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# Del Nido versus warm blood cardioplegia in adult patients with a low ejection fraction

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## Abstract

**Background:** Del Nido cardioplegia was recently introduced to adult cardiac surgery with encouraging results. The effect of Del Nido cardioplegia in patients with low ejection fraction (EF) has not been thoroughly evaluated. The objective of this study was to assess the safety of Del Nido cardioplegia in adult patients with low EF compared to intermittent warm blood cardioplegia.

**Results:** During 2018 and 2019, 73 adult patients with an EF of  $\leq 40\%$  underwent cardiac surgery using Del Nido cardioplegia. The patients were compared to a historical cohort of consecutive patients with low EF who had intermittent warm blood cardioplegia ( $n = 81$ ). Patients who had Del Nido cardioplegia had significantly lower EuroSCORE II (2.73 (1.7–4.1) vs. 4.5 (2.4–7.4),  $P = 0.004$ ). There were no differences in creatinine clearance and preoperative echocardiographic data between the groups. Cardiopulmonary bypass and cross-clamp times were non-significantly lower with Del Nido cardioplegia. There were no differences in stroke and postoperative echocardiographic data between the groups. No hospital mortality was reported in both groups. Peak troponin levels were significantly higher in patients who had Del Nido cardioplegia (0.88 (0.58–1.47) vs. 0.7 (0.44–1.01) ng/dL;  $P = 0.01$ ); however, after multivariable regression analysis, cardiopulmonary bypass time was the only predictor of postoperative troponin level (coefficient 0.005 (95% CI: 0.003–0.008);  $P < 0.001$ ). ICU stay was significantly longer in patients who had Del Nido cardioplegia (4 (3–6) vs. 2 (1–4) days,  $P < 0.001$ ), while postoperative hospital stay did not differ between the groups. After multivariable regression, the use of intermittent warm blood cardioplegia was significantly associated with shorter ICU stay (coefficient  $-1.80$  (95% CI  $-3.06 - -0.55$ );  $P = 0.01$ ).

**Conclusions:** Prolonged ICU was reported with Del Nido cardioplegia; however, there were no differences in the duration of hospital stay and the clinical outcomes between the groups. Despite the proven efficacy of intermittent warm blood cardioplegia, the use of Del Nido cardioplegia might be safe in patients with low EF.

**Keywords:** Del Nido cardioplegia, Low ejection fraction, Troponin level, Warm blood cardioplegia

## Background

Low ejection fraction (EF) is associated with increased morbidity and mortality in adult patients undergoing cardiac surgery [1, 2]. In patients with low ejection fraction, proper myocardial protection is essential to reduce ischemic-reperfusion injury and preserve myocardial function [3].

Del Nido cardioplegia (Compass-Baxter Healthcare Inc., Edison, NJ, USA) was initially introduced to pediatric cardiac surgery with good outcomes and lower troponin T levels compared to warm blood cardioplegia [4, 5]. Del Nido cardioplegia was recently introduced to adult cardiac surgery with encouraging results [6, 7]. Del Nido cardioplegia can decrease the operative time because of the single-dose regimen compared to other cardioplegia solutions.

The effect of Del Nido cardioplegia in patients with low ejection fraction has not been thoroughly evaluated

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in the literature [8]. It is unknown whether Del Nido cardioplegia is used for patients with high-risk scores or low ejection fraction presents a valid option [9]. This study's objective was to evaluate the safety of Del Nido cardioplegia in adult patients with a low ejection fraction ( $\leq 40\%$ ) in comparison with intermittent warm blood cardioplegia.

## Methods

### Design and patient

We performed a retrospective study on 73 patients with an ejection fraction  $\leq 40\%$  who underwent cardiac surgery using Del Nido cardioplegia from September 2018 to September 2019. Those patients were compared to a historical cohort of 81 consecutive patients who had surgery prior to September 2018 using intermittent warm blood cardioplegia. We included patients who underwent coronary artery bypass grafting (CABG), valve surgery, or combined CABG and valve surgery.

### Technique of Del Nido cardioplegia

Cardioplegia was infused in a dose of 1000 mL at 4 °C in the aortic root or the coronary arteries if the patients had severe aortic regurgitation. The intervals between infusions were 90 min, and further doses of 300–500 mL were used if necessary.

### Data and outcomes

Preoperative data were collected, including patients' demographics, comorbidities, and laboratory data. Postoperative complications, length of intensive care, hospital stay, and mortality were reported. Preoperative echocardiographic data included ejection fraction, left ventricular dimensions, and pulmonary artery systolic pressure. High-sensitive cardiac troponin T was measured postoperatively, and the peak troponin value was compared between the groups.

### Ethical consideration

The Institutional Review Board approved the study protocol and waived the need for patients' consent (reference number: R19017).

### Statistical analysis

The normality of the continuous variables was tested using the Shapiro-Wilk test. We presented the normally distributed continuous data as mean and standard deviation and the non-normally distributed data as median and (25th–75th percentiles). Normal data were compared using the Student *t*-test and non-normal data with the Man-Whitney test. Categorical variables were described as numbers and percentages and compared with the chi-square test or Fisher exact test if the expected frequency

was less than five. Multivariable quantile (median) regression was used to study the factors affecting the peak troponin levels and postoperative intensive care unit stay. Model selection was based on the clinical significance and the absence of collinearity among the included variables. Factors included in the EuroSCORE II were not included as separate variables in the model, and all variables included had a variance inflation factor of less than 2.5. Stata 16.1 (Stata Corp., College Station, TX, USA) was used to perform all statistical analyses, and a *P*-value  $< 0.05$  was considered statistically significant.

## Results

### Preoperative and operative data

Patients who had Del Nido cardioplegia were significantly younger (61 (55–66) vs. 65 (57–72) years,  $P = 0.002$ ) and had significantly lower EuroSCORE II (2.73 (1.7–4.1) vs. 4.5 (2.4–7.4),  $P = 0.004$ ). There were no differences in creatinine clearance and preoperative echocardiographic data between the groups. Isolated CABG was more common in the Del Nido group, and combined valve and CABG were more common in the warm blood cardioplegia group; however, there was no difference in valve surgery between the groups. Cardiopulmonary bypass and cross-clamp times were non-significantly lower with Del Nido cardioplegia (Table 1).

### Postoperative outcomes

There were no differences in stroke, re-exploration, pulmonary artery systolic pressure, and ejection fraction between the groups. No hospital mortality was reported in both groups (Table 2).

Peak troponin levels were significantly higher in patients who had Del Nido cardioplegia; however, after multivariable regression analysis, cardiopulmonary bypass time was the only predictor of postoperative troponin level (coefficient 0.005 (95% CI: 0.003–0.008);  $P < 0.001$ ) (Table 3).

ICU stay was significantly longer in patients who had Del Nido cardioplegia, while postoperative hospital stay did not differ between the groups. After multivariable regression analysis, the use of intermittent warm blood cardioplegia was significantly associated with shorter ICU stay (coefficient  $-1.80$  (95% CI  $-3.06 - -0.55$ );  $P = 0.01$ ) (Table 4).

## Discussion

Proper myocardial protection is an essential component of successful cardiac surgery. The optimal solution for myocardial protection is still the subject of ongoing research. Del Nido cardioplegia showed good results in pediatric cardiac surgery and was introduced in the last decade to adult procedures [10]. Del Nido cardioplegia's

**Table 1** Comparison of the patients' preoperative and operative characteristics between Del Nido cardioplegia and warm intermittent blood cardioplegia

Variable	Del Nido (n = 73)	Warm-blood (n = 81)	P-value
Age, years	61 (55–66)	65 (57–72)	0.002
Male, n (%)	57 (78.1)	65 (80.3)	0.74
Body mass index, kg/m <sup>2</sup>	27.7 (23.7–32.7)	27.1 (23.3–30.8)	0.27
EuroSCORE II, %	2.73 (1.7–4.1)	4.5 (2.4–7.4)	0.004
Diabetes mellitus, n (%)	39 (53.4)	56 (75.7)	0.01
Chronic lung disease, n (%)	3 (4.1)	3 (4.0)	> 0.99
Mod-severe renal impairment, n (%)	39 (53.4)	45 (55.5)	
Dialysis, n (%)	4 (5.6)	2 (2.5)	0.42
Previous cardiac surgery, n (%)	4 (5.5)	4 (4.9)	> 0.99
Laboratory data			
Creatinine, $\mu$ mol	96 (72–126)	107.5 (77–129.5)	0.34
Creatinine clearance, mL/min	54.5 (59–111)	77 (60–95)	0.22
Baseline echocardiography			
LV ejection fraction, %	35 (30–40)	35 (30–40)	0.30
LV EDD, mm	54.9 $\pm$ 6.7	54.1 $\pm$ 9.7	0.60
LV ESD, mm	42.1 $\pm$ 7.7	43.6 $\pm$ 8.7	0.29
PASP, mmHg	40 (30–47.5)	42.5 (30–60)	0.161
Emergency surgery, n (%)	3 (4.11)	3 (3.7)	> 0.99
Surgery			
CABG only, n (%)	40 (55.6)	24 (29.6)	0.001
CABG + valve surgery, n (%)	16 (22.2)	44 (54.3)	< 0.001
Valves only, n (%)	17 (23.6)	13 (16.1)	0.24
CPB time, min	131.9 $\pm$ 41.5	141.2 $\pm$ 45.4	0.19
Cross-clamp time, min	96 (71–126)	107.5 (77–129.5)	0.28

EuroSCORE European System for Cardiac Operative Risk Evaluation, LV left ventricle, EDD end-diastolic diameter, ESD end-systolic diameter, PASP pulmonary artery systolic pressure, CABG coronary artery bypass graft, CPB cardiopulmonary bypass time

**Table 2** Comparison of the postoperative outcomes between Del Nido cardioplegia (group 1) and warm intermittent blood cardioplegia (group 2)

Variable	Del Nido (n = 73)	Warm blood (n = 81)	P-value
<b>Postoperative outcomes</b>			
Peak troponin T, ng/dL	0.88 (0.58–1.47)	0.7 (0.44–1.01)	0.01
Stroke, n (%)	2 (2.8)	1 (1.2)	0.60
Return to OR for bleeding, n (%)	3 (4.2)	2 (2.5)	0.67
ICU stay, days	4 (3–6)	2 (1–4)	< 0.001
Hospital stay, days	11 (8–16)	9 (7–15)	0.35
<b>Postoperative echocardiography</b>			
LV ejection fraction, %	37.2 $\pm$ 9.6	35.4 $\pm$ 8.7	0.21
PASP, mmHg	40 (30–45)	30 (30–44)	0.22

LV left ventricle, PASP pulmonary artery systolic pressure, CABG coronary artery bypass graft, OR operation room, ICU intensive care unit

single-dose administration is a potential benefit, which could reduce the ischemic time with a potentially positive effect on the operative outcomes. Despite these potential advantages, no difference in ischemic and cardiopulmonary bypass times was reported in other reports [11, 12]. This finding is similar to our study; we found that the

ischemic and bypass times were non-significantly lower in patients who had Del Nido cardioplegia, which can be attributed to the different surgical procedures and surgeons' experience between the groups. Several studies compared single- versus multiple-dose cardioplegia, and they found that the single-dose regimen was associated

**Table 3** Multivariable quantile regression analysis for factors affecting postoperative troponin T levels

Variable	Coefficient (95% confidence interval)	P-value
EuroSCORE II	0.009 (−0.015–0.032)	0.44
Preoperative LV EDD	0.005 (−0.014–0.024)	0.61
Preoperative LV ESD	−0.0004 (−0.019–0.0189)	0.97
Warm blood cardioplegia	−0.18 (−0.42–0.06)	0.13
CPB	0.005 (0.003–0.008)	< 0.001

EuroSCORE European System for Cardiac Operative Risk Evaluation, LV left ventricle, EDD end-diastolic diameter, ESD end-systolic diameter, CPB cardiopulmonary bypass

**Table 4** Multivariable quantile regression analysis for factors affecting the postoperative intensive care unit stay

Variables	Coef. (95% confidence interval)	P-value
Warm blood cardioplegia	−1.80 (−3.06 - −0.55)	0.01
EuroSCORE II	0.08 (−0.05–0.21)	0.21
Preoperative LV EDD	−0.04 (−0.14–0.06)	0.45
Preoperative LV ESD	0.01 (−0.9–0.11)	0.86
CPB	0.01 (−0.01–0.02)	0.35

EuroSCORE European System for Cardiac Operative Risk Evaluation, LV left ventricle, EDD end-diastolic diameter, ESD end-systolic diameter, CPB cardiopulmonary bypass

with shorter ischemic and CPB times with no difference in cardiac troponin T levels or complications [13, 14].

The application of Del Nido cardioplegia in high-risk patients has not been extensively evaluated in the literature. Yerebakan and associates compared Del Nido cardioplegia to blood cardioplegia in high-risk CABG patients with acute myocardial infarction. Their study included 88 patients. They did not find a difference between the two groups regarding the need for postoperative inotropic support; however, cardiopulmonary bypass and ischemic times were significantly lower in the Del Nido group [8].

The outcome of Del Nido cardioplegia in patients with low ejection has not been reported separately in the literature. Marzouk and coworkers evaluated the effect of Del Nido cardioplegia on the troponin levels in 131 patients compared to patients who received cold blood cardioplegia [15]. There was no difference in the operative outcomes and troponin levels between the groups. Ten patients with low ejection fraction received Del Nido cardioplegia in Marzouk et al.'s study.

Troponin levels were higher in patients who received Del Nido cardioplegia. After multivariable adjustment, cardioplegia type was not associated with troponin levels. There are no consistent results about the effect of Del Nido cardioplegia on the postoperative enzyme levels compared to other cardioplegic solutions. Kim and

associates found no difference in cardiac enzyme levels in patients who received Del Nido versus blood cardioplegia; however, there was a significantly lower transfusion and fluid requirements in patients who received Del Nido cardioplegia [12]. Timek and coworkers found no difference in troponin levels between Del Nido and blood cardioplegia in patients who had isolated CABG, and the levels did not differ in patients older than 75 years, with a left main disease, ejection fraction less than 35%, or STS score more than 2.5% [16]. Other series found significantly lower levels of troponin in patients who received Del Nido [6, 7].

Despite the growing evidence of Del Nido cardioplegia's use in adult patients, there is a lack of sufficient clinical trials. Ad and associates performed a randomized trial comparing Del Nido to whole blood cardioplegia. They found a higher return to spontaneous rhythm and lower troponin levels in patients who received Del Nido cardioplegia [17]. The mean EF of the Del Nido group in this study was  $54.3 \pm 11.9\%$ .

Our study found no differences in the clinical outcomes and 30-day mortality between patients who received Del Nido versus intermittent warm blood cardioplegia. ICU stay was significantly longer with Del Nido; however, postoperative hospital stay did not differ between the groups. These findings can be partially explained by the different time eras of the two groups and different surgeons. Additionally, the distribution of surgical procedures was different between the groups. The findings of this study indicate the safety and feasibility of the use of Del Nido in patients with low ejection fraction, and prospective comparative studies are recommended.

#### Study limitations

The study's major limitation is the retrospective design with its inherent drawbacks. We compared two groups of patients who had surgery at two different times with different surgeons. Several unmeasured variables could have affected the outcomes, including the surgeons' experience. Additionally, there were variations in the baseline and operative characteristics between the groups, which were corrected by the multivariable analysis. Other limitations include the single-center experience. Given that the control group is a historical cohort, it was not possible to calculate the statistical power for a non-inferiority study design.

#### Conclusions

Prolonged ICU was reported with Del Nido cardioplegia; however, there were no differences in the duration of hospital stay and the clinical outcomes between the groups. Despite the proven efficacy of intermittent warm blood cardioplegia, the use of Del Nido cardioplegia might be

safe in patients with low EF. A larger randomized clinical trial is required to compare Del Nido cardioplegia with other types and confirm our findings.

#### Abbreviations

CABG: Artery bypass grafting; CPB: Cardiopulmonary bypass; EF: Ejection fraction; LV: Left ventricle; EDD: End-diastolic diameter; ESD: End-systolic diameter; PASP: Pulmonary artery systolic pressure; ICU: Intensive care unit; OR: Operating room.

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#### Authors' contributions

AA: analysis and writing. EH: data collection and drafting. JA: data collection and revision. EA: data collection and revision. AS, AM, and KO: data collection and drafting. AIA, KA, and CP: research design, supervision, and drafting. The authors read and approved the final manuscript.

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#### Availability of data and materials

The authors declare that the data supporting the findings of this study are available upon request.

#### Declarations

##### Ethics approval and consent to participate

IRB approval number: R19017. Prince Sultan Cardiac Center, Riyadh, Saudi Arabia, 2019. Consent to participate was waived by the Ethical Committee.

##### Consent for publication

Not applicable

##### Competing interests

The authors declare that they have no competing interests.

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#### References

- Langer NB, Ando M, Simpson M, van Boxtel BS, Sorabella RA, Patel V et al (2019) Influence of left ventricular ejection fraction on morbidity and mortality after aortic root replacement. *J Thorac Cardiovasc Surg* 158(4):984–991.e1. <https://doi.org/10.1016/j.jtcvs.2018.10.147>
- Li Z, Ye YQ, Wang MY, Xu HY, Teng SY, Qian J et al (2016) Impact of reduced left ventricular ejection fraction on all-cause mortality of 75 years old and over patients with moderate to severe aortic stenosis. *Zhonghua Xin Xue Guan Bing Za Zhi*. 44(10):854–861. <https://doi.org/10.3760/cma.j.issn.0253-3758.2016.10.006>
- Buja LM, Weerasinghe P (2010) Unresolved issues in myocardial reperfusion injury. *Cardiovasc Pathol Off J Soc Cardiovasc Pathol*. 19(1):29–35. <https://doi.org/10.1016/j.carpath.2008.10.001>
- Pourmoghadam KK, Ruzmetov M, O'Brien MC, Piggott KD, Plancher G, Narasimhulu SS et al (2017) Comparing Del Nido and conventional cardioplegia in infants and neonates in congenital heart surgery. *Ann Thorac Surg*. 103(5):1550–1556. <https://doi.org/10.1016/j.athoracsur.2016.10.070>
- O'Brien JD, Howlett SE, Burton HJ, O'Blenes SB, Litz DS, Friesen CLH (2009) Pediatric cardioplegia strategy results in enhanced calcium metabolism and lower serum troponin T. *Ann Thorac Surg*. 87(5):1517–1523. <https://doi.org/10.1016/j.athoracsur.2009.02.067>
- Pragliola C, Hassan E, Ismail H, Al Otaibi K, Alfonso JJ, Algarni KD (2020) Del Nido cardioplegia in adult patients: a propensity-matched study of 102 consecutive patients. *Heart Lung Circ*. 29(9):1405–1411. <https://doi.org/10.1016/j.hlc.2019.08.019>
- Algarni KD (2020) Routine use of Del Nido cardioplegia compared with blood cardioplegia in all types of adult cardiac surgery procedures. *J Card Surg*. <https://doi.org/10.1111/jocs.15060>
- Yerebakan H, Sorabella RA, Najjar M, Castillero E, Mongero L, Beck J et al (2014) Del Nido cardioplegia can be safely administered in high-risk coronary artery bypass grafting surgery after acute myocardial infarction: a propensity matched comparison. *J Cardiothorac Surg*. 9(141):10.1186/s13019-014-0141-5
- Lazar HL (2018) Del Nido cardioplegia: passing fad or here to stay? *J Thorac Cardiovasc Surg*. 155(3):1009–1010. <https://doi.org/10.1016/j.jtcvs.2017.09.126>
- Matte GS, Del Nido PJ (2012) History and use of Del Nido cardioplegia solution at Boston Children's Hospital. *J Extra Corpor Technol*. 44(3):98–103 PMID: PMC4557532
- Timek T, Willekes C, Hulme O, Himelhoch B, Nadeau D, Borgman A et al (2016) Propensity matched analysis of Del Nido cardioplegia in adult coronary artery bypass grafting: initial experience with 100 consecutive patients. *Ann Thorac Surg*. 101(6):2237–2241. <https://doi.org/10.1016/j.athoracsur.2015.12.058>
- Kim WK, Kim HR, Kim JB, Jung S-H, Choo SJ, Chung CH et al (2018) Del Nido cardioplegia in adult cardiac surgery: beyond single-valve surgery. *Interact Cardiovasc Thorac Surg*. 27(1):81–87. <https://doi.org/10.1093/icvts/ivy028>
- Siddiqi S, Blackstone EH, Bakaeen FG (2018) Bretschneider and Del Nido solutions: are they safe for coronary artery bypass grafting? If so, how should we use them? *J Card Surg*. 33(5):229–234. <https://doi.org/10.1111/jocs.13539>
- Spellman J (2019) Pro: In favor of more generalized use of Del Nido cardioplegia in adult patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth*. 33(6):1785–1790. <https://doi.org/10.1053/j.jvca.2018.01.041>
- Marzouk M, Lafreniere-Bessi V, Dionne S, Simard S, Pigeon C, Dagenais F et al (2020) Transitioning to Del Nido cardioplegia for all-comers: the next switching gear? *BMC Cardiovasc Disord*. 20(1):215. <https://doi.org/10.1186/s12872-020-01506-0>
- Timek TA, Beute T, Robinson JA, Zalizadeh D, Mater R, Parker JL et al (2020) Del Nido cardioplegia in isolated adult coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 160(6):1479–1485.e5. <https://doi.org/10.1016/j.jtcvs.2019.09.027>
- Ad N, Holmes SD, Massimiano PS, Rongione AJ, Fornaresio LM, Fitzgerald D (2018) The use of Del Nido cardioplegia in adult cardiac surgery: a prospective randomized trial. *J Thorac Cardiovasc Surg*. 155(3):1011–1018. <https://doi.org/10.1016/j.jtcvs.2017.09.146>

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