ORIGINAL ARTICLE

Del Nido cardioplegia as a safe and effective method of myocardial protection in adult patients undergoing cardiac surgery: a single-center experience

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KEY WORDS
cardiac surgery, del Nido cardioplegia, myocardial protection

ABSTRACT

BACKGROUND Del Nido (DN) cardioplegia is increasingly popular in adult cardiac surgery. It allegedly allows for up to 90 minutes of safe myocardial ischemia with a single dose.

AIMS We aimed to evaluate the benefits of DN cardioplegia.

METHODS Of the 2108 patients undergoing coronary or heart valve surgery with the use of cardiopulmonary bypass (CPB) between January 1, 2016, and September 30, 2017, 1236 (59%) received DN and 872 (41%) received cold blood cardioplegia. We retrospectively analyzed the collected data of all consecutive on--pump patients to assess early mortality and postoperative troponin T release. A multivariable analysis of both outcomes adjusted for propensity to receive DN cardioplegia was performed.

RESULTS Patients protected with DN cardioplegia had longer CPB and aortic cross-clamp times (P <0.001) but received fewer doses of cardioplegia. Median postoperative troponin T levels were higher in the DN-cardioplegia than CB-cardioplegia group: 0.324 ng/ml (interquartile range [IQR], 0.210–0.559 ng/ml) vs 0.285 ng/ml (IQR, 0.191–0.496 ng/ml); P = 0.01. However, when adjusted for the cross-clamp time, propensity to receive DN cardioplegia, and other factors, DN cardioplegia was associated with lower postoperative troponin T levels. Early mortality rates did not differ between DN and CB cardioplegia (3.6% vs 3%; P = 0.54).

CONCLUSIONS Del Nido cardioplegia is a safe and effective method of myocardial protection in adults. It allows for a longer redosing interval with a safety profile and mortality comparable to those for CB cardioplegia, as shown by lower troponin T release when corrected for the time of myocardial ischemia.

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Received: June 21, 2019.
Revision accepted: September 5, 2019.
Published online: September 5, 2019.
Kardiol Pol. 2019; 77 (11): 1040-1046
doi:10.33963/KP.14964

INTRODUCTION Recently, del Nido (DN) cardioplegia has gained increasing popularity in adult cardiac surgery. This solution was formulated by researchers from Pittsburgh University in the early 1990s.[1] It was primarily used in neonatal and pediatric cardiac surgery and has been in common use for almost 20 years.[2] Del Nido cardioplegia contains a calcium-free, potassium--rich base solution of PlasmaLyte A (Baxter Polska, Warsaw, Poland) and an electrolyte composition similar to extracellular fluid. It also contains lidocaine (a sodium channel blocker that inhibits the negative effects of hyperkalemic depolarization), mannitol (which reduces postischemic myocardial edema and scavenges free radicals), and other additives such as magnesium sulfate or potassium chloride. These constituents serve as a crystalloid component, which is mixed with fully oxygenated whole blood of the patient in a ratio of 4 parts of crystalloid to 1 part of blood. Del Nido cardioplegia is administrated as a single dose with the effect that lasts up to 90 minutes.

Cold blood (CB) cardioplegia has long been the standard solution for cardiac arrest in adult

WHAT'S NEW?

In this paper, we report that del Nido cardioplegia is an equally safe and effective method of myocardial protection in adult cardiac surgery as cold blood (CB) cardioplegia. Moreover, del Nido cardioplegia allows for a longer redosing interval and thus an uninterrupted flow of surgery.

cardiac surgery. After an induction dose is given to arrest the heart, additional doses are ordered every 20 to 30 minutes. During an average procedure, multiple doses are given, which may interrupt the flow of the surgery.

A recent meta-analysis has demonstrated significant advantages of DN cardioplegia over CB solution in adults in terms of several parameters.[3] It has been reported that DN cardioplegia is effective and safe in adult patients undergoing isolated mitral and aortic valve surgery.[4] Moreover, it can be an alternative to CB solution in concomitant aortic valve replacement and coronary artery bypass grafting (CABG).

In our department, DN cardioplegia was first used in May 2016 and is now used in more than 80% of cases. We designed this study to evaluate the efficacy and safety of DN cardioplegia and to verify its perceived benefits. Therefore, we compared the clinical outcomes and postoperative troponin T release between patients who received either DN or CB cardioplegia.

METHODS Patient population, study design, and surgical procedures A total of 2108 patients who underwent coronary or heart valve surgery under cardioplegic arrest between January 1, 2016, and September 30, 2017, were identified in the Institutional Cardiac Surgical Database of Leszek Giec Upper-Silesian Medical Centre of the Medical University of Silesia (Katowice, Poland). They were divided into 2 cohorts based on the type of cardioplegia administered during surgery (FIGURES 1 and 2). Del Nido cardioplegia was used in 1236 patients, and CB cardioplegia, in 872. The adequacy of myocardial protection during cardiac arrest was assessed by the measurement of postoperative high-sensitive cardiac troponin T levels using the electrochemiluminescence immunoassay (Roche Diagnostics International Ltd., Rotkreuz, Switzerland). Demographic and clinical outcome data were prospectively collected in our department's database. They included patients' age, sex, body mass index, and comorbidities such as hypertension, renal failure, diabetes, and others. The preoperative clinical status was documented, including the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) score for the risk of mortality, New York Heart Association (NYHA) functional class, and requirement for intra-aortic balloon pump (IABP) before surgery. The intra- and postoperative data collected for the 2 cohorts included cardiopulmonary bypass (CPB) time, aortic cross-clamp time (ACC), the number of cardioplegia doses, and early mortality. Patients with aortic aneurysm were excluded. The primary outcome was the troponin T level on the first morning post-surgery. The secondary outcome was in-hospital mortality.

All surgical procedures were performed using a standard general anesthesia protocol, median sternotomy approach, and CPB with mild hypothermia. Cardiac arrest was achieved with either DN or CB cardioplegia. Postoperative in-hospital complications included need for IABP, myocardial infarction (MI), reoperation, and death.

Statistical analysis Continuous variables were presented as mean (SD) or medians and interquartile range and were compared using the *t* test or the Mann–Whitney test depending on distribution. Categorical variables were reported as frequency and percentage and compared using the χ^2 test. The multivariable

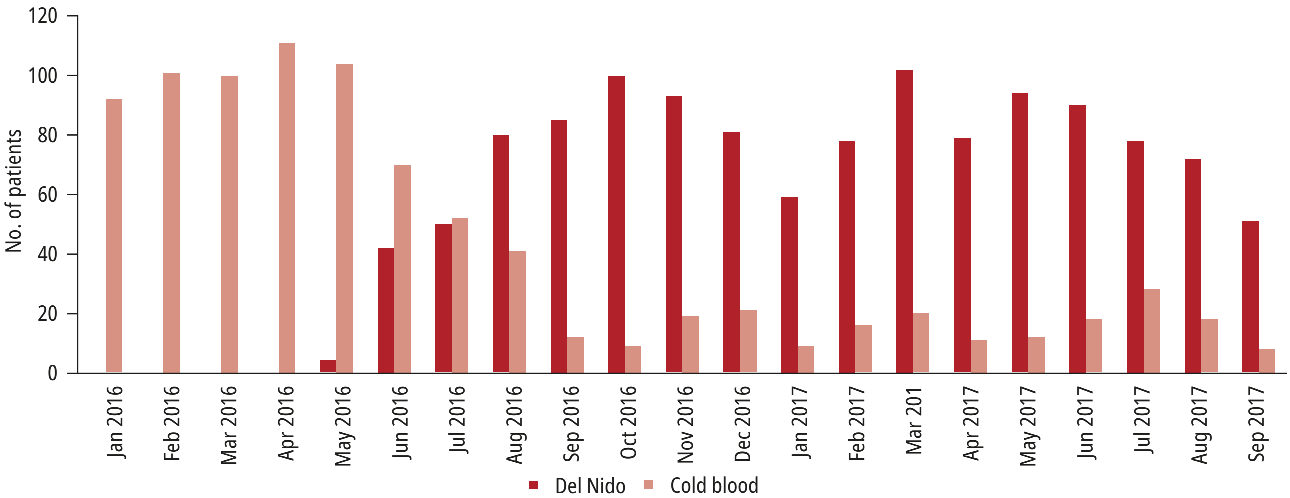

FIGURE 1 Use of del Nido and cold blood cardioplegia during the study

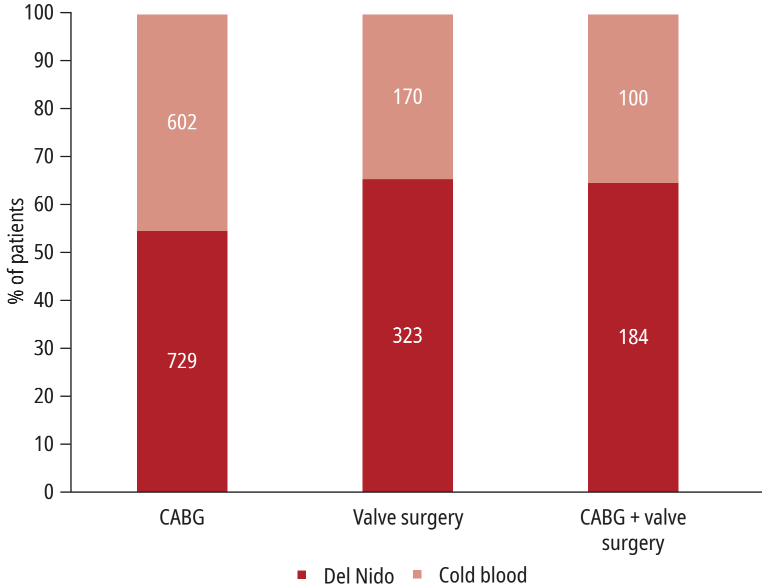

FIGURE 2 Type of surgery depending on the type of cardioplegia (P <0.001). Values on the bars are absolute numbers of patients.

Abbreviations: CABG, coronary artery bypass grafting

logistic regression was adjusted for the propensity score for DN cardioplegia. The variables used to estimate the propensity score were age, sex, preoperative troponin T levels, EuroSCORE II, date of surgery, estimated glomerular filtration rate, ejection fraction, single or multiple valve surgery, number of operated valves, coronary artery surgery, IABP before surgery, Canadian Cardiovascular Society class, NYHA class, acute MI, previous MI, percutaneous coronary intervention in the past, pulmonary hypertension, diabetes mellitus, and operating surgeon. The multivariable analysis of the predictors of postoperative troponin T levels and mortality was performed using a linear and logistic regression, respectively. The conditional forward method of selecting the variables was used. The propensity score and the use of DN cardioplegia were forced into the model. Troponin T values were log-transformed for the analysis because of their skewed distribution. All other log-normally distributed data, including ACC and CPB times, were log-transformed. A P value of 0.05 or lower was considered significant. The data were analyzed using the SPSS Statistics version 22 software (IBM, Armonk, New York, United States).

RESULTS Baseline and preoperative characteristics are presented in TABLE 1. The study included 2108 patients: 1236 in the DN-cardioplegia group and 872 in the CB-cardioplegia group. The distribution of the surgery types (CABG, valve, or combined) depending on the type of cardioplegia is presented in FIGURE 2. There were no differences in the patient age, preoperative troponin T levels, and the EuroSCORE II between cardioplegia groups (TABLE 1).

Intra- and postoperative data Patients who received DN cardioplegia had longer CPB and ACC times (TABLE 2). Del Nido cardioplegia was replenished less often than CB cardioplegia. A single dose of cardioplegia was more common in the DN group than in the CB group (P <0.001) (TABLE 2). In the DN-cardioplegia group, 99 patients (8%) required intraoperative IABP counterpulsation in comparison with 61 patients (7%) in the other group.

Our primary endpoint was the postoperative troponin T level. It was higher in patients receiving DN cardioplegia than in those receiving CB cardioplegia (TABLE 3). However, after multivariable adjustment, the multiple linear regression model showed that the use of DN cardioplegia was associated with lower postoperative troponin T levels (TABLE 4). The ACC time and preoperative troponin T levels were the main factors affecting the postoperative troponin T level.

The early mortality rate was 3.6% (44 of the 1236 patients) in the DN-cardioplegia group and 3% (26 of the 872 patients) in the CB-cardioplegia group (P = 0.54). We did not observe a significant effect of DN cardioplegia on mortality in the multivariable analysis adjusted for propensity to DN cardioplegia (TABLE 5).

DISCUSSION Myocardial protection is a crucial consideration during heart surgery. Currently, several cardioplegia solutions are available. However, there is no consensus regarding the optimal composition or the best technique.[5] Originally designed for an immature child's heart, the DN solution has offered an alternative myocardial protection.[6] Its use in adult cardiac surgery has only recently been described.[4,6-8] The present study compared the efficacy and safety of DN and CB cardioplegia in the largest group of patients described so far.

Recent studies have reported that the use of DN solution has several benefits. Most notably, it provides myocardial protection for long periods (>90 minutes) with a single-dose infusion.[1,7,9] A single dose of DN cardioplegia was administered in over 90% of our patients, while the rates reported in studies on adults from different centers range from 40% to 84%.[6,7] Del Nido cardioplegia allows for longer redosing intervals while providing comparable myocardial protection to CB. There is no consensus as to the best timing for repeat doses of DN cardioplegia. In the majority of cardiac surgeries, a single application should be sufficient.[10] Importantly, less frequent dosing allows an uninterrupted surgery.

TABLE 1 Baseline characteristics of the study groups (n = 2108)

Parameter		Del Nido cardioplegia (n = 1236)	Cold blood cardioplegia (n = 872)	*P* value
Age, y		66.6 (61.2–72.3)	66.2 (61–72.7)	0.29
Male sex, n (%)		861 (69.7)	652 (74.8)	0.01
Height, cm		170 (163–175)	170 (164–176)	0.21
Weight, kg		80 (70–90)	80 (70–90)	0.57
BMI, kg/m^2		23.6 (21.2–26)	23.5 (21.1–26.3)	0.92
CCS, n (%)	I	329 (28.9)	243 (29.6)	0.02
	II	574 (50.4)	374 (45.6)	
	III	165 (14.5)	127 (15.5)	
	IV	71 (6.2)	76 (9.3)	
NYHA, n (%)	I	212 (17.2)	168 (19.3)	0.66
	II	811 (65.6)	560 (64.2)	
	III	197 (15.9)	134 (15.4)	
	IV	16 (1.3)	10 (1.1)	
LVEF, %		55 (45–58)	50 (44–55)	0.004
SPAP, mm Hg		30 (30–30)	30 (30–30)	0.82
Diabetes status, n (%)	Diabetes mellitus	381 (30.8)	286 (32.8)	0.61
	Insulin-dependent	156 (12.6)	114 (13.1)	
	Oral antidiabetic drugs	225 (18.2)	172 (19.7)	
Preoperative troponin T, µg/ml		0.014 (0.009–0.03)	0.015 (0.01–0.04)	0.07
eGFR, ml/min/1.73 m^2		73.9 (60.2–86.7)	74 (60.1–87.6)	0.41
EuroSCORE II		1.68 (1.06–2.8)	1.79 (1.1–3.13)	0.59
Previous MI, n (%)		219 (17.7)	216 (24.8)	<0.001
Previous PCI, n (%)		274 (22.2)	200 (22.9)	0.71

Data are presented as median and interquartile range unless otherwise indicated.

Abbreviations: BMI, body mass index; CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SPAP, systolic pulmonary artery pressure

The ACC and CPB times were longer in patients undergoing surgery with DN cardioplegia, which is in contrast to previously published trials.[10,11] This was expected due to the inclusion of longer surgeries (valve and combined operations) in our trial, most of which were performed with DN cardioplegia. Compared with CB cardioplegia, patients receiving DN cardioplegia demonstrated higher postoperative troponin T levels, likely as a result of longer ACC and CPB times. In the multiple linear regression model, the ACC time proved to be the strongest predictor of postoperative troponin T levels. After adjustment for the ACC time, preoperative troponin T levels, and other factors, the multivariable analysis showed that DN cardioplegia slightly but significantly decreased postoperative troponin T levels.

In 2017, Trzeciak et al[12] reported data based on a multicenter registry of cardiac surgery procedures in Poland, KROK (Krajowy Rejestr Operacji Kardiochirurgicznych). They revealed lower in-hospital mortality than in our study. This may be explained by the fact that their report involved only patients who had isolated CABG surgery, while we also included patients undergoing single or multiple valve surgery as well as combined CABG and valve surgery. The logistic regression model showed that valve surgery significantly increased early postoperative mortality (TABLE 5).

Del Nido cardioplegia contains lidocaine (sodium channel blocker) and magnesium sulfate (calcium channel blocker), which decrease intracellular calcium concentrations, cellular metabolism, energy consumption, and myocardial excitability.[13,14] O'Blenes et al[15] reported that the use of DN solution prevented spontaneous calcium-induced hypercontraction during cardiac arrest, reduced troponin release, and provided superior myocardial protection in isolated

TABLE 2 Selected intraoperative data

Parameter		Del Nido cardioplegia (n = 1236)	Cold blood cardioplegia (n = 872)	*P* value
ACC time, min		40 (29–59)	33 (24–47)	<0.001
CPB time, min		65 (50–85)	55 (42–72)	<0.001
Type of surgery, n (%)	CABG	729 (59)	602 (69)	<0.001
	Valve	323 (26.1)	170 (19.5)	
	CABG + valve	184 (14.9)	100 (11.5)	
No. of valves operated, n (%)	0	729 (59)	602 (69)	<0.001
	1	406 (33)	217 (25)	
	2	92 (7)	49 (6)	
	3	9 (1)	4 (1)	
Type of valve operated, n (%)	Mitral	214 (17.3)	99 (11.4)	<0.001
	Tricuspid	63 (5.1)	40 (4.6)	0.61
	Aortic	339 (27.4)	188 (21.6)	0.002
No. of grafts, n (%)	0	323 (26.1)	170 (19.5)	0.008
	1	79 (6.4)	52 (6)	
	2	485 (39.2)	387 (44.4)	
	3	332 (26.9)	252 (28.9)	
	4	17 (1.4)	11 (1.2)	
No. of cardioplegia doses, n (%)	1	1086 (93.1)	384 (46.6)	<0.001
	2	71 (6.1)	327 (39.6)	
	3	9 (0.8)	106 (12.8)	
	4	–	6 (0.7)	
	5	–	2 (0.2)	
	6	–	1 (0.1)	

Data are presented as median and interquartile range unless otherwise indicated.

Abbreviations: ACC, aortic cross-clamp; CPB, cardiopulmonary bypass; others, see FIGURE 2

TABLE 3 Postoperative outcomes

Endpoints	Del Nido cardioplegia (n = 1236)	Cold blood cardioplegia (n = 872)	*P* value
Postoperative troponin T, ng/ml	0.324 (0.21–0.559)	0.285 (0.191–0.496)	0.01
Mortality, n (%)	44 (3.6)	26 (3)	0.54

Data are presented as median and interquartile range unless otherwise indicated.

cardiomyocytes in an aged rat model. Later, they also reported that a single dose of DN cardioplegia was associated with superior calcium handling of cardiomyocytes, reduced myocardial injury, and enhanced functional recovery.[16] These advantages of DN cardioplegia might facilitate myocardial protection during adult cardiac surgery. However, our findings must be confirmed in multicenter randomized trials comparing different solutions in diverse cardiac procedures.

In the literature, various modifications of DN solutions have been described. The proportions of the base solution components differ depending on clinical practice in a given center. However, the blood-to-base ratio remains constant, ie, 1:4.

Literature data concerning DN cardioplegia are inconsistent. However, the initial experience has shown that it is safe in coronary surgery as well as isolated or combined valve surgery.[11] The use of DN cardioplegia in coronary surgery has been addressed in several studies. Guajardo Salinas et al[17] compared DN (134 patients) and CB solution (230 patients). The groups demonstrated

TABLE 4 Propensity score–adjusted linear regression model for postoperative troponin T level

Parameter	B	95% CI	*P* value
Constant	0.44	0.07–0.82	0.02
Log (ACC)	0.51	0.45–0.58	<0.001
Log (preoperative troponin T)	0.12	0.1–0.15	<0.001
Log (creatinine)	0.42	0.3–0.55	<0.001
Height	–0.01	–0.01 to –0.004	<0.001
Valve surgery	0.16	0.21–0.1	<0.001
Preoperative IABP	0.19	0.3–0.09	<0.001
AMI (1st day)	0.25	0.39–0.11	<0.001
CABG	0.04	0.08–0.01	0.01
Log (EuroSCORE II)	0.06	0.01–0.11	0.01
Propensity to del Nido	0.07	0.01–0.12	0.02
BMI	–0.003	–0.01 to –0.001	0.02
Del Nido cardioplegia	–0.04	–0.001 to –0.08	0.05

Abbreviations: AMI, acute myocardial infarction; B, unstandardized regression coefficient; IABP, intra-aortic balloon pump; others, see FIGURE 2, TABLE 1, and TABLE 2

TABLE 5 Propensity score–adjusted logistic regression model for early postoperative mortality

Parameter	B	95% CI	*P* value
Constant	–4.15	–	<0.001
Log (preoperative troponin T)	0.6	1.13–2.95	0.02
Log (EuroSCORE II)	2.06	3.73–16.58	<0.001
Valve surgery	0.74	1.17–3.79	0.01
Propensity to del Nido	0.72	0.71–5.92	0.18
Del Nido cardioplegia	–0.27	0.35–1.65	0.49
Time from AMI			0.01
AMI (<1st week)	0.16	0.49–2.83	0.72
AMI (2nd–3rd week)	1.3	1.6–8.49	0.002
AMI (>3rd week)	–0.48	0.14–2.68	0.52

Abbreviations: see TABLES 1 and 4

similar intra- and postoperative parameters except for the mean cardioplegia volume, number of doses, and defibrillation after cross-clamp removal. Yerebakan et al[6] reported the safety of DN cardioplegia in high-risk CABG surgery after acute MI. An equivalent efficacy of DN solution was previously reported by Timek et al,[18] who showed the results for 100 propensity-matched patients after CABG. Regarding the use of DN cardioplegia in mitral valve surgery, Yammiine et al[13] compared DN and CB solution in 79 patients with similar clinical profiles. Aortic valve procedures were also studied by Sorabella et al.[8] They compared the use of DN (52 patients) vs CB (65 patients) cardioplegia in isolated aortic valve surgery. A recent meta-analysis including 9 studies demonstrated the effect of DN cardioplegia in 1501 patients (4 studies concerned isolated valve surgery; 3, CABG procedures; and 2, valve or CABG surgeries). The meta-analysis showed shorter CPB and ACC times with the use of DN solution. Additionally, the use of DN cardioplegia was associated with lower creatine kinase-MB and troponin levels, which are sensitive biomarkers of cardiac injury.

Finally, DN cardioplegia has been applied in mini-invasive procedures, such as minimally invasive aortic valve replacement through a J-ministernotomy,[19] and in the case of confined access to the aorta.

Limitations Our study is limited by the retrospective and observational design. Moreover, the assessment of cases treated at a single center might hamper the ability to generalize the results. Another limitation is the possibility of surgical preference bias with numerous surgeons included in the study. Nonetheless, our surgical techniques and postoperative management remained similar during the study. Finally, there was no long-term follow-up. Therefore, long-term prospective studies should be designed to confirm our findings.

Conclusions Our results showed that DN cardioplegia is as effective and safe as CB cardioplegia. The advantage of DN solution is a lower risk of surgical interruption. It allows for a longer redosing interval with a safety profile and mortality comparable to those observed for CB solution. Further research is needed to establish indications for the optimal use of DN cardioplegia.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The study was supported by statutory funds of the Medical University of Silesia (KNW-1-014/N/8/K and KNW-1-182/N/6/K; to MAD).

CONFLICT OF INTEREST None declared.

HOW TO CITE Kuciński J, Górska A, Deja MA. Del Nido cardioplegia as a safe and effective method of myocardial protection in adult patients undergoing cardiac surgery: a single-center experience. Kardiol Pol. 2019; 77: 1040-1046. doi:10.33963/KP.14964

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