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Effect of del nido cardioplegia use on kidney injury after coronary bypass operations

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SUMMARY

OBJECTIVE: After cardiac surgery, acute kidney injury is observed at a rate of 5–30%, and the second most common cause of acute kidney injury in intensive care units is cardiac surgery. In this study, we aimed to investigate the effect of del Nido cardioplegia solution use on postoperative acute kidney injury development in patients who underwent coronary artery bypass grafting operation with cardiopulmonary bypass.

METHODS: Consecutive patients who underwent an elective coronary artery bypass grafting operation with cardiopulmonary bypass in our clinic between March 15, 2019, and March 15, 2020, were included in the study retrospectively. The patients were divided into two groups as those who received del Nido cardioplegia solution (Group 1) and blood cardioplegia (Group 2), and factors affecting the development of renal failure were examined.

RESULTS: A total of 350 consecutive patients were included in the study. There were 156 patients in the del Nido cardioplegia group and 194 patients in the blood cardioplegia group. Among the patient group, 74 (21.1%) patients developed acute kidney injury. The total acute kidney injury development rate was significantly higher in Group 2 (p=0.018). In multivariate logistic regression analysis, advanced age (OR 1.128; 95%CI 1.044–1.217; p=0.042), increased blood product use (OR 1.318; 95%CI 1.154–1.998; p=0.019), preoperative creatinine elevation (OR 2.434; 95%CI 1.655–4.639; p=0.005), and increased cardioplegia volume (OR 1.254; 95%CI 1.109–2.980; p=0.009) were independent predictors of acute kidney injury.

CONCLUSION: With this study, we showed that the use of del Nido cardioplegia solution can reduce the incidence of acute kidney injury.

KEYWORDS: Coronary artery bypass surgery. Cardiopulmonary bypass. Kidney. Cardioplegia.

INTRODUCTION

Among atherosclerotic cardiovascular diseases, coronary artery disease (CAD) is especially important. In its treatment, coronary artery bypass grafting (CABG) surgery can be successfully performed in conjunction with cardiopulmonary bypass (CPB) thanks to the developing extracorporeal circulation systems[1]. However, the use of these systems brings about the risk of various complications because of activated inflammatory pathways due to the contact of blood with foreign external surfaces. One of the major complications is renal failure. After cardiac surgery, acute kidney injury (AKI) is observed at a rate of 5–30%, and the second most common cause of AKI in intensive care units is cardiac surgery[2]. Many factors such as CBP duration, advanced age, the presence of preoperative renal failure, and blood transfusion play a role[3,4].

In CABG operations with cardiopulmonary bypass, the heart is usually arrested with cardioplegic solutions. Del Nido cardioplegia solution (dNCS), which was widely used in pediatric cardiac surgery in the past, has recently been used in adult cardiac surgery[5]. Various advantages of this cardioplegia method have been demonstrated over the standard intermittent blood

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cardioplegia (BC), some of which include shortened perfusion and operation times, reduced use of blood products, and a similar level of myocardial protection[6,7].

In this study, we aimed to investigate the effect of dNCS use on postoperative AKI development in patients who underwent CABG operation with CPB.

METHODS

Consecutive patients who underwent an elective CABG operation with CPB in our clinic between March 15, 2019, and March 15, 2020, were included in the study retrospectively, which began after the approval was obtained from the local ethics committee. Emergency operations, combined surgical procedures, patients with preoperative renal insufficiency (creatinine >1.5 mg/dL), those who use platelet aggregation drugs, those who had acute myocardial infarction within the last month, those with a preoperative hemoglobin value <11 g/dL, reoperations, patients who were reoperated due to bleeding or peroperative myocardial infarction, those who needed preoperative inotropic drugs, and those who received intra-aortic balloon support were excluded from the study. As a surgical team, we started using dNCS in coronary surgery at the end of 2018. After the implementation of the exclusion criteria, 350 consecutive patients were included. The data of the patients were obtained from the hospital registry and the intensive care unit daily observation cards. Demographic data, preoperative characteristics, and operative and postoperative data were recorded. The patients were divided into two groups as those who received dNCS (Group 1) and BC (Group 2), and factors affecting the development of renal failure were examined.

Cardioplegia technique

In the BC group, cardiac arrest was achieved with an initial blood cardioplegia of approximately 1000 mL (10–15 mL/kg). Continuation of cardiac arrest was maintained with approximately 300 mL BC at 15–20-min intervals. In the del Nido cardioplegia group, cardiac arrest was achieved with 1000 mL of the dNCS. In patients whose aortic cross-clamping time would exceed 90 min, an additional 500 mL dNCS was administered 60 min after the first dose. Plasma-Lyte A (a basic solution with a pH value of 7.4 containing 140 mmol/L sodium, 5 mEq/L potassium, 3 mEq/L magnesium, 98 mEq/L chloride, 27 mEq/L acetate, and 23 mEq/L gluconate) is used in the preparation of dNCS[5]. However, balanced electrolyte solutions are used instead in many heart centers due to the difficulty of access[8]. In our center, we used Isolyte-S instead of Plasma-Lyte A.

Identification of postoperative renal failure

Hemogram and biochemical measurements were performed in all patients for three postoperative days. After these evaluations, in-hospital AKI development was defined as the primary end point of the study. Postoperative renal insufficiency was determined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria (Stage 1, Stage 2, and Stage 3)[9]. Development of one of the stages after surgical operations was defined as AKI.

Statistical analysis

SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) program was used in the analysis of the data in our study. Continuous and ordinal data were expressed with means and standard deviations. Kolmogorov–Smirnov and Shapiro-Wilk tests were used to evaluate the distribution of normality. Student's *t*-test and the Mann-Whitney U test were used in the analysis of normally and non-normally distributed data, respectively. Frequency and percentage analyses were performed for nominal data, and the chi-square test was used for comparison. To analyze the factors affecting postoperative AKI development, univariate and multivariate logistic regression analyses were performed. $p<0.05$ was considered statistically significant.

RESULTS

A total of 350 patients were included in the study. There were 156 patients in the del Nido cardioplegia group and 194 patients in the BC group. There was no difference between the groups in terms of age, smoking, hypertension, and diabetes mellitus rates (Table 1).

Preoperative blood parameters of all patients are given in Table 1. There was no difference between the groups in terms of preoperative blood parameters such as hemoglobin, platelet counts, creatinine values, and C-reactive protein value. Operative and postoperative characteristics of the patients are presented in Table 2. The two groups were comparable in terms of total perfusion time, inotropic support needs, postoperative troponin T values, total intensive care stay, and mortality rates. Cross-clamp time, total amount of blood product used, total hospital stays, and AKI development rates were significantly higher in Group 2 ($p=0.014$, $p<0.001$, $p<0.001$, $p=0.018$, respectively).

Among the patient group, 74 (21.1%) patients developed AKI. The total AKI development rate was significantly higher in Group 2 ($p=0.018$). The rates of patients with Stage 2 and 3 renal insufficiency were similar between the groups. To analyze the factors affecting the development of AKI in the postoperative

Table 1. Preoperative features and preoperative laboratory variables of the patients.

	Group 1 (n=156)	Group 2 (n=194)	p-value
Age (years)	61.3±9.1	62.6±9.8	0.294
Male gender, n (%)	111 (71.1)	150 (77.3)	0.198
BMI (kg/m²)	28.3±5.2	29.1±4.9	0.313
Hypertension, n (%)	75 (48)	105 (54.1)	0.237
Diabetes mellitus, n (%)	55 (35.2)	77 (39.6)	0.410
COPD, n (%)	30 (19.2)	35 (18)	0.797
Previous PCI, n (%)	51 (32.6)	69 (35.5)	0.315
EuroSCORE II	3.3±1.4	3.5±1.5	0.418
Smoking, n (%)	22(14.1)	30 (15.4)	0.710
Hiperlipidemia, n (%)	65 (41.6)	83 (42.7)	0.821
Ejection fraction (%)	51.3±9.1	50.2±9.2	0.478
ASA use, n (%)	67 (42.9)	78 (40.2)	0.613
ACEI/ARB use, n (%)	70 (44.8)	89 (45.8)	0.790
White blood cell ($10^3/\mu L$)	8.78±2.44	8.55±2.56	0.118
Hemoglobin (mg/dL)	13.3±1.2	12.9±1	0.274
Platelet ($10^3/\mu L$)	241.9±58.5	233.6±60.9	0.192
Neutrophil ($10^3/\mu L$)	5.4±1.82	5.33±1.86	0.312
Lymphocyte ($10^3/\mu L$)	2.28±0.82	2.21±0.79	0.226
Creatinine (mg/dL)	0.96±0.21	0.97±0.23	0.445
BUN (mg/dL)	19.9±6.8	20.1±5.9	0.528
CRP (mg/dL)	9.18±14.76	10.12±17.28	0.478

BMI: body mass index; COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; EuroSCORE II: European system for cardiac operative risk evaluation II; ASA: acetylsalicylic acid; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BUN: blood urea nitrogen; CRP: C-reactive protein.

period, univariate logistic regression analysis was performed first. Advanced age (OR 1.224; 95%CI 1.090–1.414; p=0.003), hypertension (OR 0.878; 95%CI 0.621–0.914; p=0.022), total perfusion time (OR 0.819; 95%CI 0.499–0.916; p=0.034), need for inotropic support (OR 1.678; 95%CI 1.228–2.748; p=0.011), increased blood product use (OR 1.816; 95%CI 1.336–02.956; p=0.007), preoperative creatinine elevation (OR 3.156; 95%CI 1.874–4.614; p<0.001), and increased cardioplegia volume (OR 1.714; 95%CI 1.156–2.467, p<0.001) were correlated with the development of AKI (Table 3).

Based on the results of multivariate logistic regression analysis, advanced age (OR 1.128; 95%CI 1.044–1.217; p=0.042), increased blood product use (OR 1.318; 95%CI 1.154–1.998; p=0.019), preoperative creatinine elevation (OR 2.434; 95%CI 1.655–4.639; p=0.005), and increased cardioplegia volume (OR 1.254; 95%CI 1.109–2.980; p=0.009) were independent predictors of AKI (Table 3).

DISCUSSION

In coronary bypass operations performed with cardiac arrest, superior quality anastomoses can be achieved when excellent visibility is provided. Cardioplegia solutions are used for cardiac arrest in this technique. Previously known for its use in pediatric cardiac surgery, dNCS has become increasingly common in adult cardiac surgery in recent years. In this study, we aimed to investigate the effect of dNCS use on the development of AKI in CABG operations with CPB and found that patients receiving BC developed AKI more frequently than those receiving dNCS. Our multivariate analysis showed that besides parameters such as advanced age, increased blood product use, and preoperative creatinine height, increased cardioplegia volume was also an independent predictor of AKI (OR 1.254; p=0.009).

In recent years, various clinical studies have been published on the use of dNCS in open heart operations. Marzouk et al. compared the clinical results of dNCS and BC use in their study and

Table 2. Operative and postoperative features of the patients.

	Group 1 n=156	Group 2 n=194	p-value
Total perfusion time	90.28±25.56	93.56±24.78	0.175
Cross-clamp time	57.75±16.96	63.56±18.45	0.014
Number of distal anastomoses	3.35±0.9	3.29±0.9	0.102
Cardioplegia volume (mL)	1794.7±304.5	1090±144.6	<0.001
Packed blood products (units)	3.86±1.54	4.28±1.66	<0.001
Inotropic support, n (%)	18 (11.5)	25 (12.8)	0.184
Troponin T (ng/L)	208±32.55	215.34±34.79	0.210
Total ICU stay (days)	2.94±3.2	2.9±3.3	0.494
Total hospital stay (days)	7.34±3.12	7.7±4.14	<0.001
Development of AKI, n (%)	24 (15.3)	50 (25.7)	0.018
Stage 1 (%)	18 (11.5)	38 (19)	0.024
Stage 2 (%)	5 (3.2)	10 (5.1)	0.272
Stage 3 (%)	1 (0.6%)	2 (1)	0.794
Mortality, n (%)	6 (3.8)	9 (4.6)	0.898

ICU: intensive care unit, AKI: acute kidney injury.

Table 3. Logistic regression analysis to identify factors affecting postoperative acute kidney injury.

	Univariate analysis			Multivariate analysis		
	p-value	Exp(B) Odds Ratio	95%CI Lower–Upper	p-value	Exp(B) Odds Ratio	95%CI Lower–Upper
Age	0.003	1.224	1.090–1.414	0.042	1.128	1.044–1.217
Hypertension	0.022	0.878	0.621–0.914	0.214	1.114	0.716–1.134
Diabetes mellitus	0.056	0.768	0.448–1.278	–	–	–
Total perfusion time	0.034	0.819	0.499–0.916	0.312	0.779	0.596–1.020
Cross-clamp time	0.376	1.118	0.894–1.144	–	–	–
Inotropic support	0.011	1.678	1.228–2.748	0.118	0.986	0.657–1.295
Blood product use	0.007	1.816	1.336–2.956	0.019	1.318	1.154–1.998
Pre-creatinine	<0.001	3.156	1.874–4.614	0.005	2.434	1.655–4.639
Lymphocyte count	0.156	0.987	0.678–1.090	–	–	–
Cardioplegia volume	<0.001	1.714	1.156–2.467	0.009	1.254	1.109–2.980

found that perfusion time, operative time, and total cardioplegia volume were significantly lower in patients who received dNCS. They also demonstrated that dNCS provides similar myocardial protection with intermittent cold blood cardioplegia[7]. In another study performed by Ucak et al.[6], the administration of dNCS and intermittent warm BC during CABG surgery were compared. Similarly, the authors determined that perfusion times were shorter with dNCS. They also found that the duration of mechanical ventilation, length of stay in the intensive care unit, length of hospital stays, and 30-day mortality were significantly reduced in patients receiving dNCS[6]. In line with this information, aortic cross-clamp times and hospital stay were shorter in the dNCS group in our study as well. Our mortality rate was similar in both groups.

One of the key factors affecting postoperative AKI rates is increased blood transfusion. The key reason for increased blood transfusion in our operations is hemodilution. In a study comparing blood cardioplegia and dNCS, postoperative hemoglobin levels were higher in patients receiving dNCS[10]. In another study, less cardioplegia volume was required in patients who were administered dNCS[11]. Increased use of blood products in these patients means increased hemolysis. Due to hemolysis, free-flowing hemoglobin consumes haptoglobin in the bloodstream. This catalyzes the production of free radicals and leads to sediment formation with Tamm-Horsfall proteins in the renal collecting system. Additionally, renal damage may occur because of increased nitric oxide consumption and consequent vasoconstriction in renal arterioles[12]. Hemolysis may cause AKI by increasing the free iron rate in the blood[13]. Increased blood product use has been shown as an independent predictor of AKI development in the study by Ramos et al.[14] In our study, we also found that increased blood product use was an independent predictor of AKI development (OR 1.224; p=0.019). We think that this may be due to decreased hemodilution because of decreased cardioplegia volume in patients receiving dNCS, because our multivariate analysis revealed that increased cardioplegia volume was also an independent predictor for AKI development (OR 1.254; p=0.009).

Total perfusion time and inotropic support were also associated with AKI development in our study. Hemolysis may occur due to extracorporeal circulation, and the renal risk increases due to atheroembolism[15]. In fact, there are publications showing that AKI development can be reduced by 40% in off-pump coronary bypass surgery[16]. Inotropic agents used in cardiac surgery practice are vasoconstrictor substances, which may also induce renal damage.

Advanced age is considered a risk in terms of mortal and morbid outcomes after surgery in all fields of medicine. With increasing age, the number of atherosclerotic foci and the risk of atheroembolism increase, especially in cardiac surgery operations performed with CPB. In addition, the vasoconstrictor response increases in the renal arteries of these patients, setting the groundwork for possible renal damage[17]. In our study, advanced age was an independent predictor of AKI. Recently, studies showing the clinical results of dNCS use in adult cardiac surgery are being published with increasing frequency. One of the key benefits of using dNCS is that cardioplegia is administered less frequently through the root needles. Frequent administration of pressurized fluid through the aortic root cannula may cause atherosclerotic embolism. Accordingly, microembolism incidence in different cardioplegia techniques was investigated in a prospective study by Mukdad et al., middle cerebral artery was visualized by transcranial Doppler ultrasonography at cross-clamp and cardioplegia times, and microembolism was scanned by monitoring. They found that single-dose dNCS strategy resulted in less cerebral microembolisms compared with conventional multi-dose cardioplegia. The authors suggested that this may be due to cardioplegia being delivered in fewer sessions[18]. Although we could not perform Doppler scans in our study, we believe that this parameter should be incorporated into further studies.

The most important limitations of our study include its single-centered, retrospective nature, and the sparse number of patients. In addition, evaluation of cystatin C, which is an important predictor of AKI, and similar blood parameters was not performed in our study. Also in our study, we found a relationship between Stage 1 AKI and cardioplegia type. More studies are needed with a larger number of patients.

CONCLUSION

In this study, we showed that the use of dNCS, which has become popular in adult cardiac surgery in recent years, can reduce the incidence of AKI. Novel studies are needed to elucidate the exact mechanism of this reduction.

AUTHORS' CONTRIBUTIONS

AKA: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **ME:** Writing – original draft, Writing – review & editing. **BA:** Writing – original draft, Writing – review & editing. **UA:** Writing – original draft, Writing – review & editing. **CE:** Writing – original draft, Writing – review & editing. **TT**: Writing – original draft, Writing – review & editing. contributed to drafting the manuscript and revising it critically for important intellectual content and made the final approval of the version to be published. **YA:** Formal analysis, Writing – original draft, Writing – review & editing.

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