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Comparative Myocardial Protection Effects of Buckberg and del Nido in Mitral Valve Surgery: A Prospective Randomized Trial

Mostafa Mousavizadeh [1], MD; Amene Ghanbari [1,*], MS; Nahid Zirak [2], MD; Behshid Ghadrdoost [1], MD; Mohsen Yaghubi [3], MS; Saeid Hosseini [1], MD

[1] Heart Valve Disease Research Center, Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, IR Iran
[2] Lung Disease Research Center, Mashhad University of Medical Sciences, Mashhad, IR Iran
[3] Department of Extra Corporeal Circulation, Razavi Hospital, Imam Reza International University, Mashhad, IR Iran

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ABSTRACT

Background: Myocardial protection during cardiopulmonary bypass requires essential techniques to preserve myocardial function and protect the myocardium from cellular damage.

Objectives: This study aimed to investigate the efficacy of del Nido cardioplegia in mitral valve surgery compared to Buckberg solution.

Methods: All patients who underwent mitral valve surgery from April 2018 to December 2018 were recruited in the present trial. The patients were assigned randomly into del Nido and Buckberg groups. Trans-thoracic and trans-esophageal echocardiography were performed before and after the procedure to evaluate left ventricular ejection fraction, as the primary outcome.

Results: A total of 152 patients (77 in the del Nido group and 75 in the Buckberg group) were included in the final analysis. The mean age of the participants was 51.3 ± 13.4 years, and 55.3% of the patients were female. The two groups were comparable in terms of all baseline characteristics. The results also showed no significant difference between the two groups regarding pre-operative ejection fractions (P = 0.063). However, ventilation time and the mean length of ICU stay were higher in the Buckberg group (0.018 and 0.001, respectively). Moreover, the results indicated a more prominent reduction in left ventricular ejection fraction measured via trans-thoracic and trans-esophageal echocardiography in the Buckberg group compared to the del Nido group (13.7% versus 4.7%, P < 0.001 for trans-thoracic echocardiography).

Conclusions: Del Nido cardioplegia solution exerted beneficial effects on myocardial protection evaluated by echocardiography compared to Buckberg in adult patients with preserved ejection fraction undergoing mitral valve surgery.

1. Introduction

In the early years of heart surgery, there was little interest in the likelihood of non-lethal or lethal injuries to the heart during surgery, especially cardiac muscle arrest (1-3). Through the early years of experience, the cross-clamp technique and fibrillation were used to create a silent heart with a clean and blood-free surgical field. These methods were accompanied by an increased risk of ischemic cardiac muscle injuries. Additionally, the clamping of the aorta alone did not inhibit the heart's activity and resulted in hypoxia and cellular acidosis (1, 2, 4). To overcome these complications, Melrose et al. used the first chemical arrest in 1950 (1, 5). Subsequently, with the advances made in the initial formulation and acceptable results, this solution was developed worldwide and resulted in a significant improvement in protecting the myocardium (6, 7). Consequently, several cardioplegia formulations were introduced and evaluated to achieve the protection of the myocardium by inducing diastolic arrest, reducing myocardial energy wasting, preventing cellular damage during the intentional ischemia period required for cardiac surgery, and minimizing reperfusion injury after the restoration of blood flow in the coronary arteries (5, 7).

In the 1980s and 1990s, the Buckberg (BB) method was introduced by Buckberg and it is still widely accepted (1, 3, 6).

*Corresponding author: Amene Ghanbari, Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, Iran, Cellphone: +98-9126218230,
Email: a.mghanbari@yahoo.com.

In this method, a similar formulation is administered for children but is adjusted for the volume, flow, and cardioplegia pressure (8, 9), because children's immature heart is more sensitive to increased intracellular calcium owing to the undeveloped voltage-dependent calcium channel and endoplasmic reticule system (9, 10). Although a normally functioning heart can tolerate different concentrations of calcium, low-calcium cardioplegia solution may improve the function of the vessels' endothelial layers in a hypoxic stressed heart, thereby reducing the damage caused by hypoxia reperfusion (5, 9). Accordingly, Del Nido (DN) cardioplegia has been introduced and utilized to address the requirements of both premature and immature hearts (9, 11).

Cardioplegia solutions have a great deal of variations regarding the type and amount of compounds, basal solutions, and the injection temperature. DN was only applied for pediatric cardiac surgeries from 1995 to 2012. Then, cardiac surgeons began to utilize DN in adult patients with congenital heart surgeries (12, 13). After that, it has been routinely used in patients undergoing other cardiac surgeries (12, 14, 15). However, there is currently no reliable and robust shred of evidence demonstrating a cardioplegia solution's superiority over other methods.

2. Objectives

the present study aims to investigate the myocardial protective effects of BB compared to DN cardioplegia in adult patients undergoing surgical replacement or repair of the mitral heart valve.

3. Patients and Methods

3.1. Recruitment of Participants and Design Overview

After obtaining the approval of the Institutional Review Board, adult patients presented for elective isolated mitral valve surgery requiring Cardiopulmonary Bypass (CPB) between April 2018 and December 2018 were enrolled consecutively. The protocol of the present single-center, single-blinded, randomized clinical trial was registered retrospectively in the Iranian Registry of Clinical Trials (IRCT20191024045227N1). The patients were considered eligible if they (i) aged 18 - 75 years, (ii) had Left Ventricular Ejection Fraction (LVEF) ≥ 40%, and (iii) were able to sign the informed consent form. The exclusion criteria were (i) having a history of previous cardiac surgery, (ii) having pre-operative inotrope support, (iii) having an implanted pacemaker or implantable cardioverter-defibrillator, (iv) pulmonary arterial pressure ≥ 50 mmHg, (v) requiring intra-aortic balloon pump or mechanical circulatory support, and (vi) returning to the operation room for any reason after surgery.

After obtaining informed consent forms from eligible patients, they were assigned to the BB or the DN arm via block randomization with the block size of four. In this way, the patients were allocated to each block as A for the BB group and B for the DN group until each group included 77 participants. For each block, one card was prepared and placed in a closed non-transparent packet. All packets were placed in an envelope. Then, a nurse who was not informed about the study groups was asked to draw a card and determine the related cardioplegia solution for each patient.

Primary outcomes were LVEF measured via Trans-thoracic (TTE) and Trans-esophageal Echocardiography (TEE). Baseline TTE was performed one day before the surgery, while the post-operative TTE evaluation was carried out on the last day of Intensive Care Unit (ICU) admission before transfer to the ward. TEE assessment was also performed before skin incision and post-operatively after weaning from CPB. All LVEF measurements were done using the "eyeball" method by one echocardiography-certified attending cardiologist who was blinded to the study.

The secondary outcomes also included the time interval between cardioplegia delivery and heart arrest, rhythm reaching arrest, rhythm after de-clamping, time interval to reach spontaneous rhythm, defibrillator or anti-arrhythmic drugs requirement, bypass and cross-clamp time, cardioplegia re-dosing, total volume of cardioplegia, and total ventilation time in the ICU.

3.2. CPB, Cardioplegia Delivery, and Surgical Procedure

A standard bypass system with a uniform setting was prepared for all the patients using Hollow fiber membrane oxygenator. For primers, the bypass system was primed with the conventional methods of colloid or crystalloid fluids (starch and ringer serum, ringer lactate, or normal saline) and heparin (about 7,500 to 10,000 units). Mannitol (maximum of 500 cc) was also added to the system at 0.5 - 1 g/kg. The patients' temperature was reduced to at least 28 °C on the basis of the surgical procedure and the bypass length.

The compositions of 1 L of the DN and BB cardioplegia solutions have been illustrated in Table 1. The cardioplegia injection method was adjusted with two pump heads and was fitted for each type of cardioplegia. In both groups, the heart was arrested with an induction dose using antegrade delivery. After induction with 1000 mL of BB (dose of cardioplegia + blood volume), the maintenance dose (400 mL) was repeated every 15 - 20 minutes. DN cardioplegia delivery was performed at a dose of 1250 mL (1000 mL DN + 124 mL blood) at the first injection followed by an additional 625 mL (500 mL DN + 125 mL blood) administered after 45 minutes. It is worth mentioning that all the patients were operated on by a single surgeon (SH) to replace or repair the mitral valve.

3.3. Ethical Approval

All the participants were required to sign the informed consent form approved by the Institutional Committee on Human and/or Animal Research. The trial was conducted according to the guidelines laid down in the declaration of Helsinki. The study protocol was also approved by the Board of Ethics of Mashhad University of Medical Sciences.

3.4. Statistical Analysis

All statistical analyses were carried out using the SPSS 19.0 for Windows (IBM Corporation, New York, NY, USA). In all statistical tests, $P < 0.05$ was considered statistically significant. Continuous quantitative variables were presented as mean ± Standard Deviation (SD), while categorical variables were reported as frequencies. Chi-square test was employed to compare the categorical variables. In addition, student's t-test or Mann-Whitney U

Table 1. Composition of Buckberg and del Nido Cardioplegia Solutions

Carrier	Buckberg	Del Nido	
	1:4 blood to crystalloid ratio	1:4 blood to crystalloid	
Ringer	1000 mL	N/S 0.9%	1000 mL
KCL	80meq	KCL	26 meq
Magnesium sulfate 50%	2 g	Magnesium sulfate 50%	2 g
Lidocaine	100 mg	Lidocaine	130 mg
Sodium bicarbonate 7.5%	15 cc	Sodium bicarbonate 7.5%	13 mL
		Mannitol 20%	16 mL

Abbreviations: KCL, potassium chloride.

Table 2. Baseline Characteristics of the Two Groups

		Del Nido (n = 77)	Buckberg (n = 75)	P-value
Age (years)		51.35 ± 13.08	51.25 ± 13.97	0.688
Gender	Female	46 (59.7%)	38 (50.7 %)	0.422
	Male	31 (40.3%)	37 (49.3%)	
BMI (Kg/m^2)		26.64 ± 3.66	25.37 ± 4.37	0.466
BSA (m^2)		1.77 ± 0.18	1.75 ± 0.18	0.859
Preoperative LVEF (%)	TTE	47.14 ± 5.53	49.21 ± 5.69	0.063
	TEE	48.18 ± 6.33	49.40 ± 6.72	0.146
Comorbidities				
Hypertension, n		12 (15.6%)	10 (13.3%)	0.333
Hyperlipidemia, n		10 (13%)	12 (16%)	0.189
Diabetes, n		8 (10.4%)	11 (14.6.7%)	0.708
Prior Endocarditis, n		0 (0.0%)	1 (1.3%)	0.308
Prior stroke, n		1(1.3%)	0 (0.0%)	0.321
Rheumatic fever history, n		2 (2.6%)	1 (1.3%)	0.572

Abbreviations: BMI, body mass index; BSA, body surface area; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiography; TEE, trans-esophageal echocardiography.

test was utilized to analyze the continuous variables based on their distribution.

4. Results

There was no significant difference between the two groups regarding the baseline characteristics and comorbidities (Table 2). At first, 152 patients were recruited, two of whom returned back to CPB due to impaired valve function. The remaining 75 patients in the BB group and 77 patients in the DN group were included in the final analysis. The mean age of the patients was 51.3 years, and 55.3% (n = 84) of them were female. The initial volume of the used cardioplegia solution was similar in the two groups (982.43 ± 100.15 mL in the BB group vs. 967.56 ± 152.39 mL in the DN group, P = 0.391). In the DN group, 13 patients only received the second dose of cardioplegia with a mean volume of 336.15 ± 68.25 mL. Meanwhile, the second and third doses were administered in all the patients in the BB group. In the final analysis, 83.1% of the patients in the DN group underwent mitral valve replacement and 16.9% required mitral valve repair. These measures were respectively obtained as 90.7% and 9.3% in the BB group. The difference between the two groups was not statistically significant (P = 0.23). Maze procedure was performed for only one patient in the DN group. Additionally, 15 patients in each group had concomitant procedure including tricuspid valve repair or replacement.

Comparison of the two study groups in terms of pre-and intra-operative outcomes has been presented in Table 3. In both groups, the majority of the patients (91% in the DN group and 94.6% in the BB group) had sinus rhythm before cardioplegia administration (P = 0.47). After utilizing cardioplegia, the heart reached arrest in a shorter time in the DN group compared to the BB arm (1.24 ± 0.43 minutes vs. 1.67 ± 0.78 minutes, P = 0.004). In the DN group, cardiac activity gradually reduced without rapid dysrhythmia in all the patients. In the BB group, nine patients (12%) reached cardiac arrest with Ventricular Fibrillation (VF). Nonetheless, the difference between the two groups was not statistically significant (P = 0.24). However, the patients in the DN group experienced a significantly shorter interval from cardioplegia administration to complete cardiac arrest compared to the BB group (1.24 ± 0.43 versus 1.67 ± 0.78, P = 0.004). A significant difference was also observed between the two groups regarding the heart rhythm after removing the aortic cross-clamp. Furthermore, 10.5% of the patients in the DN group and 54.1% of those in the BB group had impaired functional recovery and dangerous rhythmic dysfunction (VT or VF) (P = 0.001).

The DN administration led to a significantly shorter time of returning to the spontaneous heart rhythm (2.56 ± 1.68 versus 7.18 ± 3.79, P = 0.001). Anti-arrhythmic drug administration was significantly more prevalent in the BB group (P = 0.001) compared to the DN group. Moreover, a significantly larger proportion of patients in the BB group (24%) received inotrope during CPB compared to the DN group (5.2%, P = 0.003). At the time of removing the aortic cross-clamp and returning the heart rhythm, 12 patients in the DN group

Table 3. Pre- and Intra-Operative Comparisons between the Study Groups

		Del Nido (n = 77)	Buckberg (n = 75)	P-value
Pre-operative rhythm	Sinus rhythm	70 (91%)	71 (94.6%)	0.47
	Atrial fibrillation	7 (9%)	4 (5.4%)	
Rhythm reaching arrest	Without VF	77 (100.0%)	66 (88%)	0.24
	With VF	0 (0.0%)	9 (12%)	
Time reaching arrest (minutes)		1.243 ± 0.43	1.67 ± 0.78	0.004
Heart rhythm after opening the aortic clamp	Without VF or VT	60 (77.9%)	49 (65.3.%)	0.001
	With VF or VT	17 (22.1%)	26 (34.7%)	
Returning to spontaneous heart rhythm (minutes)		2.56 ± 1.68	7.18 ± 3.79	0.001
Need for DC shock		12 (15.6%)	16 (21.30%)	0.24
Anti-arrhythmic drugs administration		10 (13%)	30 (40%)	0.006
Need to inotropic drugs during CPB		4 (5.2%)	18 (24%)	0.003
	Number of episodes received	7	66	0.001
Inotropic drug administration for off bypass		1 (1.2%)	7 (9.3%)	0.991
Cross-clamp (minutes)		57.23 ± 16.3	63.16 ± 16.63	0.124
Bypass time (minutes)		91.78 ± 20.01	100.02 ± 18.23	0.066
Electrolytes levels during rewarming	K (mEq/L)	4.70 ± 0.49	5.05 ± 0.52	< 0.01
	Mg (mg/dL)	2.46 ± 0.38	2.51 ± 0.67	0.45
	Ca (mg/dL)	8.14 ± 0.36	8.21 ± 0.30	0.22
	Lactate (mg/dL)	2.16 ± 0.67	2.61 ± 0.66	0.22

Abbreviations: VT, ventricular tachycardia; VF, ventricular fibrillation; CPB, cardiopulmonary bypass; K, potassium; Mg, magnesium; Ca, calcium.

Table 4. Post-Operative Comparisons between the del Nido and Buckberg Groups

		Del Nido (n = 77)	Buckberg (n = 75)	P-value
Inotrope administration in ICU, n (%)	Epinephrine	12 (15.6%)	12 (16%)	0.388
	Norepinephrine	3 (3.9%)	2 (2.7%)	0.991
	Milrinone	1 (1.3%)	3 (4%)	0.200
Ventilation time (hours)		8.58 ± 2.36	11.31 ± 3.30	0.018
ICU stay (days)		2.25 ± 0.50	2.38 ± 0.59	0.460

Abbreviations: ICU, intensive care unit

Table 5. Comparison of Left Ventricular Ejection Fraction before and after the Intervention

	Del Nido (n = 77)			Buckberg (n = 75)			P-value
	Before	After	Change (%)	Before	After	Change (%)	
TTE (Mean ± SD)	46.95 ± 5.57	44.55 ± 6.29	4.7%	49.21 ± 5.69	42.41 ± 6.39	13.7%	< 0.001
TEE (Mean ± SD)	48.18 ± 6.33	45.45 ± 6.59	5.3%	49.40 ± 6.72	43.20 ± 7.99	12.6%	< 0.001

Abbreviations: TTE, trans-thoracic echocardiography; TEE, trans-esophageal echocardiography

(15.6%) and 16 in the BB group (21.30%) received DC shock, but the difference was not statistically significant.

Two patients in the DN group (2.6%) and four patients in the BB group (5.3%) required pacemaker implantation at the end of the surgery. Notably, epinephrine was the first drug administered to maintain blood pressure within an acceptable range for the bypass. An additional injection of phenylephrine or ephedrine was performed if the patient did not respond to epinephrine. Both cross-clamp (P = 0.124) and CPB (P = 0.066) times were comparable between the study groups although the patients in the BB group experienced non-significantly longer cross-clamp and CPB times.

The results related to post-operative measures have been demonstrated in Table 4. Accordingly, inotrope administrations during ICU stay were comparable in the two groups (P = 0.460). Nevertheless, the mean length of ICU stay and ventilation time (hours) were significantly longer in the BB group (P = 0.018). Furthermore, the results revealed 4.7% and 5.3% reductions from the baseline EF in TTE and TEE evaluations, respectively in the DN group (Table 5). These measures were respectively 13.7% and 12.6% in the BB group, demonstrating a more considerable reduction in myocardial function in the BB group.

5. Discussion

In the present study, the protective effects of DN and BB cardioplegia solutions on myocardium were assessed in the adult patients undergoing surgical replacement or repair of the mitral heart valve. It has been proposed that using DN cardioplegia in infants can cause 90 - 180 minutes of cardiac arrest without requiring re-injection (9, 16). However, previous reports indicated that despite the long-term effects of DN cardioplegia in children, repeating the dose should be considered in adult patients at 90-minute intervals (15-19).

In concert with earlier reports, only 24 out of the 77 patients in the DN group required the second dose of cardioplegia, while all the patients in the BB group took the second dose, 22 had the third dose, and 10 received the fourth dose of cardioplegia during CPB. This was related to the protective impact of the DN solution on the heart as well as the reliable and long-lasting arrest produced with no mechanical or electrical activity. The two groups were also compared regarding cross-clamp and bypass times. Although the lengths of cross-clamp and bypass times were shorter in the DN arm, the differences were not statistically significant. On the contrary, Robin, Nuygun, and Kuserli et al. found that cross-clamp and bypass times were significantly shorter with DN administration compared to BB (12, 15, 20).

The presence of dysrhythmias in patients with mitral valve diseases has attracted colossal attention in myocardial protection during CPB among investigators. In the present study, all the patients in the DN group with both sinus and AF rhythms gradually reached arrest without any rhythm disturbances. This is of paramount importance due to the loss of myocardial energy reserves during myocardial arrhythmias. Generally, rhythm disturbances lead to more acidosis during myocardial arrest. Therefore, during the reperfusion period and returning the beat after the cross-clamp removal, the heart will start to work with limited energy reserves. In the DN group, the heart was returned to the spontaneous rhythm in 79% of the patients without dysrhythmia, while this measure was only 65.3% in the BB group. This significant difference in cardiac activity without disorientation in the DN group might be attributed to the proper and adequate protection of cardiovascular resources during the arrest, ischemia, and reperfusion periods. In the same line, Smigla, Niv Ad, and Kavala noted in their trials that the prevalence of rhythmic disorders was lower in patients who received DN (14, 21, 22). The interval between removing the cross-clamp and returning the cardiac contractility was also significantly lower in the DN group compared to the BB group. Nagre et al. also carried out a research in 2018 and reported that DN provided better protection and functional recovery pursuant to reperfusion injury through the inhibition of intracellular calcium influx (18).

In the patients who underwent CPB, 100 mg lidocaine was injected prior to the removal of the transverse aortic clamp and 2 gr magnesium was injected two minutes after opening the clamp of the aorta. However, a number of patients with rhythm disturbances required an additional anti-arrhythmic drug. As mentioned earlier, a larger number of patients in the BB group needed additional anti-arrhythmic drugs. In some patients in this group, in addition to lidocaine, a repeated dose of magnesium was required due to continued dysrhythmia.

In general, the higher the protective effect of cardioplegia on myocardial function, the less inotrope will be required for maintaining blood pressure in an acceptable range. Although the patients in both groups needed a similar amount of inotrope for weaning from CPB, the BB group received a significantly higher amount of inotrope during CPB, which could explain the increased contractility of the cardiac muscle for weaning from CPB.

Nagre et al. disclosed that the time of ventilation was shorter in the patients who received ND cardioplegia (18). Consistently, the present study findings revealed a significantly shorter mechanical ventilation time in the patients with DN. Surabella et al. also showed that the length of ICU stay was shorter in the patients receiving DN cardioplegia. The length of ICU stay was also shorter in the DN group in the present research, but the difference was not statistically significant (17).

Contradictory data are available in the literature regarding EF, as an outcome after CBP, and cardioplegia administration. Smigla et al. and Hamed et al. did not report any differences between the study groups in terms of EF. However, Prushnut Mishra and Kuserli stated that the EF was better in the patients who received DN cardioplegia compared to the blood cardioplegia group (14, 15, 20, 23). The reduction of EF observed early after CPB in both groups is acceptable, because the function of the heart muscle is overshadowed by surgical procedures in addition to myocardial arrest during CPB. Although a reduction in EF after surgery is acceptable, the patients in the BB group experienced a significantly more prominent reduction evaluated by both TTE and TEE. The higher decrement in the BB group compared to the DN group could be linked to the higher myocardial energy loss, cellular damage during the ischemia period, and reperfusion injury after the restoration of blood flow in the coronary arteries in the patients in the BB group (3, 24).

5.1. Conclusion

DN solution, with promising results in myocardial protection amongst children, also offered superior protection compared to BB in the adult patients undergoing surgical repair or replacement of the mitral valve. Yet, future studies are needed to elucidate how these outcomes regarding myocardial protection contribute to short- and long-term clinical outcomes.

5.2. Ethical Approval

All the study participants were required to sign the informed consent form approved by the Institutional Committee on Human and/or Animal Research. The trial was conducted according to the guidelines laid down in the Declaration of Helsinki. The study protocol was also approved by the Board of Ethics of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1398.627).

5.3. Informed Consent

All the study participants were required to sign the informed consent form approved by the Institutional Committee on Human and/or Animal Research.

5.4. Clinical Trial Registration Code

Code: IRCT20191024045227N1; IRCT link: https://irct.ir/trial/46820.

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Authors' Contribution

Authors' Contribution: Study concept and design: S.H. and

N.Z. and A.GH. Analysis and interpretation of data: B.GH. and M.M. and A.GH. Drafting of the manuscript: A.GH. and M.Y. Critical revision of the manuscript for important intellectual content: A.GH., M.Y., and S.H. Statistical analysis: B.GH. and M.M.

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