

Is Modified Del Nido Cardioplegia as Effective as Del Nido Cardioplegia in Patients With Isolated Coronary Artery Bypass Surgery?

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[HI]ABSTRACT

Objective: Is modified del Nido cardioplegia superior to del Nido cardioplegia in coronary artery bypass patients?

Material and methods: All patients underwent cardiopulmonary bypass and retrospectively were analyzed. A total of 70 patients were included in the study. Thirty-four patients who were given cold (+ 4-8C ') modified del Nido cardioplegia antegrade were evaluated. Other patients received classical del Nido cardioplegia. Hot shot warm blood cardioplegia was given to all patients before the cross-clamp was removed. The results of both groups were compared.

Results: There was no significant difference between cardiac arrest times in both groups. A statistically significant difference was found in the modified del Nido cardioplegia group in the working of the heart. Less fibrillation was observed in the modified del Nido cardioplegia group. No difference found between the groups, regarding myocardial preservation. No decrease in hemoglobin was observed in the modified del Nido group on the postoperative first day.

Conclusions: We know that return to spontaneous sinus rhythm and fibrillation reduces ischemia-reperfusion injury. At the same time, we can see that epicardial edema was less in the modified del Nido group. We think that less anemia is an advantage of modified del Nido cardioplegia.

INTRODUCTION

In cardiac surgery, cardiac arrest is provided by cardioplegia to provide a bloodless and immobile surgical field. During surgery when the aorta is clamped, the heart remains ischemic and myocardial damage occurs in this way [Kim 2014]. Myocardial damage is the main source of postoperative mortality and morbidity. Therefore, myocardial protection is very important [Li 2018]. Various myocardial protection methods have been described to prevent myocardial damage.

Hypothermia and diastolic arrest are the most commonly used methods to slow the basal metabolic rate of the heart and reduce oxygen consumption [Buckberg 2016]. Many studies have been conducted on cardioplegia applied for myocardial protection, and in line with the results of these studies, various cardioplegia techniques have developed, which are applied in different contents, at different temperatures, and with different application methods [Scott 2009]. Cold blood cardioplegia, known as the Buckberg protocol, has become the most popular cardioplegia technique, with maintenance doses given at regular intervals in many centers. The Buckberg protocol combined with hot shot blood cardioplegia given just before aortic cross-clamp removal has been suggested as the most appropriate myocardial preservation technique. Dr. Pedro del Nido and his team developed a cardioplegia solution called del Nido. This solution, which initially was used in pediatric patients, has been used in adult cardiac surgery in later years [Sanetra 2018]. Its use in adult patients has not been limited to minimally invasive and robotic surgery, but its use also has become widespread in other surgeries. Studies on its safety and efficacy have been conducted by comparing Del Nido solution with conventional cardioplegia solutions [Mishra 2016; Hamad 2017]. Therefore, we routinely started to use del Nido cardioplegia clinically. Epicardial and myocardial edema can be seen, due to hemodilution of the crystalloid part of Del Nido cardioplegia [Ota 2016]. Thanks to the whole blood content of the modified del Nido cardioplegia, free radical scavenging and providing more oxygen to the tissues can be achieved [Owen 2020]. In line with all this information, we started to use the modified del Nido cardioplegia solution, which we routinely have been using in recent years in our isolated coronary bypass surgery cases. We planned this study, considering that myocardial protection results may be equivalent or superior to conventional del Nido cardioplegia, especially in our routine coronary bypass patients.

MATERIALS AND METHODS

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 December 2020 and June 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

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Declaration of Helsinki. Ninety patients, who underwent coronary artery bypass surgery in our clinic between December 2020 and June 2021, were evaluated. While del Nido cardioplegia has been used in our clinic since 2020, we routinely started to use the modified version of del Nido cardioplegia, as of the beginning of 2021. Exclusion characteristics of the study are shown in Table 1. (Table 1) The inclusion criteria also are summarized in Table 2. (Table 2) Fifty patients, who were given cold (+4-8C) del Nido cardioplegia antegrade, were evaluated. Modified del nido cardioplegia was given to 34 patients out of 90 (MDN Group). Another 36 patients were given conventional del Nido cardioplegia (DN Group). Terminal warm blood cardioplegia was given to all patients before removal of the cross-clamp. The perioperative and postoperative data of the patients were recorded and compared. To assess myocardial damage, cardiac markers and echocardiographic data at 4 hours after postoperative cross-clamp removal in both groups were evaluated and compared. How long the heart stopped and worked was evaluated by keeping time. Patients who needed defibrillation, patients who needed blood transfusion in the postoperative period, and those who needed inotropes and IABP (intra aortic balloon pump) were recorded.

Coronary artery bypass surgery and cardioplegia application: All patients underwent conventional coronary artery bypass surgery. After graft preparation and standard cannulation, cardiopulmonary bypass was started and cooling was started. A cross-clamp was placed at 32 degrees. While

modified del Nido cardioplegia was given to 34 patients in the MDN group by calculating a dose of 20cc/kg, 36 patients in the DN Group were given conventional del Nido cardioplegia antegrade. All patients underwent LIMA-LAD bypass. It was used as saphenous vein graft in other coronary artery bypasses. All patients received 500/700cc terminal warm blood cardioplegia before the cross-clamp was removed. After the coronary artery distal bypass procedures, the patients were heated and the cross-clamp was removed at 34 degrees, and the proximal bypasses of the distal bypasses made with vein grafts with side clamps were performed to the ascending aorta. An additional dose of 500 cc (modified or classical) del Nido cardioplegia was given to patients whose cross-clamp time exceeded 60 minutes. The contents of cardioplegia are given in Table 3. (Table 3) Del Nido cardioplegia was 1:4 (1 unit blood 4 units crystalloid) ratio, while 4 units of blood (700cc) and 1 unit (300cc) crystalloid was used as modified del Nido cardioplegia. Unlike conventional del Nido cardioplegia, 7.5% potassium chloride 40 cc was added.

Statistical analysis: The analysis was performed using IBM SPSS Statistics for Mac Version 20 (IBM Corp. Released 2011, Armonk, NY). Numeric variables were summarized as mean ±SD values. Numerical data were compared using Mann-Whitney U test. Categorical variables were evaluated with cross-table analysis. 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. Exclusion criteria

1.	Patients who underwent additional surgical intervention (valve surgery, aortic surgery,) other than CABG
2.	Patients who had a myocardial infarction (MI) within the last 3 weeks
3.	Patients with chronic renal failure (CKD), advanced chronic obstructive pulmonary disease (COPD)
4.	Patients who urgently were taken to CABG surgery
5.	Patients with malignancy and liver failure
6.	Preoperative warfarine and/or fibrinolytic agent treatment
7.	Re-operations for CABG
8.	LVEF ≥ 40%

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

Table 2. Inclusion criteria

1.	CABG with 2 or 5 vessel bypass
2.	Ejection Fraction (EF ≥40%)
3.	Normally preoperative TnT and CK-MB levels

EF, ejection fraction

RESULTS

Preoperative patient characteristics and intergroup comparisons of demographic data are presented in Table 4. (Table 4) There was no statistical difference between both groups. Intraoperative and postoperative data are shown in Table 5. (Table 5) When the groups were evaluated as cross-clamp time, the group receiving modified del Nido cardioplegia was 54.35±15.20 minutes, while the group receiving classical del Nido cardioplegia was 55.12±19.51 minutes (*P* = 0.869). When total bypass time was evaluated, it was 91.62±21.14 minutes in the modified group, while it was 90.19±28.32

Table 3. Composition of cardioplegia solutions (del Nido:1:4 Crystalloid:Blood/Modified del Nido: 4:1 Blood:Crystalloid)

	del Nido Cardioplegia	Modified DNC
isolyte-S solution	700cc	300cc
20% Mannitol	17cc	17cc
15% Magnesium sulfate	14cc	14cc
8.4% NaHCO3	13cc	13cc
7.5% Potassium chloride	26cc	40cc
2% Lidocaine	6.5cc	6.5cc
Blood	300cc	700cc

minutes in the del Nido cardioplegia group ($P = 0.587$). There was no statistically significant difference between the groups, in terms of both periods. Intensive care and hospital stay durations were similar in both groups. No statistical difference was observed. There was no significant difference between the groups, in terms of CK-MB, troponin T, EF change, mortality, development of postoperative ARF, and development of low cardiac output syndrome. There was no significant difference in terms of the need for preoperative inotropic support and intraaortic balloon pump. Although there was no significant difference between the two groups in cardiac arrest, and a statistical difference was found in favor of the modified del Nido group in cardiac rework. The heart beat again in the group that received modified del Nido cardioplegia in an average of 13.42 ± 19.25 seconds, while the heart beat in an average of 18.50 ± 20.83 seconds in the group that received classical del Nido ($P = 0.002$). There was no statistical difference between the groups in return to spontaneous sinus rhythm. The heart was less fibrillated in the group receiving the modified del Nido. There was a statistical difference between the two groups in terms of fibrillation. Only 1 patient (2.9%) in the modified del Nido group had to be defibrillated because it was fibrillated. In the group receiving classical del Nido, 6 patients (16.6%) became fibrillated and needed defibrillation ($P = 0.012$). There was a statistical difference in favor of the modified del Nido group, in terms of need for blood transfusion ($P = 0.023$). While only 3 of the patients receiving modified del Nido cardioplegia needed blood transfusion, 7 patients in the group receiving classical del Nido cardioplegia required blood transfusion. Considering the Hb levels on postoperative day 1, there was a statistical difference in favor of the group receiving modified del Nido cardioplegia. Hemoglobin level was 10.10 (6.90 – 14.15) mg/dl in the modified

group, while hemoglobin levels were 9.10 (6.40 – 12.10) mg/dl in the classical del Nido group ($P = 0.001$).

DISCUSSION

With cardiopulmonary bypass, open heart surgeries have become possible in a bloodless and inactive environment. In addition, myocardial protection is an important factor that greatly affects the success of open heart surgery. Therefore, the management of myocardial protection plays a key role in the success of the operation. Although there are various cardioplegia techniques used alone or in combination, the optimal method for ideal myocardial preservation is still a matter of debate. The basis of myocardial protection is hypothermia and cardioplegic arrest. It is seen that there are still many applications regarding the content, temperature, frequency, and route of administration of the cardioplegia solution [Buckberg 2016]. With maintenance doses given at regular intervals, the Buckberg protocol has become the most popular cardioplegia technique known. The Buckberg protocol combined with the hot shot has been suggested as the most appropriate myocardial preservation technique. However, minimally invasive surgical developments and multi-dose cardioplegia interruption of the surgical flow have led to the search for a longer-lasting cardioplegia solution (like Customial-HTK cardioplegia). Del Nido cardioplegia solution, which has been successfully used in pediatric cardiac surgery for years and has been used in adult cardiac surgery in recent years, has been an ideal solution because it provides cardiac arrest for a long time [Valooran 2016].

It contains mannitol, which scavenges free radicals and reduces edema, magnesium sulfate, which blocks calcium channels, and lidocaine, which is an antiarrhythmic agent and

Table 4. Demographic characteristics and comorbidities

	Group A (M-DNC) (N = 34)	Group B (DNC) (N = 36)	P-value
Age (years, std)	64.23 ± 8.09	61.27 ± 10.38	0.298
Male gender, n (%)	14 (41.1)	18 (50.0)	0.563
Diabetes mellitus, n (%)	9 (26.4)	10 (27.7)	0.403
Hypertension, n (%)	15 (44.1)	16 (44.4)	0.393
Hyperlipidemia, n (%)	10 (29.4)	12 (33.3)	0.292
Peripheral arterial disease, n (%)	8 (23.5)	6 (16.6)	0.220
COPD, n (%)	6 (17.6)	5 (13.8)	0.652
Hematocrit (%) std	39.0±4.33	41.3±3.57	0.544
Creatinin, mg/dl std	0.98±0.21	0.91±0.18	0.168
BMI (kg/m ²)	26.5±3.2	28.0±3.1	0.402
EUROSCORE (%) std	3.9±1.5	4.5±1.4	0.413

BMI, body mass index; COPD, chronic obstructive pulmonary disease

sodium channel blocker. These components provide successful myocardial protection in immature myocardium, which has a lower tolerance to calcium ion flux during reperfusion, and have been used safely in pediatric surgery. In recent years, its use in adult cardiac surgery has become widespread. Studies have been conducted on its effects on adult patients, and the superiority of del Nido solution in myocardial protection has been reported in these studies [Ler 2020]. Joseph Lamelas used del Nido cardioplegia solution in minimal aortic valve replacement surgeries by modifying it in a 4:1 (blood:crystalloid) ratio [Lamelas 2015]. Michele Gallo also used a modified del Nido cardioplegia solution at a ratio of 4:1 (blood:crystalloid) during heart transplantation [Gallo 2019]. Loberman, on the other hand, used it by modifying it at a ratio of 8:1 (blood:crystalloid) and showed that the modified del Nido cardioplegia solution is effective and safe in adult cardiac surgery [Loberman 2014]. Publications on the use of del Nido solution in CABG surgeries indicate that del Nido cardioplegia can be used safely [Cayir 2020]. There is no study in the literature comparing the results of del Nido and modified del Nido cardioplegia in coronary bypass patients. It is extremely important to consider the routine use of del Nido cardioplegia in patients with isolated CABG and the advantages of modified del Nido cardioplegia along with its good results.

Therefore, we share the results of both del Nido cardioplegia in our center. In our study, the decrease in hemoglobin concentration (hemodilution) observed on postoperative day 1 was lower in patients receiving modified del Nido. Reducing the crystalloid volume in crystalloid cardioplegia solutions and adding blood to it alleviates the problem of hemodilution in open heart surgery [Nardi 2018]. Similarly, in some studies, an improved hemoglobin level can be achieved with the amount of blood given instead of the decreased crystalloid volume in del Nido cardioplegia, and oxygen delivery of the blood to the tissues is increased. It also is known that blood is a very good physiological buffer [Loberman 2014]. In open heart surgery, ventricular fibrillation often can be encountered after aortic cross-clamping. Although fibrillation can be treated quickly with electrical defibrillation, defibrillation itself can cause myocardial damage. Elevated serum troponin T levels are a specific marker of myocardial injury. Dysfunction of cardiac myocytes resulting from defibrillation may be due to changes in membrane permeability and disruption of calcium homeostasis. Therefore, it is more important to prevent ventricular fibrillation with an effective cardioplegia strategy than to treat it after it occurs [Buel 2020]. Low defibrillation rates were associated with del Nido cardioplegia in a total of six studies consisting of three studies, each involving 465 adult and 550

Table 5. Intraoperative and postoperative parameters

	M-DNC (N = 34)	DNC (N = 36)	P-value
CK-MB U/L std	39.73±8.14	42.34±9.23	0.374
Troponin T, ng/L std	396.60±28.21	498.33±28.51	0.453
Preop-EF (%) std	52.78±5.62	50.34±6.88	0.645
Postop-EF(%) std	50.27±5.45	49.35±8.72	0.568
Cross-clamp time (minutes) std	54.35±15.20	55.12±19.51	0.869
Total CPB time (minutes) std	91.62±21.14	90.19±28.32	0.587
Number of anastomoses std	3.15±0.45	3.41±0.63	0.631
Preop-inotrop, n (%)	3 (8.8)	5 (13.8)	0.824
IABP support, n (%)	1 (2.9)	3 (8.3)	0.285
Cardiac arrest-time (sn) std	25.50±13.65	22.30±12.80	0.065
Cardiac start-time (sn) std	13.42±19.25	18.50±20.83	0.002
Spontaneous recovery of heart beat, n (%)	23 (67.6)	20 (55.5)	0.645
Fibrillation, n (%)	1 (2.9)	6 (16.6)	0.012
Blood transfusion, n (%)	3 (8.8)	7 (19.4)	0.023
Postoperative first day Hb level (mg/dl)	10.10 (6.90–14.15)	9.10 (6.40–12.10)	0.001
ICU stay (days) std	2.75±3.22	3.18±4.36	0.682
Hospital stay (days) std	6.21±2.45	7.56±3.22	0.856
LCOS, n (%)	1 (2.9)	2 (5.5)	0.289
ARF, n (%)	2 (5.8)	4 (11.1)	0.656
Total mortality, n (%)	1 (2.9)	2 (5.5)	0.856

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

pediatric patients, in which del Nido and St Thomas II solution were compared [Ler 2020]. Various studies have shown the superiority of del Nido cardioplegia, especially in spontaneous return to sinus rhythm and low defibrillation need [Almeida 2021; Misra 2021]. In addition to this superior feature of del Nido cardioplegia, in our study, the need for defibrillation was found to be significantly less in the MDN group compared with the classical del Nido group. There was no statistically significant difference between MDN and classical del Nido in all parameters related to myocardial protection.

Study Limitations: Our study had several limitations. A major limitation of this study was the retrospective nature of the data collection, with relatively small sample sizes.

CONCLUSION

Optimal myocardial protection during cardiac surgery is one of the key components of successful surgery. Since the 1950s, many strategies consistently have been developed to improve myocardial protection and prevent further ischemic damage. There is no standard for cardioplegia technique, and long-acting or single-dose solutions seem closer than expected to an ideal solution. Considering the advantages of Del Nido solution, we can easily prefer classical or modified del Nido cardioplegia solutions. We can easily use modified del Nido cardioplegia, especially in high-risk patients who will undergo isolated coronary artery bypass surgery, because of the less need for defibrillation and less blood transfusion. We think that preventing myocardial damage due to ventricular fibrillation will be very important in reducing morbidity. In addition, it will be possible to keep patients away from side effects that may occur due to the need for blood transfusion after hemodilution and myocardial edema.

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