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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Early postoperative outcomes of modified del Nido cardioplegia in coronary artery bypass surgery in patients with low ejection fraction

Ejeksiyon fraksiyonu düşük olan hastalarda koroner arter baypas cerrahisinde modifiye del Nido kardiyoplejinin erken dönem sonuçları

Mehmet Emir Erol, Deniz Sarp Beyazpınar, İsa Civelek, Sertan Özyalçın, Ufuk Mungan

Department of Cardiovascular Surgery, Ankara Etlik City Hospital, Ankara, Türkiye

ABSTRACT

Background: This study aimed to investigate the intraoperative and early postoperative effects of modified del Nido cardioplegia (DNC) compared to classic blood cardioplegia (BC) in patients with impaired left ventricular ejection fraction (EF) who underwent isolated coronary artery bypass grafting (CABG).

Methods: A total of 123 patients (108 males, 15 females; mean age: 62.2±8.5 years; range, 42 to 78 years) with an EF of 35% or lower who underwent on-pump CABG were included in the retrospective study between December 2022 and December 2023. The patients were divided into two groups according to the type of cardioplegia used: Group 1 (n=74) was designated as the BC group, and Group 2 (n=49) was designated as the DNC group. The groups were compared in terms of aortic cross-clamp duration, cardiopulmonary bypass (CPB) duration, need for defibrillation during weaning from CPB, positive inotrope requirement, intra-aortic balloon pump requirement, postoperative troponin-I levels, postoperative atrial fibrillation occurence, postoperative prolonged ventilation, development of postoperative neurologic complications, need for reintervention due to postoperative bleeding, postoperative transfusion requirement, and EF values at one month after the operation.

Results: There was no significant difference between the two groups in the terms of aortic cross-clamp and CPB duration (p=0.955 *vs.* p=0.816). Additionally, there was no significant difference in the need for intra-aortic balloon pump usage between the two groups (p=0.105). Dopamine and dobutamine usage were significantly lower in Group 2 (p=0.04 and p=0.05, respectively). The intraoperative requirement for defibrillation was significantly lower in Group 2 (p=0.01). In addition, troponin levels at 12 h postoperatively were significantly lower in Group 2 (p=0.03). The incidence of postoperative atrial fibrillation was significantly lower in Group 2 (p=0.02). Moreover, there was no significant difference in EF values at one month after the operation (p=0.08).

Conclusion: In patients who underwent CABG with reduced EF, modified DNC provided myocardial protection comparable to classic BC. Additionally, the need for intraoperative defibrillation and postoperative inotropic agents, as well as the incidence of postoperative atrial fibrillation, were lower in patients operated with DNC.

Keywords: Coronary artery bypass grafting, del Nido cardioplegia solution, ventricular ejection fraction.

ÖZ

Amaç: Bu çalışmada sol ventrikül ejeksiyon fraksiyonu (EF) bozulmuş koroner arter baypas cerrahisi (KABG) geçirmiş hastalarda, modifiye del Nido kardiyoplejisi (DNC) ile klasik kan kardiyoplejisinin (BC) ameliyat sırası ve erken ameliyat sonrası etkileri incelendi.

Çalışma planı: Bu retrospektif çalışmaya Aralık 2022 - Aralık 2023 arasında on-pump KABG uygulanan EF değeri %35 veya daha düşük olan 123 hasta (108 erkek, 15 kadın; ort. yaş: 62.2±8.5 yıl; dağılım, 42-78 yıl) dahil edildi. Hastalar, kullanılan kardiyopleji çeşidine göre iki gruba ayrıldı: Grup 1 (n=74), BC grubu olarak belirlendi ve Grup 2 (n=49), DNC grubu olarak belirlendi. Gruplar aortik kros klemp süresi, kardiyopulmoner baypas (CPB) süresi, CPB'den ayrılma sırasında defibrilasyon gereksinimi, pozitif inotrop gereksinimi, intra-aortik balon pompası gereksinimi, ameliyat sonrası troponin-I seviyeleri, ameliyat sonrası atriyal fibrilasyon gelişmesi, ameliyat sonrası uzamış ventilasyon, ameliyat sonrası nörolojik komplikasyon gelişmesi, ameliyat sonrası kanama nedeniyle tekrar müdahale gereksinimi, ameliyat sonrası transfüzyon ihtiyacı ve ameliyat sonrası birinci aydaki EF değerleri açısından karşılaştırıldı.

Bulgular: İki grup arasında aortik kros klemp ve CPB süresi açısından anlamlı bir farklılık bulunamadı (sırasıyla p=0.955 ve p=0.816). Ayrıca, iki grup arasında intra-aortik balon pompası kullanımı açısından anlamlı bir farklılık yoktu (p=0.105). Dopamin ve dobutamin kullanımı Grup 2'de belirgin olarak daha düşüktü (sırasıyla, p=0.04 ve p=0.05). Grup 2'de ameliyat sırası defibrilasyon gereksinimi anlamlı olarak daha düşüktü (p=0.01). Ek olarak, ameliyat sonrası 12. saatteki troponin düzeyleri Grup 2'de anlamlı olarak daha düşüktü (p=0.03). Ameliyat sonrası atriyal fibrilasyon insidansı Grup 2'de anlamlı olarak daha düşüktü (p=0.03). Ayrıca, ameliyat sonrası birinci aydaki EF değerlerinde anlamlı bir farklılık bulunmadı (p=0.08).

Sonuç: Düşük EF'ye sahip KABG yapılan hastalarda, modifiye DNC, klasik BC'ye kıyasla benzer miyokardiyal koruma sağladı. Ek olarak, DNC kullanılan hastalarda ameliyat sırası defibrilasyon ve ameliyat sonrası inotropik ajan gereksinimi ile ameliyat sonrası atriyal fibrilasyon insidansı daha düşüktü.

Anahtar sözcükler: Koroner arter baypas cerrahisi, del Nido kardiyopleji solüsyonu, ventrikül ejeksiyon fraksiyonu.

Corresponding author: Mehmet Emir Erol.

E-mail: erolm91@gmail.com

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In patients with impaired left ventricular function, adequate myocardial protection can influence the success of the operation and postoperative mortality and morbidity. Myocardial protection techniques aim to mitigate the undesirable effects of global ischemia that occur during the surgical procedure, ensuring a smooth separation from cardiopulmonary bypass (CPB) and adequate maintenance of myocardial function during the postoperative period.[1] Cardioplegic solutions are the cornerstone of myocardial protection, but the ideal cardioplegic solution has not been defined.[2,3]

The commonly used blood cardioplegia (BC) can be both antegradely and retrogradely administered according to the Buckberg protocol.[4] Blood cardioplegia exerts its effect by inducing diastolic arrest by inhibiting hyperkalaemia-induced repolarization in myocytes. During arrest, BC also leads to intracellular sodium and calcium accumulation,[5] and dosage repetition is required every 15 to 20 min.

Del Nido cardioplegia (DNC), discovered in the 1990s by del Nido to prevent reperfusion injury in pediatric cardiac surgery, has gained widespread use in adult cardiac surgery due to its ability to provide myocardial protection for up to 90 min, reduce dilution when used in a single dose, reduce potassium content, prolong the refractory period of myocytes, extend arrest duration by adding lidocaine (a sodium channel blocker), and mitigate energy consumption by preventing intracellular calcium and sodium accumulation through the sodium channel blockade facilitated by DNC.[6]

Low left ventricular function is an independent risk factor for mortality and morbidity after coronary artery bypass grafting (CABG).[7] While complete revascularization represents the initial step in ensuring adequate myocardial protection, the myocardial protection techniques employed during the intraoperative period also influence the success of the surgery in the early postoperative period.

Although there is information available regarding the use of DNC in adult cardiac surgery, there is limited data on the use of DNC in CABG patients with low ejection fraction (EF). Thus, this study aimed to investigate whether there are differences between BC and DNC in terms of aortic cross-clamp (XCL) duration, CPB duration, defibrillation requirement, inotropic requirement, intra-aortic balloon pump (IABP) requirement, postoperative troponin-I levels, and EF at one month after the operation in CABG patients.

PATIENTS AND METHODS

The retrospective study evaluated 1,152 patients who underwent on-pump CABG at the Ankara Etlik City Hospital between December 2022 and December 2023. Low EF was defined as 35% or below, which was measured by transthoracic echocardiography using the Simpson method. A total of 123 patients (108 males, 15 females; mean age: 62.2±8.5 years; range, 42 to 78 years) whose EF was 35% or below were included in the study. Patients who received BC (n=74) were classified as Group 1, while those who received DNC (n=49) were classified as Group 2. Two different surgical teams decided on the type of cardioplegia based on their preferences. Patients who were admitted urgently, those with EF greater than 35%, those who did not receive retrograde cardioplegia, those with chronic kidney disease requiring dialysis, those with chronic liver disease, and those who required concomitant surgical procedures were excluded from the study. The study was conducted after obtaining approval from the Ankara Etlik Hospital Clinical Research Ethical Committee (date: 18.10.2023; no: AEŞH-EK1-2023-629). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the participants.

The same surgical technique was applied to all patients, beginning with a median sternotomy, followed by harvesting of the pedicled left internal mammary artery. Subsequently, all patients underwent anastomosis to the left anterior descending coronary artery. The saphenous vein graft was used for anastomosis to other coronary arteries. Del Nido cardioplegia was administered at a total volume of 1000 mL, using a one-to-four ratio with blood (200 mL blood and 800 mL DNC), with 600 mL antegradely administered, and 400 mL retrogradely administered at a temperature of 4°C. If the XCL duration exceeded 60 min, a repeat dose was administered.

On the other hand, BC was administered in a total volume of 1500 to 2000 mL in a four-to-one ratio with blood. It was applied antegradely and retrogradely during XCL, repeated every 15 to 20 min, and maintained at a temperature of 4°C. In addition, topical hypothermia was used in both DNC and BC groups according to the surgeon's preference. Cardiopulmonary bypass flow was maintained at 2.2 to 2.4 L/min/m^2 and under mild hypothermia (30 to 32°C). All operations were performed by two teams of surgeons, and the anesthesia method utilized was standardized for all patients. The cardioplegia

formulations utilized in both groups are depicted in Table 1.

The durations of both XCL and CPB, post-XCL inotropic requirement, and IABP requirements were obtained by reviewing patients' operative records. In instances where the systolic arterial pressure did not reach or exceed 90 mmHg (and the mean arterial pressure did not surpass 60 mmHg) upon weaning from CPB, inotropic agents were administered. The primary inotropic agent employed in our clinic was dopamine at a dosage of 5 mcg/kg/min. Should this dosage fail to achieve sufficient hemodynamic stability, supplementary agents were introduced. The dosage of inotropic agents was meticulously adjusted based on hemodynamic parameters (systolic arterial pressure, urine output, and lactate levels in arterial blood gas) throughout the period of intensive care monitoring following CPB separation.

Troponin-I levels were evaluated at postoperative 12 h and on the first postoperative day. Ejection fraction values were assessed at the one-month follow-up using transthoracic echocardiography. Preoperative data were obtained by scanning the hospital database. Postoperative prolonged ventilation, postoperative neurological complications, postoperative bleeding, and postoperative hemodialysis requirement data were obtained from the intensive care unit database.

Statistical analysis

Data were analyzed using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables were displayed as mean ± standard deviation (SD), and blood cardioplegia and del Nido cardioplegia groups were compared using the independent sample t-test. Categorical variables were expressed as percentages and frequencies and were compared between groups using the chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

The mean Society of Thoracic Surgeons score was 7.85 5.37 (range, 3.68 to 29.6), and the mean EuroSCORE (European System for Cardiac Operative Risk Evaluation) II was 4.06±5.5 (range, 0.88 to 22.76). There were no differences in the demographic data between the two groups. The demographic characteristics of the patients are presented in Table 2.

The operative data of the patients were compared. There was no significant difference between the two groups in terms of body surface area, XCL duration, CPB duration, number of bypasses performed, and the need for IABP during separation from CPB. A comparison of the inotropic agent support between the two groups revealed that Group 2 had significantly lower requirements for dopamine and dobutamine (p=0.04 and p=0.05, respectively), while the requirements for adrenaline and noradrenaline were similar in both groups (p=0.654 and p=0.935, respectively). Moreover, the need for intraoperative defibrillation was significantly lower in Group 2 (p=0.01). The comparison of intraoperative data between the groups is presented in Table 3. No differences were observed between the DNC and BC groups in terms of postoperative neurological complications, prolonged ventilation, need for hemodialysis, requirement for postoperative exploration due to bleeding, and development of low cardiac output syndrome.

Table 1. Composition of del Nido cardioplegia and blood cardioplegia

	Modified del Nido cardioplegia	Blood cardioplegia
Potassium (mmol/L)	26	16
Sodium bicarbonate (mmol/L)	15	10
Magnesium (mmol/L)	15 mL (1 mEq/mL)	32
Mannitol (gram)	3.6 g 20%	12.5 g 20%
Lidocaine (mg)	100	None
Calcium (mmol/L)	None	2.4 mmol/L
Clor (mmol/L)	None	160 mmol/L
Blood/cyrstalloid rate	1/4	4/1
Solution	Isolye S 1 L	Blood 1 L

Table 2. Demographic characteristics of the patients

	Group 1 (n=74)			Group 2 (n=49)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			62.4±8.6			62.0±8.6	0.838
Sex							1.00
Male	66	89		43	88		
Female	8	11		6	12		
Preoperative EF (%)			32.44±2.65			32.44±2.73	0.995
Body surface area (cm^2)			1.93±0.15			1.92±0.16	0.85334
SYNTAX score			7.87±5.43			7.83±5.33	0.966
EuroSCORE			4.35±5.84			3.61±5.05	0.531
STS score			7.51±4.79			7.38±5.87	0.549
Diabetes mellitus (%)	43	58		29	59		1.00
COPD (%)	10	14		6	12		1.00
CVD (%)	1	0.1		1	0.2		1.00
CKD (%)	5	0.6		4	0.8		1.00

SD: Standard deviation; EF: Ejection fraction; EuroSCORE: European System for Cardiac Operative Risk Evaluation; STS score: Society of Thoracic Surgeons Score; COPD: Chronic obstructive pulmonary disease; CVD: Cerebrovascular disease; CKD: Chronic kidney disease.

Table 3. Operative data of the patients

	Group 1 (n=74)			Group 2 (n=49)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Cross-clamp (min)			71.92±35.44			72.29±32.92	0.955
CPB (min)			112.12±50.86			114±48.41	0.816
Greft number			2.53±1.16			2.35±1.35	0.755
Defibrillation (%)	34	46		12	24		0.01
Adrenalin			0.08±0.02			0.08±0.02	0.935
Noradrenalin			0.14±0.19			0.17±0.23	0.654
Dopamine			9.96±5.45			783±3.44	0.04
Dobutamine			8.76±4.11			6.89±3.82	0.05
IABP	26	35		10	20		0.105

CPB: Cardiopulmonary bypass; IABP: Intra-aortic balloon pump.

A comparison of the postoperative data of the patients revealed that there was no significant difference between the groups in terms of postoperative CRP levels, troponin values on the first postoperative day, duration of intensive care unit stay, duration of hospital stay, and mortality. However, Group 2 had lower transfusion rates (p=0.03). In addition, troponin values at 12 h postoperatively and incidence of postoperative atrial fibrillation were significantly lower in the DNC group (p=0.032 and p=0.034, respectively). The postoperative data of the patients are presented in Table 4.

DISCUSSION

Del Nido cardioplegia was initially introduced to prevent ischemia-reperfusion injury and reduce calcium sensitivity in the pediatric population.[7] Nowadays, its use has expanded to adult cardiac surgery, not only in isolated CABG surgery[8] but also in combined surgical procedures involving coronary artery disease.[9] Recent research on the use of

Table 4. Postoperative comparison of the patients

	Group 1 (n=74)			Group 2 (n=49)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Postoperative CRP			161.73±77.66			164.95±76.85	0.832
Troponin 0			1248.82±2229±99			437.58±1178.84	0.03
Troponin 1			887.97±1333.05			455.1±711.19	0.06
Postoperative EF			35.18±2.78			35.85±3.11	0.785
Postoperative AF (%)	19	26		5	10		0.03
Blood transfusion (mL)			357±128			334±139	0.687
Ventilation time (h)			6.8±3.2			5.9±2.9	0.245
ICU time (days)			5.42±5.42			5.08±5.05	0.738
Hospital time (days)			8.0±4.76			7.92±4.51	0.939
Mortality (%)	8	11		5	10		1.000

SD: Standard deviation; CRP: C-reactive protein; EF: Ejection fraction; AF: Atrial fibrillation; ICU: Intensive care unit.

DNC in adult cardiac surgery reveals that it is often evaluated as part of a subgroup analysis, particularly focusing on patients with poor ventricular function.[8]

We evaluated the intraoperative and early postoperative effects of DNC in patients with impaired left ventricular function. Our study demonstrated that in patients undergoing CABG with low EF and high risk, DNC is as effective and reliable in terms of myocardial protection as BC. In addition, patients treated with DNC were found to require less defibrillation, which may suggest that the occurrence of ventricular fibrillation following the removal of the cross-clamp is related to the myocardial ATP (adenosine triphosphate) reserves not being fully replenished. These patients also had lower requirements for inotropic agents, such as dopamine and dobutamine, showed no difference in the use of adrenaline and noradrenaline, and had a similar rate of IABP requirement compared to those who received BC. Undoubtedly, complete revascularization following CPB is the most significant inotropic factor. However, patients with compromised ventricular function may require inotropic agents, primarily dopamine and dobutamine. In our study, patients administered with DNC demonstrated a reduced need for dopamine and dobutamine. We attribute this finding to the DNC's capacity to decrease energy consumption.[6]

In addition, the incidence of postoperative atrial fibrillation was lower, and troponin-I levels at 12 h postoperatively were lower in the DNC group. Moreover, there was no difference in EF values at the one-month follow-up in both groups. Considering all results together, we can conclude that DNC offers promising results and sufficient safety in patients with impaired EF.

While the importance of complete revascularization in CABG patients is undisputed, myocardial protection is also crucial. In patients with impaired ventricular function, the effectiveness of cardioplegic solutions used for myocardial protection is of great interest to researchers. Furthermore, the durations of CPB and XCL are independent risk factors for morbidity and mortality in open heart surgery.[10] One of the key reasons for the current increase in the use of DNC in adult cardiac surgery is that it reduces the durations of CPB and XCL.[11] It was also emphasized that surgical flow and procedure concentration are not disrupted with DNC use[12] and that there is no need for repeat dosing.[13] However, in our study, no difference was found between the two groups in terms of the CPB duration and XCL time. The reasons for this result may be attributed to the fact that all patients in our study had low EF, and another reason could be linked to the distinct surgical teams involved. Furthermore, no difference was observed between the two groups in terms of intensive care unit and hospital stays and mortality rates. These results indicate that DNC is as safe as BC in patients with low EF. Another reason that led us to this conclusion is the lower troponin levels at 12 h postoperatively in patients treated with DNC. In addition, no differences were observed between

DNC and BC groups in terms of postoperative neurological complications, prolonged ventilation, need for hemodialysis, requirement for postoperative exploration due to bleeding, and development of low cardiac output syndrome. However, postoperative atrial fibrillation was observed at lower rates in patients treated with DNC, which is consistent with the findings in numerous studies.[8,9,12] When the need for inotropic agents was examined, it was evident that patients treated with DNC had significantly lower requirements for inotropes. This result is consistent with other studies on DNC.[8-14] Another advantage of DNC is that it is inherently administered in much lower volumes compared to BC, thereby resulting in lower hemodilution.[14] The lower volume administered can affect the rates of postoperative transfusion.[15] However, in our study, no difference was found in postoperative red blood cell transfusion rates between two groups.

Despite advances in medical therapy, advanced surgical techniques, and contemporary postoperative care in CABG surgery, low EF remains a risk factor for mortality and morbidity.[13-17] One of the major aspects of debate surrounding DNC is the lack of consensus due to the absence of randomized trials providing conclusive evidence in this regard. Additionally, to the best of our knowledge, there is no study to date that fully demonstrates the efficacy of DNC in myocardial protection at the molecular level in CABG patients. However, researchers have demonstrated that DNC can provide adequate and homogenous distribution of cardioplegia in the ischemic myocardium in patients with coronary artery disease.[18]

This study had several limitations. First, the study was retrospective in design. Another significant limitation was the lack of randomization across groups due to the surgeon-determined selection of cardioplegia, leading to bias in patient selection. Additionally, a significant limitation was the involvement of two different surgical teams.

In conclusion, there is no definitive information regarding the use of del Nido cardioplegia in patients with impaired ventricular function. This study suggests that del Nido cardioplegia is as safe as blood cardioplegia, as evidenced by lower postoperative troponin levels, reduced incidence of postoperative atrial fibrillation, and decreased need for dopamine and dobutamine in patients who received del Nido cardioplegia. Although not entirely conclusive, lower postoperative troponin levels in patients receiving del Nido cardioplegia may suggest that more effective myocardial protection is achieved.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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