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Original Article

A Comparative Study of the Clinical Implications of Cardioplegia Infusion Between the Microplegia Technique and Del Nido Cardioplegia Among Patients Undergoing Coronary Artery Bypass Surgery

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ABSTRACT

Background: Cardioplegia is used to protect the heart from ischemic injury during cardiovascular bypass. We randomly selected candidates for coronary artery bypass surgery undergoing either microplegia or del Nido cardioplegia.

Methods: We performed a controlled randomized double-blind study to evaluate 60 patients undergoing coronary artery bypass surgery in Rajaie Cardiovascular Medical and Research Center during a 3-month period. During surgery, the case group received microplegia, and the control group received del Nido cardioplegia. Preoperative, intraoperative, and postoperative personal information was collected from the patients' records, and the data were analyzed using the SPSS software, version 22, using appropriate statistical tests.

Results: Out of 60 patients under study, 28 patients underwent microplegia, and 32 patients received del Nido cardioplegia. The patients, randomly assigned to the groups, did not significantly differ concerning height, weight, and body surface area. No significant differences existed between the 2 groups. The levels of postoperative decreases in hemoglobin and hematocrit were significant in the microplegia group and led to an increase in the number of blood transfusions in the intensive care unit. A significant increase in CK-MB was observed in the del Nido group 24 hours after surgery.

Conclusions: Microplegia, compared with del Nido cardioplegia, conferred proper myocardial protection. However, the use of the microplegia technique was associated with more significant decreases in hemoglobin and hematocrit postoperatively, and the beneficial effects of microplegia in reducing hemodilution were not well-reflected. ***(Iranian Heart Journal 2023; 24(1): 31-38)***

KEYWORDS: Cardiac surgery, Microplegia technique, Cardioplegia

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Cardiovascular diseases are a leading cause of death and disability in the world. According to the World Health Organization (WHO), these diseases were responsible for 17.7 million deaths worldwide in 2015, among which 7.4 million deaths occurred due to coronary artery disease. In Iran, cardiovascular diseases are regarded as a major cause of death and disability, such that they have contributed to 46% of all deaths. [1, 2]

Some myocardial damage is inevitable during cardiac surgery. Such damage may alter the myocardial blood flow and, subsequently, lead to some changes in the supply and demand for oxygen. A cardiac surgery team should avoid this damage as much as possible. Cardioplegia prevents ischemic injury and postoperative heart failure caused by cardiopulmonary bypass. Improving heart protection techniques during an aortic cross-clamping procedure significantly leads to more desirable cardiac surgery outcomes.

One of the currently available solutions is del Nido cardioplegia. This solution was first introduced in Boston, the United States, and was used in pediatric and neonatal cardiac surgeries. Now, del Nido cardioplegia is widely employed as a standard method for myocardial protection, which should be repeated every 60 to 90 minutes, such that, at the injection times, the surgical procedure is stopped to inject cardioplegia. [3]

Nonetheless, the del Nido cardioplegia solution, owing to its high volume of crystalloids, increases the hemodilution and hemorrhage, resulting in a reduced postoperative cardiac output.

Blood, unlike crystalloids, potentially improves the postoperative cardiac output since blood is closer to the physiological conditions of the body due to its oxygen-carrying capacity and reduced correlations with hemodilution. [4]

In patients with unstable angina, microplegia significantly reduces cardio injury caused by the surgery and improves the patient's hemodynamic conditions, including peripheral blood flow and systolic and diastolic functions of the left ventricle. These can dramatically decrease blood transfusions and increase the speed of discharge from the hospital. [5]

The present study aimed to compare the clinical implications of cardioplegia infusion between the microplegia technique and del Nido cardioplegia among patients undergoing coronary artery bypass surgery.

METHODS

The current investigation is a controlled randomized double-blind study. The study protocol was approved by the Ethics Committee of Rajaie Cardiovascular Medical and Research Center (IR.RHC.REC.1397.062), and informed consent was provided by all eligible patients before the study commencement. Sixty patients were randomly assigned to 2 groups of microplegia and del Nido cardioplegia for assessment based on the following inclusion criteria: obtaining the patient's full consent to participate in this study, being in the age range of 18 to 60 years old, having an ejection fraction exceeding 30%, having no history of transient cerebral ischemic disease or stroke, having no history of previous cardiac surgery, and having no carotid artery stenosis exceeding 50%.

The exclusion criteria were as follows: being under deep hypothermia, experiencing a cardiac arrest during surgery, needing cardiopulmonary resuscitation in the operating room or the intensive care unit (ICU), undergoing a second cross-clamping procedure during surgery, and suffering from coagulation disorders.

The information-gathering form used in this study features 3 parts.

The first part, extracted from the patients' records, related to preoperative information, including age, sex, weight, height, body surface area, number of grafts, hemoglobin and hematocrit levels, cardiac and hepatic blood enzyme levels, creatinine, blood urea nitrogen, left ventricular ejection fraction, history of diabetes, hypertension, increased blood lipids, smoking, and drug abuse before surgery.

The second part, gathered when the patients were leaving the operating room, related to intraoperative information, including the amount of the cardioplegia solution, the duration of cardiopulmonary bypass, the length of aortic cross-clamping, the time to return of spontaneous circulation, the type of returned rhythm, inotropic use, the number of received cardioversion after aortic clamping, the need for intra-aortic balloon pumps after separation from the cardiopulmonary pump, the amount of input and output fluids from the body, the transmission of blood products, and the levels of hemoglobin, hematocrit, and lactate during cardiopulmonary bypass.

The third part, gathered at hospital discharge, related to postoperative information in the ICU, including the duration of mechanical ventilation, the duration of hospitalization in the ICU, the hemoglobin levels up to 3 hours after surgery, cardiac and hepatic blood levels, creatinine, blood urea nitrogen, inotropic use, the consumption of blood products, the incidence of arrhythmia sup to 48 hours after surgery, and the ejection fraction.

Procedure

To increase the coagulation time, we injected heparin into the patients after anesthesia induction and median sternotomy. For all the patients, a total volume of prime (1250–1500 mL) was added to 150 mL of mannitol, together with 100 kg/unit of heparin, in the prime fluid after complete attachment to the cardiopulmonary bypass pump. Cardiopulmonary bypass was conducted with roller pumps, membrane oxygenators, and non-pulsatile blood flow (2.4 mL/m^2) under normothermia (34–36 °C), and the mean arterial pressure up to 50–80 mm Hg was preserved. To make the heart stop moving, we used the del Nido cardioplegia solution in the control group and the microplegia solution in the experimental group. The base del Nido cardioplegia solution included 1 liter of the PlasmaLyte A solution, which is electrolytically similar to the extracellular fluid. It was used at a temperature of 4 °C with a volume of 15 mL/kg 15 via 2 roller pumps specially designed for cardioplegia infusion. One of these roller pumps pumped the crystalloid line, and the other pumped the oxygenated bloodline taken from the oxygenator. The ratio of del Nido cardioplegia to blood was 4 to 1.

In the microplegia group, the cardioplegia solution was added to the oxygenated bloodline taken from the oxygenator at a rate of 550 to 600 mL/h using the TE.SS700 Terumo infusion pump and a Luer and rotated with a roller pump at 0.3 L/min. The ratio of microplegia to blood was 1 to 60. In both groups, after opening aortic clamping, 100 mg of lidocaine and 2 g of magnesium were administered via the cardiopulmonary circuit, and electromechanical return of the heart, monitoring, and possible arrhythmias, such as ventricular tachycardia and fibrillation, were recorded. If required, the number of defibrillators was also recorded.

Table 1: Components

Component	Microplegia	del Nido
KCl 1.5%	50 mEq/L	27 mEq/L
M gSO_4 50%	5 g	8 g
$NaHCO_3$ 7.5%	10 mmol	13 mmol
Lidocaine 2%	150 mg	130 mg
Mannitol 20%	1.5g	32.6g

After the forms were completed, variables were presented as the mean ± the standard deviation (SD) and were analyzed using the SPSS software, version 22. The quantitative findings were checked in terms of normal

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and non-normal distributions using the Kolmogorov–Smirnov Z test. Given the specific objectives and the research hypotheses, the findings related to the research objectives were analyzed using the Mann–Whitney *U*, Friedman, and Wilcoxon signed ranks tests. The significance level was considered a *P* level below 0.05.

RESULTS

According to Table 2, no significant differences existed concerning demographic characteristics, including height, weight, body surface area, age, sex, and smoking, and underlying diseases, including hypertension, diabetes, asthma, and thyroid. Nevertheless, an elevation in blood lipids was significantly higher in the microplegia group than the other group. About 63.3% of all the patients had 3 grafts, 65.6% of them being in the del Nido group. Nearly 31.7% of the patients had 4 grafts, 32.1% of them being in the microplegia group.

According to Table 3, considering the duration of cross-clamping and cardiopulmonary bypass, the amount of input and output fluids and the return of rhythm, the duration of mechanical ventilation, and the duration of hospitalization in the ICU, there were no significant differences between the 2 groups. This is while the use of the cardioplegia solution was significantly higher in the del Nido group than in the other group.

Table 2: Preoperative characteristics

Variable	Microplegia (n=28)	del Nido (n=32)	*P* value
Sex (female)	11 (40%)	7(22%)	0.142
Body surface area	1.86(1.67-2)	1.85(1.70-1.97)	0.876
Age	58(50.50-68.75)	61(50.70-72.70	0.331
Hypertension	20(71.4%)	19(61.3%)	0.411
Diabetes	13(46.4%)	11(35.5%)	0.393
Asthma	2(7.14%)	0	0.124
Dyslipidemia	20(71.4%)	10(31.2%)	0.002
Smoking	8(28.5%)	11(34.3%)	0.782

Table 3: Operative characteristics

Variable	Microplegia (n=28)	del Nido (n=32)	*P* value	Test
Clamp time, min	45(27-55)	40(35.25-42.75)	0.784	Mann-Whitney
Pump time, min	75(54-100)	82.5(63.25-95)	0.286	Mann-Whitney
Blood product	11(39.2%)	12(37.5%)	1	Mann-Whitney
DC Shock	1(3.5%)	3(9.3%)	0.616	X^2
Inotrope through CPB off CPB	 11 7	 12 12	1 0.406	X^2 X^2
Pacemaker	6	5	0.74	X2
Return of rhythm (sinus)	24	22	0.14	X^2
Cardioplegia liquid	42.5(30-50)	75(60-80)	<0.001	Mann-Whitney
Input fluids	1355(1208-1545)	1360(1152.5-1652.5)	0.876	Mann-Whitney
Output fluids	499(352.5-700)	583(408.25-675.25)	0.63	Mann-Whitney

CBP, Cardiopulmonary bypass

Table 4: Lactate changes during CPB and surgery

Lactate	Microplegia	del Nido	*P* value
Before CPB	0.55(0.50-0.80)	0.7(0.60-1.21)	0.075
Beginning CPB	1.3(0.85-2)	1.9(1-1.2)	0.148
End of CPB	1.45(1.02-2.40)	1.65(1.32-2.57)	0.519
End of surgery	2.15(0.92-2.6)	2.55(1.70-3.75)	0.055
Changes during surgery	<0.001	<0.001	*P* value (Friedman)

CBP, Cardiopulmonary bypass

One patient in the microplegia group and 2 in the del Nido group needed DC shocks after aortic clamping. None of the patients needed intra-aortic balloon pumps.

The hematocrit level was specifically compared between the 2 groups at 7 time points. The hematocrit level rose significantly in the del Nido group up to 3 hours after surgery. The hematocrit levels were studied 2 by 2 using the Bonferroni correction to obtain a *P* value. Figure 1 shows that the reduction in hematocrit was more severe in the del Nido group during the surgery than in the other group. Based on the χ^2 test, there were no significant differences between the 2 groups regarding the need for blood transfusion and blood products, such as fresh frozen plasma, platelets, and packed red blood cells ($P>0.05$).

According to Figure 2, the CK-MB level in the del Nido group significantly increased. The creatinine level was significantly higher in the del Nido group immediately after the surgery. Preoperative and postoperative ejection fractions in the 2 groups were not significantly different according to the χ^2 test ($P>0.05$).

The results showed no significant differences between the 2 groups in terms of hepatic enzymes and blood urea nitrogen levels. However, considering the changes over time (immediately after surgery until 48 hours after surgery), aspartate aminotransferase significantly increased in the microplegia group.

The blood lactate level in both del Nido and microplegia groups significantly rose from the first minute until the last minute of surgery. This change was more pronounced in the del Nido group than in the microplegia group. No meaningful differences were detected between the 2 study groups apropos of inotropic levels during cardiopulmonary bypass, at the time of shutting off the pump, and in the ICU.

Furthermore, none of the patients needed pump balloons and/or DC shocks and assist devices, nor any deaths were reported in the groups.

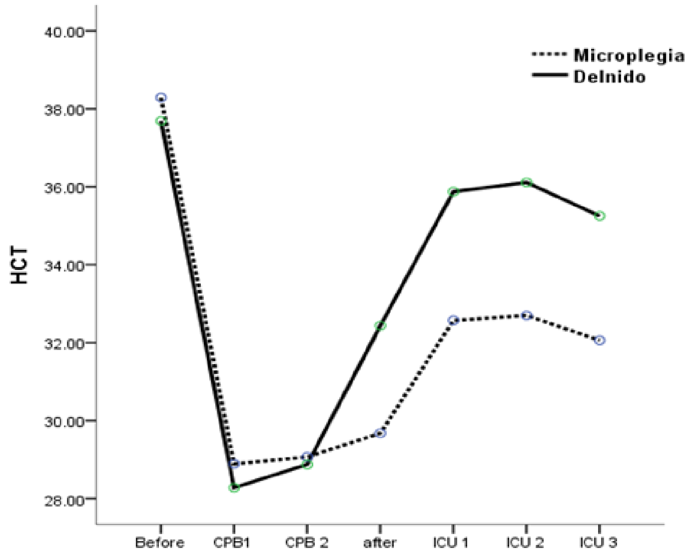

Figure 1: The image depicts hemoglobin changes in the microplegia and del Nido groups.

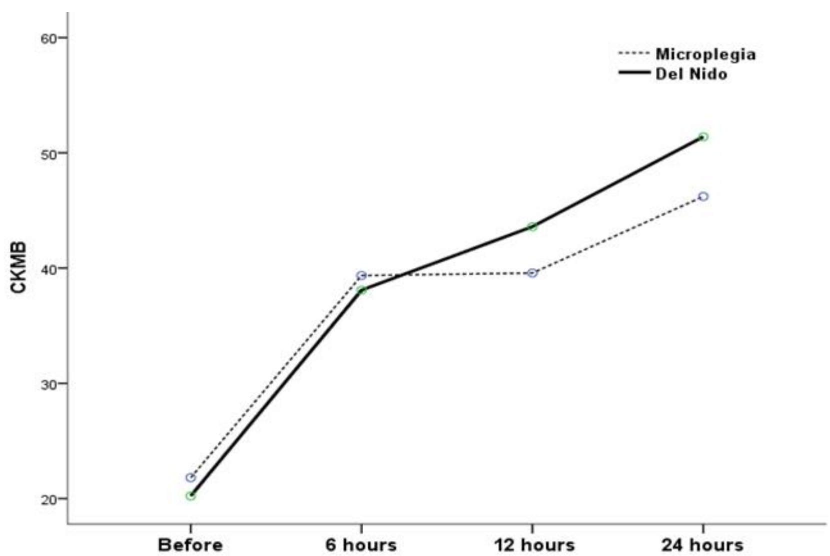

Figure 2: The image illustrates the CK-MB levels in the microplegia and del Nido groups.

DISCUSSION and CONCLUSIONS

Cardioplegia is applied to stop all electrical activities and contractions of the heart, and it significantly reduces energy consumption even at normal temperatures.[7]

Regarding the absence of significant statistical differences in some components, such as the patient's postoperative ejection fraction, the need for inotropic support in the operating room and the ICU, and the relative similarity of the mean arterial pressure hemodynamic factor, it can be concluded that both methods had almost similar and acceptable effects on maintaining myocardial function and avoiding low cardiac output syndrome. Similar studies have achieved the same results. A study conducted by Kuhn et al [12] showed that Calafiore cardioplegia conferred good myocardial protection in emergency coronary artery bypass patients. The maximum levels of troponin T and CK-MB in Buckberg cardioplegia were higher than those of microplegia, although these differences were not significant.

The time elapsed between opening the cross-clamping and shutting off the pump was lower in the microplegia group than in the del Nido group; still, this difference was not statistically significant. According to a study done by Onorati et al, [8] the duration of cross-clamping and cardiopulmonary bypass was significantly lower in the microplegia group than in the Buckberg cardioplegia group. Additionally, the return of the heart rhythm after cross-clamp removal in the microplegia group was faster than that of the other group. These findings are in line with the results of the current study.

Although the microplegia group was expected to show a decrease in hemodilution, the data obtained from this study proved the opposite, and the beneficial effects of microplegia on the reduction of hemodilution were not well-reflected. These findings are inconsistent with the results of a study conducted by Menasché et al, [9] who demonstrated that reducing blood transfusions after microplegia surgery (due to reduced hemodilution) led to a fall in myocardial edema subsequently. This inconsistency may be due to the increased use of hemofiltration in the del Nido group, the use of diuretic drugs in some patients, the failure to observe the blood transfusion protocol by some staff members in the operating room and the ICU, and the prescription of fibrinolytics and blood products for the patients who took part in this study.

A prior study reported that microplegia decreased the use of hypertensive medications. Nevertheless, there was no significant difference in inotropic use between the 2 groups. [10] As mentioned in a study carried out by Vinten-Johansen, [11] the need for blood transfusions and packed cells was reduced in the microplegia group. Except for long-term surgeries with systemic hemorrhage, other studies have not indicated any significant differences in the reduction of hemodilution.

The mean consumption volume of cardioplegia was 42.5 mL in the microplegia group and 75 mL in the del Nido group; the difference was statistically significant. Despite the lack of significant differences in the amount of intraoperative input and output fluids between the 2 groups of microplegia and del Nido, the drop in the intraoperative levels of hemoglobin and hematocrit was significant in the del Nido group; however, this decrease occurred with a smaller slope in the microplegia group. This is because microplegia is more compliant with body conditions.

Our analysis of arterial blood gasses and renal function indices, including creatinine and blood urea nitrogen, revealed no significant differences between the 2 groups. It can, therefore, be concluded that the type of cardioplegia did not have a clear and distinct effect on arterial blood gasses and renal statuses.

We recommend that clinical trials with more patients be conducted to show the superiority of microplegia over blood cardioplegia in complicated cardiac surgeries with long cardiopulmonary bypass duration. Additionally, when cardioplegia infusion is carried out using retrograde and anthracite aids, microplegia is very useful. It is also possible to measure lactate levels after cardioplegia infusion. Furthermore, for more accurate measurements of myocardial protection, the ejection fraction should be assessed during cardiopulmonary system removal and in the operating room.

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Conflict of Interest: The authors declare that there is no conflict of interest in the research.

Ethical Approval: The study protocol was approved by Rajaie Cardiovascular Medical and Research and Center, and it followed the ethical principles and national norms and standards for conducting medical research in Iran. This article was extracted from an MS thesis on Circulation Technology conducted by Ms Sepideh Nazari in 2018 (code: 1397/062) and was supported by Rajaie Cardiovascular Medical and Research and Center.

Informed Consent: All the patients gave consent to be included in the study, and individuals unwilling to participate were excluded.

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