent treatment
5. Acute MI with emergent surgery
6. Re-operations for CABG
7. Concomitant valve and/or vascular surgery
8. Existence of preoperative atrial fibrillation
9. Off-pump CABG operations
10. LVEF $\geq 40\%$
11. Postoperative severe neurologic and/or other systemic complications
12. Reoperations for early massive bleeding after surgery
13. Patients with preoperative high troponin levels

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; LVEF, left ventricle ejection fraction; MI, myocardial infarction

Table 2. Inclusion criteria

1. Patients only on-pump CABG with 2 or 4 vessel bypass
2. Patients cardiac segment functions (EF $\geq 40\%$)
3. Patients with normally preoperative TnT and CK-MB levels (without preoperative MI)

Table 3. Composition of del Nido cardioplegia solution

isolyte-S solution	1 lt
20% Mannitol	17 cc
15% Magnesium sulfate	14 cc
8.4% NaHCO ₃	13 cc
7.5% Potassium chloride	26 cc
2% Lidocaine	6.5 cc

RESULTS

Both groups were statistically similar, in terms of demographic data, preoperative characteristics and comorbidities. (Table 4) The preoperative and postoperative data of both groups are shown in Table 5. (Table 5) All patients were weaned off from cardiopulmonary bypass without problems. While the total cross-clamp time was 55.68 ± 16.18 minutes in 63 patients to whom we added terminal warm blood cardioplegia, the cross-clamp time was 56.22 ± 20.49 minutes in 59 patients who only received del-Nido cardioplegia. While the total perfusion time was 93.77 ± 24.58 minutes in the group in which we added terminal warm blood cardioplegia, it was 92.17 ± 31.42 minutes in the other group, where we did not use additional warm blood cardioplegia. Total perfusion time was 93.77 ± 24.58 minutes in group A and 92.17 ± 31.42 minutes in group B. There was no statistical difference, in terms of cross-clamp and total perfusion time. Mean intubation time, ICU, and hospital stay times were similar in both groups. There was no statistically significant difference in both groups. There was no significant difference between the groups, in terms of CK-MB, troponin T, EF change, mortality, postoperative ARF development, and development of low cardiac output syndrome. There was no significant difference, in terms of need for perioperative inotropic support and intraaortic balloon pump. A statistically significant difference, in terms of volume, was detected in 63 patients who additionally received terminal warm blood cardioplegia. Although there was a significant difference between the cardiac arrest times in both groups, a statistically significant difference was found in the heart study in the del Nido+warm blood cardioplegia group. In 63 patients to whom we added terminal warm blood cardioplegia, the heart worked in a shorter time after

cross-clamp (14.58 ± 21.08 18.70 ± 21.92 , $P = 0.002$). Similarly, the heart's need for defibrillation was statistically less in the same patient group than in patients who received del Nido cardioplegia alone (3 (5.1%) 7 (13.2%), $P = 0.013$). Supraventricular arrhythmia was statistically less common in patients who received additional terminal warm blood cardioplegia (1 (1.7%) 5 (9.4%), $P = 0.015$).

DISCUSSION

In a high-risk patient group with CABG within the first 7 days due to acute myocardial infarction, Yerebakan et al. showed that del Nido cardioplegia was equivalent to blood cardioplegia, in terms of mortality, complications, and myocardial protection [Yerebakan 2014]. In a recently published meta-analysis, del Nido cardioplegia was shown to have significant advantages over blood cardioplegia for a variety of parameters in adults [Li 2018]. The literature conclusions of use of a single-dose, long-acting, extracellular cardioplegia solution, such as del Nido in the adult heart, are encouraging. Del Nido cardioplegia is known to result in lower postoperative troponin release compared with blood cardioplegia in pediatric patients and rat cardiomyocytes [Li 2018]. It has been shown that rapid myocardial recovery [Li 2018] and providing spontaneous sinus rhythm can be achieved with terminal warm blood cardioplegia used in blood cardioplegia. In an animal study, spontaneous sinus rhythm was achieved with the addition of terminal hot blood cardioplegia to a single dose of del Nido cardioplegia [Nakao 2020]. In prolonged ischemia and in high-risk patients, myocardial recovery may be delayed, due to increased inotrope support and preload in the early period after bypass. With terminal

Table 4. Preoperative demographic characteristics and comorbidities

	del Nido+TWBCP (N = 63)	Pure del Nido (N = 59)	P-value
Age years, std	67.33 ± 10.09	65.44 ± 12.68	0.316
Male gender, n (%)	35 (60.3)	39 (73.5)	0.675
Diabetes mellitus, n (%)	26 (44.8)	21 (39.6)	0.423
Hyperlipidemia, n (%)	10 (17.2)	12 (22.6)	0.382
Hematocrit (%) std	38.0 ± 5.24	40.2 ± 4.63	0.646
Creatinin mg/dl std	0.88 ± 0.25	0.94 ± 0.38	0.147
BMI (kg/m ²)	26.8 ± 3.5	27.0 ± 3.8	0.412
HT, n (%)	21 (36.2)	16 (30.2)	0.443
Family history of CABG, n (%)	14 (24.1)	18 (33.9)	0.485
PAD, n (%)	10 (17.2)	6 (11.3)	0.231
COPD, n (%)	7 (12.0)	6 (11.3)	0.771
EUROSCORE (%) std	3.8 ± 1.4	4.6 ± 1.4	0.423
History of PCI, n (%)	9 (15.5)	12 (22.6)	0.482

BMI, body mass index; HT, hypertension; PAD, peripheral arterial disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention

warm blood cardioplegia, these negative effects can be eliminated in the energy depleted myocardium [Volpi 2019]. In addition, although the superiority of del Nido cardioplegia in preventing intracellular acidosis is known, there is always a potential risk of Na and Ca overload. In addition to correcting this overload by minimizing the Na⁺ flow of lidocaine, the additional hot shot blood cardioplegia provides extra support to maintain the intracellular pH balance. Ionic imbalance and delayed aerobic metabolism in ischemia/reperfusion can be reversed with terminal warm blood cardioplegia without mitochondrial damage [O'Brien 2009; Govindapillai 2013]. Lidocaine in del Nido cardioplegia has been shown to better maintain intracellular pH by limiting the intracellular entry of calcium [Ad 2018]. In this study of Ad and her colleagues, no difference was found between the groups in the conversion of the heart to spontaneous sinus rhythm. On the contrary, in our study, we found a statistically significant difference in favor of the group in which we gave del Nido and terminal warm blood cardioplegia on return to sinus rhythm [Ad 2018]. We already know that the superiority of del Nido cardioplegia in preventing ventricular arrhythmias during coronary reperfusion after the aortic cross-clamp is lifted is due to its increase in nitric oxide release [Ad 2018]. It is known that in patients with systolic left ventricular dysfunction or significant cardiac dilatation, faster recovery of

cardiac rhythm after aortic cross-clamp removal may reduce the risk of myocardial damage and therefore the risk of postoperative low cardiac output syndrome [Ad 2018]. Additionally, there is evidence in animal models that del Nido solution can provide superior myocardial protection in elderly hearts [Govindapillai 2013; O'Blens 2011]. In isolated coronary bypass operations, low cross-clamping time, shorter perfusion time, and less postop CK-MB and Troponin T levels have been reported with the use of del Nido cardioplegia [Yerebakan 2014; Timek 2016; Ramanathan 2015]. All this literature information is on the superior aspects of del Nido cardioplegia in myocardial protection. We know from blood cardioplegia results that terminal warm blood cardioplegia provides rapid myocardial recovery from ischemia-reperfusion [Caputo 1998]. The concern that the dose of del Nido cardioplegia may not be sufficient in CABG patients with seriously troublesome multi-vessel disease and in patients with left ventricular hypertrophy has limited its use in these patients. Therefore, due to the heterogeneous distribution problem, multiple applications of del Nido cardioplegia have come to the fore in order to provide adequate myocardial protection and to avoid postoperative myocardial dysfunction [Pieri 2016]. Myocardial glycogen storage is restored by terminal warm blood cardioplegia, possibly due to accelerated glycogenesis. These ultrastructural changes contribute to the

Table 5. Preoperative and postoperative parameters

	del Nido+TWBCP (N = 63)	Pure del Nido (N = 59)	P-value
Cross-clamp time (minutes) std	55.68±16.18	56.22±20.49	0.958
Total CPB time (minutes) std	93.77±24.58	92.17±31.42	0.561
Number of anastomosis std	3.05±0.75	3.27±0.79	0.648
Cardioplegia volume (mL) std	1489.85±313.07	1008.82±308.34	0.001
Preop-inotrope, n (%)	5 (8.6)	8 (15)	0.917
IABP support, n (%)	1 (1.7)	3 (5.6)	0.393
Arrest-time (sn) std	20.50±12.55	21.20±11.90	0.079
Start-time (sn) std	14.58±21.08	18.70±21.92	0.002
Fibrillation, n (%)	3 (5.1)	7 (13.2)	0.013
Supraventricular arrhythmia, n (%)	1 (1.7)	5 (9.4)	0.015
ICU stay (days) std	2.89±3.51	3.01±3.6	0.764
Hospital stay (days) std	6.78±2.36	7.02±3.47	0.966
CK-MB U/L std	42.73±8.09	44.59±10.02	0.398
Troponin T, ng/L std	454.60±34.17	501.53±32.61	0.558
Preop-EF (%) std	54.91±6.77	52.36±7.79	0.738
Postop-EF (%) std	54.38±6.55	51.55±7.93	0.670
Total mortality, n (%)	2 (3.4)	2 (3.7)	0.632
LCOS, n (%)	1 (1.7)	2 (3.7)	0.393
ARF, n (%)	3 (5.6)	4 (7.5)	0.776
Entubation time (hour) std	7.85±2.5	8.5±3.5	0.980

CPB, cardiopulmonary bypass; IABP, intraaortic balloon pump; ICU, intensive care unit; LCOS, low cardiac output syndrome; ARF, acute renal failure

improvement of myocardium function after terminal warm blood cardioplegia and rapid spontaneous restoration of sinus rhythm after ischemia. Post-reperfusion terminal warm blood cardioplegia has been shown to reduce reductions in tissue ATP and glycogen [Siddiqi 2018; Timek 2016]. This contributes to myocardial protection and spontaneous return of the rhythm to the sinus [Timek 2016]. Spontaneous conversion to normal sinus rhythm was observed more frequently in del Nido cardioplegia than blood cardioplegia [Hamad 2017]. This could possibly be explained as a result of better myocardial protection, the antiarrhythmic effect of lidocaine, or the effect of terminal warm blood cardioplegia combined with both [Hamad 2017]. Terminal warm blood cardioplegia reduces intracellular calcium ions in cardiac myocytes, may prevent post-reperfusion myocardial damage and ventricular fibrillation [Matte 2012; Ristagno 2008]. In the Houston, Texas heart study [Schutz 2020], no terminal warm blood cardioplegia was given in the del Nido group. Rhythm problems were less common in this group compared with blood cardioplegia. However, in the study of Cagdas et al. [Cagdas 2020], del Nido was given to one of the groups and STH (St. Thomas' Hospital) crystalloid cardioplegia was given to the other. In addition, terminal warm blood cardioplegia was given to both groups. As a result, they found that the return of the heart to spontaneous sinus rhythm was statistically significant in the group with del Nido. In our study, all groups were in cardiac arrest with del Nido cardioplegia, and only one group was given terminal warm blood cardioplegia. We think that the significant statistical difference observed in the terminal warm blood cardioplegia in addition to del Nido in returning to sinus rhythm adds to the superiority of del Nido cardioplegia in coronary bypass surgery.

Study limitations: Our study had several limitations. A major limitation was the retrospective nature of the data collection, with relatively small sample sizes. Other important limitations were the non-randomised design of study and the lack of objective adjustment methods, such as propensity-matched analysis for the comparability of two groups.

CONCLUSION

The diversity of techniques used alone or in combination for optimal myocardial protection underscores the fact that optimal implementation remains difficult. It is known that in isolated CABG surgery after myocardial infarction, myocardial protection with del Nido solution is at least as good as or even superior to blood cardioplegia. In addition, we can add spontaneous conversion to sinus rhythm to the advantages of terminal hot-shot blood cardioplegia and del Nido cardioplegia mentioned above. We think that extending the safe ischemic time limit of del Nido to 120 minutes with a terminal hot-shot blood cardioplegia would be a good strategy and offer an opportunity to extend the del Nido indication to higher-risk patients. It seems that cardioplegia techniques that will be developed by adding the successful and superior results of crystalloid cardioplegia applications, such as single dose del Nido in various open heart surgery operations and

the superior myocardial return effects of terminal warm blood cardioplegia, will routinely be used in the future. The easy applicability of the technique is an advantage. Further studies involving different patient populations and their modifications hold promise for safer adoption of this ingenious and cost-effective technique.

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