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Article

Comparison of Clinical Outcomes between del Nido Cardioplegia and Microplegia among Patients Undergoing Elective Mitral Valve Replacement

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Abstract

Background: Cardioplegia solutions are used to protect the myocardium from ischemic injury caused by cardiopulmonary bypass and various types of cardioplegia solutions have been introduced for cardiac surgery. In this study, we aimed to compare the effects of del Nido cardioplegia and microplegia, which were mostly used in our clinic for intraoperative and postoperative processes among patients who underwent elective mitral valve replacement. As a result, the comparison could be performed in a specific patient group without additional valvular or coronary disease, and cardioplegia distribution could be achieved more efficiently. **Methods**: Between 2018 and 2023, a total of 120 patients who underwent elective mitral valve replacement via sternotomy with del Nido cardioplegia or microplegia were included in the study. Patients were divided into two groups; group 1 (del Nido, n = 64) and group 2 (microplegia, n = 56). Preoperative characteristics, intraoperative and postoperative early clinical data as primary outcomes, and postoperative mortality rates and intensive care costs as secondary outcomes were compared statistically. **Results**: There were no statistically significant differences in terms of preoperative characteristics between the two groups. Duration of cross clamp differences between group 1 versus group 2 (45 $\pm$ 16 *vs*. 57 $\pm$ 19 min), cardiopulmonary bypass (56 $\pm$ 17 *vs*. 65 $\pm$ 21 min), intensive care length of stay (18.04 $\pm$ 7.41 *vs*. 22.37 $\pm$ 6.86 h), requirement of intraoperative defibrillation (n = 5 *vs*. n = 13), and intensive care costs were found to be statistically significantly lower in del Nido group. **Conclusion**: Either del Nido or microplegia solutions can be used safely in mitral valve replacement operations, however, del Nido cardioplegia has some advantages over intraoperative processes, such as lowering the cross clamp and cardiopulmonary bypass time. Furthermore, patients who received del Nido cardioplegia had shorter intensive care stay and required less intraoperative defibrillation compared with the microplegia group. Therefore, less exposure to anesthesia, the prevention of infection due to shortened operation duration, and greater cost-effectiveness can be achieved by using del Nido cardioplegia instead of microplegia.

Keywords

cardioplegia; del Nido; microplegia; mitral valve replacement

Introduction

Cardiopulmonary bypass is mostly required to maintain blood supply during open cardiac surgery. Cardioplegia status is described as cardiac arrest and protection of myocardium is stimulated by the administration of cardioplegia solution into the myocardial tissue [1]. Myocardial ischemia occurs during aortic cross-clamp. After removal of the cross-clamp, reperfusion injury occurs due to the initiation of reperfusion. Most of the complications related to cardiac surgery are associated with this mechanism [2].

For efficient cardioplegias, it is important to provide rapid diastolic arrest to reduce the consumption of adenosine triphosphate and phosphocreatine by myocytes, and to prevent reperfusion injury [3]. Cardioplegia solutions can be classified as crystalloids or blood cardioplegias according to their composition, and either cold or hot according to the temperature at which they are infused. Despite different types of cardioplegia solutions, such as St. Thomas, Bretschneider, del Nido, and microplegia to name a few, the optimal one for myocardial protection remains controversial [4]. The aim of this study was to compare del Nido with microplegia solutions among patients who underwent isolated mitral valve replacement. The rationale for selecting these two solutions is that both are used widely in our clinic and worldwide. We designed this study for patients with isolated mitral valve replacement to study a specific patient group and achieve significant cardioplegia distribution.

Materials and Methods

Between 2018 and 2023, a total of 120 patients who underwent isolated mitral valve replacement were included in the study. The del Nido group (group 1) consisted of

Table 1. Ingredients of del Nido and microplegia solutions.

	del Nido	Microplegia
Plasma Lyte A	1000 mL	-
Autologous blood	-	Weight × 10 mL
Mannitol (20%)	16.3 mL	-
Magnesium sulphate, %	4.0 mL, 50%	10 mL, 15%
Sodium bicarbonate	13 mL	-
Lidocaine (1%)	13 mL	-
Potassium chloride (7.5%)	13 mL	30 mL

64 patients and microplegia group (group 2) consisted of 56 patients. As the demographic characteristics of the patients were similar, cardioplegia solutions were randomly selected for each patient. Sample size was determined by power analysis. The minimum number of patients required for a difference of 10 ± 12.72 (Cohen's d = 0.78) minutes in clamping time using del Nido and Microplegia (according to the study established by Kavala *et al*. [1]) to be statistically significant was determined as 36 per group ($\alpha = 0.05$, 1-$\beta = 0.90$). Analysis was performed with Gpower version 3.1.9.7 (Heinrich Heine Universtat, Düsseldorf, Germany).

Written informed consent was acquired from all participants and this single center retrospective study was approved by the Clinical Ethics Committee of the institute (date: 26.04.2023, no: 2023/135) and complies with the declaration of Helsinki. All patients had severe mitral regurgitation or stenosis without any additional valve disease. Vena contracta >0.7 cm, effective regurgitant orifice area ≥0.4 cm^2, and regurgitant fraction ≥50% were classified as severe mitral regurgitation and a mitral valve area <1.0 cm^2 with gradient >15 mmHg were categorized as severe mitral stenosis [5,6]. Coronary angiography was performed before the operation to detect any coronary artery disease. Operations were performed via full sternotomy and cardioplegia solutions were delivered antegradely. Pregnant women, patients under 18 years old, patients with any additional valve and/or coronary artery disease that require surgery or any kind of neoplasia, and patients that require redo interventions were excluded from the study.

Mixed blood and Plasma-Lyte A (1:4) was the composition of del Nido. 16.3 mL (3.3 g) mannitol (20%), 4.0 mL (2g) magnesium sulfate (50%), 13 mL potassium chloride 2 mEq-mL, 13 mL sodium bicarbonate, and 13 mL lidocaine (1%) were added to the solution. del Nido cardioplegia was administered as a single dose of 1000 mL at 4 °C. Redosing was planned at 1 hour after the first dose if the duration of cross-clamp was anticipated to last over 90 minutes. Microplegia consisted of the patient's weight times 10 mL autologous blood, 30 mL potassium chloride (7.5%), and 10 mL magnesium sulphate (15%). Microplegia was administered continuously with a perfusor, 300 mL every 25 minutes during cross-clamp (Table 1).

Patient data including demographic characteristics (age and gender), laboratory findings (hemogram, urea, creatinine, aspartate aminotransferase, and alanine aminotransferase), comorbidities (hypertension, diabetes mellitus, hyperlipidemia, and chronic obstructive pulmonary disease), electrocardiographic and echocardiographic findings, volume of administered cardioplegia, duration of cross-clamp, cardiopulmonary bypass, and the length of intensive care and hospital stay were collected from medical records. Patients who required intraoperative defibrillation were also noted. Postoperative drainage and reoperations due to hemorrhage were also noted. Death within 30 days after surgery was classified as operative mortality.

Statistical Analyses

SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Descriptive statistical methods were also used. Student's *T*-test was used to compare normal distribution of quantitative data and Mann-Whitney U test was used to compare non-normal distribution of quantitative data. Paired sample *T*-test was used to compare data of the groups with normal distribution and Wilcoxon sign test was used to compare data of the groups without normal distribution. Fischer's Exact test and Pearson's Chi-square tests were used for qualitative data. Significance was accepted for *p* values less than 0.05.

Results

There were no statistically significant differences in demographics between the groups (Table 2).

Patients who were operated on due to mitral regurgitation were 34 for group 1 and 26 for group 2. 30 patients were operated on due to mitral stenosis in both groups. Those who were operated on due to mitral stenosis did not differ in terms of ejection fraction, mitral valve area, or gradient. Vena contracta, effective regurgitant orifice area, ejection fraction, and regurgitant fraction also did not differ in patients operated on due to mitral regurgitation.

Preoperative laboratory values, presence of atrial fibrillation, ejection fraction rate, and comorbidities of the groups are summarized in Table 3.

Duration of cross-clamp, cardiopulmonary bypass time, and length of intensive care stay were statistically significantly lower in group 1. As the cross-clamp duration was not over 90 minutes, an additional del Nido so-

Table 2. Patient demographics.

	Group 1 (n = 64)	Group 2 (n = 56)	*p* value
Female: n (%)	29 (45.31%)	26 (46.42%)	0.284
Male: n (%)	35 (54.68%)	30 (53.57%)	0.234
Average age (years)	68.46 ± 6.63	67.44 ± 5.48	0.486

Table 3. Preoperative laboratory and clinical findings.

	Group 1	Group 2	*p* value
Hemoglobin (g/dL)	13.54 ± 1.07	13.28 ± 1.25	0.841
Urea (mg/dL)	13.16 ± 4.79	14.27 ± 3.54	0.254
Creatinine (mg/dL)	0.86 ± 0.14	0.82 ± 0.16	0.788
Alanine aminotransferase (IU/L)	22.4 ± 11.35	23.2 ± 10.48	0.541
Aspartate aminotransferase (IU/L)	21.64 ± 8.46	22.44 ± 7.73	0.563
Hypertension: n (%)	38 (59.3%)	31 (55.3%)	0.215
Diabetes mellitus: n (%)	10 (15.6%)	8 (14.2%)	0.442
Hyperlipidemia: n (%)	8 (12.5%)	6 (10.71%)	0.342
COPD: n, (%)	5 (7.81%)	4 (7.14%)	0.774
Atrial fibrillation: n, (%)	11 (17.1%)	10 (17.8%)	0.746
Ejection fraction (%)	47.54 ± 5.56	46.30 ± 7.43	0.412
CK-MB (IU/L)	22.8 ± 11.6	25.4 ± 12.8	0.284
Tr-T	0.56 ± 1.4	0.48 ± 1.27	0.884

CK-MB, creatine kinase myoglobin; COPD, chronic obstructive pulmonary disease.

lution was not required. Furthermore, patients in group 1 were required less intraoperative defibrillation compared with group 2. Intraoperative and postoperative data of the groups are given in Table 4.

Variance inflation factor (VIF) was high, therefore, multivariate regression analysis could not be performed. The results of univariate analysis and odds ratio values of the groups based on intraoperative defibrillation, are given in Table 5.

Four patients in group 1 and three patients in group 2 were reoperated on due to hemorrhage, on the same day as the first procedure. Three patients died due to permanent cerebrovascular disease and two died from sepsis in group 1. Causes of mortality were same for group 2; two deaths from permanent cerebrovascular disease and two deaths from sepsis.

Discussion

Cardioplegia solutions are important for cardiovascular surgery. In conjunction with hypothermia, cardioplegia protect the myocardium against the undesirable effects of ischemia-reperfusion injury during cardiac surgical procedures. Furthermore, electromechanical arrest provided by cardioplegia allow bloodless and stable surgery [7].

Cardioplegia can be prepared as either hot or cold solutions. In general practice, cardioplegia is usually applied with hypothermia to decrease the energy requirement for myocytes. Maintaining the heart temperature between 10 °C–15 °C provides 4 hours of protection against ischemia [8].

Cardioplegia can be classified as either crystalloid or blood cardioplegic solutions according to their composition. Crystalloid cardioplegia have been used for over 40 years in clinical practice and are subdivided into two groups as extracellular or intracellular according to the concentration of sodium, calcium, and magnesium. STH 1, STH 2, Celsior, Custodiol, University of Wisconsin, and Eurocollins are examples of crystalloid cardioplegia solutions [9]. Blood cardioplegia was introduced in the late 1970s and incorporates advantages of the blood such as, higher oxygen carrying capacity, increased microcirculatory perfusion linked with red blood cells, and the addition of free fatty acids that are used in anaerobic states [10].

del Nido cardioplegia was initially formulated for use in congenital heart surgery and has been used for nearly 30 years and recently, has been used in adult cardiac surgery. The del Nido solution is the mixture of blood and crystalloid cardioplegia at a ratio of 1:4 [11]. The solution contains Plasma-Lyte A as a base solution with an electrolyte composition similar to the extracellular environment. Mannitol, sodium bicarbonate, magnesium sulfate, potassium chloride, and lidocaine are also added. Oxygenated patient whole blood is then added to complete the solution [12].

del Nido cardioplegia is widely used by cardiovascular surgeons in aortic, mitral, tricuspid, and coronary artery interventions [13]. Reducing the consumption of energy, blocking calcium ion entry, depurating hydrogen ions, preserving high-energy phosphates, and promoting anaerobic respiration during myocardial arrest are the most important features of the solution [14].

Table 4. Intraoperative and postoperative data.

	Group 1	Group 2	*p* value
Duration of cross-clamp (min)	45 ± 16	57 ± 19	<0.01*
Duration of CPB (min)	56 ± 17	65 ± 21	<0.01*
Cardioplegia volume (mL)	950 ± 50	800 ± 100	0.642
Intraoperative defibrillation: n (%)	5 (7.8%)	13 (23.21%)	<0.01*
Drainage (mL)	356 ± 45	371 ± 24	0.174
ICU stay (hours)	18.04 ± 7.41	22.37 ± 6.86	0.021*
Hospital stay (days)	5 ± 1	6 ± 1	0.669
ICU cost ($)	253 ± 15	305 ± 21	<0.05*
CK-MB difference	12.8 ± 18	14.4 ± 16	0.416
Tr-T difference	0.7 ± 2.2	0.9 ± 2.1	0.523

CK-MB, creatine kinase myoglobin; CPB, cardiopulmonary bypass; ICU, intensive care unit. *$p < 0.05$ = significant difference.

Table 5. Univariate and odds ratio analyses.

	Univariate odds ratio (95% CI)	*p* value
Groups	3.57 (1.18–10.76)	0.024*
Duration of cross-clamp (min)	1.69 (1.28–2.23)	0.001*
Duration of CPB (min)	0.98 (0.93–1.05)	0.608
Cardioplegia volume (mL)	0.99 (0.99–1.00)	0.100
Drainage (mL)	1.01 (0.98–1.03)	0.660
ICU stay (hour)	1.05 (0.93–1.20)	0.423
Hospital stay (days)	1.40 (0.77–2.55)	0.265
ICU cost ($)	1.03 (1.01–1.05)	0.009*

CPB, cardiopulmonary bypass; ICU, intensive care unit. *$p < 0.05$ = significant difference for binary logistic regression analysis.

Microplegia solution consists of blood obtained from cardiopulmonary bypass circuit and small amounts of crystalloid additives. It is used in all cardiac valvular and coronary operations in current era [15].

In general, four or eight parts of blood to one part crystalloid cardioplegia is the standard formulation of blood cardioplegia. Microplegia formulation consists of a reduced volume and is delivered continuously. Reduced hemodilution, rapid improvement of ventricular function, and reduced myocardial edema are the main advantages of microplegia that are reported in the literature [16].

The volume of crystalloid cardioplegia used in microplegia differs to previous studies. Specific volumes weren't mentioned in some of the studies whereas it was described as minimal in others. In addition, there are atudies available in the literature in which the volume of the cardioplegia were formulated [17].

There are several studies comparing del Nido cardioplegia and microplegia in different aspects of cardiovascular surgery. Mick *et al*. [18] evaluated the results of del Nido cardioplegia and microplegia solutions in patients who underwent isolated aortic valve replacement and mitral valve replacement. They reported that del Nido cardioplegia presented safe results for reduced cross-clamping and cardiopulmonary bypass time in both instances. In a study conducted by Urcun *et al*. [19] the effects of del Nido cardioplegia and microplegia were compared in patients who underwent coronary artery bypass grafting operations (CABG). Shorter cross-clamp time was reported in the del Nido cardioplegia group. Similarly, Yerebakan *et al*. [20] emphasized shortened duration of cross-clamp in del Nido cardioplegia group compared with the microplegia group in patients operated on due to acute myocardial infarction. The duration of intensive care unit (ICU) stay was longer in microplegia group than del Nido cardioplegia group in a study of patients treated with CABG [21]. In a study by Stammers *et al*. [22] multiple cardioplegia solutions including del Nido cardioplegia and microplegia were compared in various cardiovascular procedures including valvular and coronary (or combined). Either cross-clamping or cardiopulmonary bypass time was significantly decreased in del Nido cardioplegia group in all instances. The use of del Nido cardioplegia was also recommended as a safe and efficient method in patients subjected to minimally invasive cardiac valvular surgery [23]. In our study, the duration of cross-clamping, cardiopulmonary bypass, and ICU stay were statistically significantly lower in del Nido cardioplegia group, in support of the current literature. Decreased ICU stay was also associated with cost-effectiveness, which was calculated in our study. In general, del Nido cardioplegia allows for the continuation of the surgery without any additional requirement of cardioplegia since it provides

long-term cardiac arrest with a unique dose, which is associated with shorter cross-clamping and cardiopulmonary bypass duration. In our study, all operations were completed with a single dose del Nido cardioplegia. Decreased cross-clamping time alone had a positive effect on clinical outcomes, such as shorter duration of ICU stay and cardiopulmonary bypass.

The del Nido cardioplegia solution has a positive effect on preventing intraoperative volume load and avoiding repetitive application by single dose administration. Kotani *et al*. [24] declared that del Nido cardioplegia doses had longer intervals before re-administration compared with other cardioplegia solutions, including microplegia. Similarly, significantly decreased numbers of cardioplegia administration was shown by using del Nido cardioplegia is a study by Charette *et al*. [25]. Kavala *et al*. [1] reported that administration of del Nido cardioplegia requires a significantly lower volume than microplegia solution. In our study, there was no statistically significant difference between the two solutions in terms of volume given. All of these inferences might be explained as a result of long-term sodium channel blockade achieved by del Nido cardioplegia, which prevents the initiation of spontaneous electrical activity of myocytes for 60 to 90 minutes [26].

One finding of our study was the reduced need for intraoperative defibrillation in patients who were given del Nido cardioplegia. Valooran *et al*. [27] reported a lower number of defibrillations when using del Nido cardioplegia. Another study compared del Nido cardioplegia and microplegia in patients who underwent coronary artery bypass graft concomitant with mitral valve replacement and the number of the patients who required intraoperative defibrillation was statistically significantly lower in del Nido cardioplegia group [1]. In a meta-analysis of randomized clinical trials, a reduced need of defibrillation was shown in patients who were given del Nido cardioplegia during open heart surgery. This can be explained by sodium and calcium homeostasis maintained by lidocaine that blocks the sodium channels and magnesium that acts as an antagonist to calcium, both of which are present in del Nido cardioplegia [28]. In our study, ventricular fibrillation rates were significantly lower while intraoperative cardiac re-beat period was longer in the del Nido cardioplegia group, which is consistent with the literature in terms of less requirement of defibrillation. Despite the multiple advantages of del Nido cardioplegia explained earlier, mortality rates, drainage volumes, and duration of hospital stay did not differ between the two tested groups in our study.

Conclusion

In conclusion, both del Nido cardioplegia and microplegia solutions can be safely used in mitral valve replacement operations according to our results, which revealed no differences in mortality, drainage, and hospital discharge. del Nido cardioplegia was superior for reducing the duration of cardiopulmonary bypass and ICU stay by decreasing the aortic cross-clamping time. Furthermore, patients who were administered del Nido cardioplegia required less intraoperative defibrillation. Moreover, del Nido cardioplegia solution had a positive effect on cost-effectiveness. Further studies with larger cohorts, longer follow-up periods, and planned in isolated mitral valve replacement operations are needed as these factors were limited in this study.

Availability of Data and Materials

Avaliability of data and materials can be provided by authors if it is on valid basis.

Author Contributions

All authors designed and conceptualized the study. ÖA, MM, and EH collected the data. IBK and MAC analyzed the data. All authors contributed to the interpretation of the data, made editorial changes to the manuscript, and approved the final version of the manuscript. All authors participated sufficiently to the study and take responsibility for appropriate portions of its contents.

Ethics Approval and Consent to Participate

The study was approved by the Clinical Ethics Committee of Gaziantep University (no:2023/135). All patients signed the informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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