Routine use of del Nido Cardioplegia compared to blood cardioplegia in all types of adult cardiac surgery procedures

Khaled Algarni[1]

[1]King Saud University

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Abstract

Background and aim of the study: Several studies reported safety and potential benefits of single dose Del Nido cardioplegia (DNC) in selected Adult Cardiac Surgery (ACS) procedures. However, studies are scarce on routine use of DNC in more complex procedures and patients with high risk profile. We sought to compare DNC with cold blood cardioplegia (BC) in all types of ACS including complex procedures. Methods: Data for 305 consecutive unselected patients who underwent ACS procedures (July/2017 to Nov/2019) were included. DNC was routinely used whenever is available (n=231) and if not available, cold BC is used (n=74). All categories of ACS procedures (primary or redo) were included. Repeated measures analysis was performed to compare baseline, peak and trough Troponins levels in both groups. Linear regression analysis was used to identify independent predictors of peak Troponins level. Results: The two groups were comparable in baseline characteristics including euro score (ES II), risk profile and surgical complexity. DNC was associated with lower cardiopulmonary bypass (CPB) and cross clamp times, cardioplegia volume and number of cardioplegia doses (P<.001). Importantly, DNC was associated with lower postoperative Troponin level (P=.001), shorter duration of inotropic support (P=.02) and shorter intensive care unit stay (P=.04). On linear regression analysis, DNC was an independent predictor of lower postoperative peak Troponin (t = -3.5, P<.001). Conclusions: Routine use of DNC in all types of ACS procedures compared to BC was associated with significantly shorter CPB and clamp times, significantly lower post-operative troponin release and shorter duration of inotropic support.

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Introduction

Conventional blood cardioplegia is given intermittently every 15-20 min. Therefore, several doses of cardioplegia are usually required and the number of cardioplegia doses rises with increasing complexity of the procedure. A novel single dose blood cardioplegia that can provide an extended period of safe myocardial ischemic arrest was developed by Matte and del Nido and was initially employed in pediatric cardiac surgery.[1] Presently, del Nido Cardioplegia (DNC) is routinely used in pediatric cardiac surgery with excellent outcomes[2-4]

Several studies confirmed the safety of DNC in selected adult cardiac surgery procedures.[5-13] However, these studies included mostly selected and relatively simple adult cardiac surgery procedures such as first time CABG or single valve surgery. Indeed, studies on routine use of DNC for all categories of adult cardiac surgery including more complex procedures with intermediate or high risk profile patients are limited.[14, 15]

Our purpose was to bridge this gap in knowledge by comparing routine use of DNC with conventional multi-dose BC in all categories of adult cardiac surgery procedures with a wide range of procedure's complexity and patient's risk profile. Our hypothesis was that DNC is potentially safe in all comers.

Materials and Methods

Data collection, design and study outcomes

This is a retrospective observational study. Clinical, operative and outcome data were collected prospectively in a computerized database and all consecutive patients (July/2017-November/2019) undergoing open cardiac surgery procedures by one surgeon (KDA) were selected from the database and included in this study (N=305). Procedures included: isolated coronary artery bypass grafting (CABG); isolated single, double, and triple valve surgery; combined CABG and valve(s) procedures as well as other procedures such as aortic dissection, aortic root replacement and surgery for mechanical complications of myocardial infarction. Both first time and redo procedures (including multiple redo procedures) were included. The only pump procedures that were excluded are: heart transplantations.

Our purpose is to compare short term clinical outcomes between cold blood cardioplegia (BC) and DNC in a wide range of adult cardiac surgery procedures, both low and high risks. The study was approved by our institutional research ethics board and individual's consent for study was waived. The DNC was adopted as a routine cardioplegia for all adult cardiac surgery procedures in our center in July/ 2017 and was used preferentially whenever is available. If DNC was not available due to supply shortage, our conventional multidose cold BC is used.

The primary outcome was hospital mortality which was defined as any postoperative death in hospital. Secondary postoperative outcomes included: Stroke, requirement for extracorporeal membrane oxygenation (ECMO), troponin levels, aortic cross clamp and cardiopulmonary (CPB) bypass times and cardioplegia volume and number of cardioplegia doses.

Cardioplegia, anaesthetics and operative management

In July/2017 we started using DNC and due to perceived advantage in terms of shorter cross clamp and CPB times and improved surgical workflow of the procedure along with the increasing evidence for its safety and advantages in adult cardiac surgery arena, we adopted it for routine use in all adult cardiac surgery procedures whenever is available. If DNC was out of stock, we used our usual multi-dose undiluted cold BC. Between July/2017 and November/2019, 305 consecutive patients were included in this study. DNC was used in 231 patients and cold BC was used in 74 patients.

Because we shifted completely to use of DNC in all cases whenever is available, there are fewer patients in the blood cardioplegia group. The components of both DNC and cold BC are detailed in **Supplemental Table S1.**

With the exception of the cardioplegia type, techniques for myocardial protection, cooling, cardiopulmonary bypass, and surgical techniques were similar between the two groups which were all performed by a single surgeon (KDA). All patients in both groups received antegrade cardioplegia (in the root or directly in coronary ostia in patients with significant aortic regurgitation). Topical ice slush was used liberally in all cases. Details of the cardioplegic technique, anesthetics and operative management are provided in the S**upplement** .

High Sensitivity Troponin T measurement (ng/ml)

To evaluate myocardial injury, data on high sensitivity troponin T were retrospectively collected on all patients. Missing data were low (<5% for both groups, n= 11 for DNC and n=4 for BC). Baseline troponin was defined as the latest available troponin value before surgery. Postoperatively, as part of the intensive care unit protocol, all adult cardiac surgery patients have their troponin levels measured routinely upon arrival to the ICU. Troponin T levels are measured 8 hourly for 24 hours and then 12 hourly for 24 hours. Thereafter, it is measured at the discretion of the treating physician if a myocardial ischemia is suspected. After 24 hours, the measurements of the Troponin levels were not consistent. Therefore, for completion of data, we relied on the Troponin levels that were measured in the first 24 hours after surgery. We defined peak troponin as the highest value of Troponin T in the first 24 hours after surgery and trough troponin was defined as the lowest value in the first 48 hours after the peak value. In the present study, 97.4 % (n=297) had a peak troponin value in the first 24 hours after surgery.

Statistical analysis

Statistical analyses were performed with SPSS version 25. The two groups were compared for statistical significance based on Chi Square or Fisher exact test for categorical variables which are expressed as percentages. All continuous variables were explored for normality using normality diagnostics. Student's t-test was used to analyze continuous variables that were normally distributed, and the Mann-Whitney U test was used for variables that had non-normal distributions. Continuous variables were expressed as means $\pm$ standard deviations and/or median with 25^{th} and 75^{th} percentile as appropriate. Statistical significance was based on a two-tailed P value of less than 0.05. Details for the repeated measures analysis and linear regression are provided in the **Supplement.**

Results

Demographics and baseline clinical profile

The two groups were comparable in baseline characteristics. In particular, the two groups were comparable in risk profile, euro score and procedure type and complexity. Isolated valve procedures (single, double and triple valves) were the most frequently performed procedures (n=151, 50%) followed by isolated CABG (n=101, 33%), combined CABG and valve(s) procedures (n=35, 12%) and other procedures (n= 12, 5%). Details of patients' baseline characteristics are presented in

Table 1.

Operative profile and postoperative outcomes

Hospital mortality was comparable (n= 1, 1.4% and n=1, 0.4%, P=.43) in BC and DNC groups respectively. Similarly, postoperative complications including myocardial infarction, stroke, ECMO, and infections were not significantly different between the two groups. However, the duration of CPB (178 $\pm$ 60 vs. 150 $\pm$ 51, P<0.001) and cross clamp (143 $\pm$ 60 vs. 118 $\pm$ 42, P<0.001) were significantly lower in the DNC group. Likewise, the volume of cardioplegia and the number cardioplegia doses were significantly lower in the DNC group. Operative and postoperative profiles are detailed in **Table 2** .

The duration of inotropic support was significantly lower in the DNC group, dobutamine (26.6 $\pm$ 19.3 vs. 21 $\pm$ 13.3, P=.02) and norepinephrine (12 (3-29) vs. 7 (2-20), P=.02) in BC and DNC, respectively (**Supplemental Table S2**).

Postoperative Troponin T Level

Postoperative Troponin T levels (ng/ml) increased significantly in BC group compared to DNC ($F = 14.3$; $P < .001$). Furthermore, the repeated measures analysis was adjusted for age and cross clamp time (**Figure 1**). Age was not associated with postoperative troponin levels ($F = 0.39$, $P = 0.5$) while the cross clamp time did ($F = 10.8$, $P = 0.001$).

Independent predictors of postoperative peak Troponin T level

The independent predictors of postoperative peak Troponin T level were: DNC ($t = -3.5$, $P < .001$); Cross clamp time ($t = 3.9$, $P < .001$) and Baseline troponin level ($t = 3.6$, $P < .001$). The linear regression multivariable model F and RS was 12.8 and .21, respectively (**Table 3)** .

Troponin T Levels stratified by surgical procedure, risk profile and cross-clamp time

Trends of troponin levels at the three time points were analyzed in patients who underwent CABG vs. Non-CABG patients. Similar trends were found with significantly lower troponin levels with DNC in patients underwent isolated CABG ($P = .018$), All CABG group ($P = .004$) and Non-CABG group ($P = .001$) **Supplemental Table S3** , **Figure S1, Figure S2 and Figure S3** . Likewise, in higher risk group patients, DNC was associated with significantly lower troponin levels ($P = .001$) as well as lower CPB (P =.01) and cross-clamp times ($P = .02$),**Supplemental Table S3 and Figure S4** .

The trend of lower troponin levels was examined based on ischemia time. Similar trends of significant lower troponins level with DNC were found in patients with aortic cross-clamp time more than 120 minutes (P

=.001). Details are included in the **Supplement Figure S5, Figure S6,** and **Supplemental Table S4 and Table S5.**

Conclusions

In the present study, both types of cardioplegia were similar in mortality and major postoperative complications. However, DNC was associated with significantly shorter CPB and aortic cross clamp times. Importantly, DNC was also independently associated with lower levels of postoperative Troponin release which may indicate less myocardial injury. Moreover, the duration of inotropic support and ICU stay were significantly lower in the DNC group (Graphical summary is depicted in**Figure 2**).

DNC seems to reduce postoperative troponin release which may indicates less myocardial damage. This is perhaps related to one or more components of the solution. The DNC has an electrolyte composition that mimics extracellular fluids with addition of potassium chloride, sodium bicarbonate, mannitol, magnesium sulphate and lidocaine.[1] Lidocaine act as a sodium channel blocker and magnesium act as a calcium competing agent which results in reduction of intracellular calcium level. As such, myocardial excitability, cellular metabolism, and energy consumption are reduced.[2,16] This is one potential explanation for the extended period of myocardial protection with the DNC and perhaps the reduced myocardial injury as indicated by significantly lower Troponin leak in the present study which was independent of aortic cross clamp time.

Additionally, DNC may have a better distribution throughout the coronary bed due to the vasodilatory effect of Lidocaine.[17]This may provide more myocardial preservation and lessen myocyte injury. Furthermore, the shorter cross clamp time with DNC ($p < .0001$) is potentially another factor that may have contributed to lower postoperative troponin levels in the DNC group. Indeed, Erkut et al. found a direct and linear relationship between aortic cross clamp duration and postoperative Troponin levels in patients undergoing isolated CABG.[18]

Nonetheless, the lower level of postoperative troponin in our study was independent of the aortic cross clamp time. In addition, since all procedures were performed by a single surgeon, the potential confounding effect of differences in surgical and myocardial protection techniques is likely minimized. This include factors such as the degree of systemic hypothermia, use of topical ice, cardioplegia route, coronary surgery techniques among others which were similar between the groups in the present study. Therefore, the observed advantage of lower Troponin release with DNC in the present study is perhaps related to one or more components of the DNC solution itself.

The findings from our study, which included a wide range of simple and complex, low and high risk adult cardiac surgery procedures, are consistent with a recent randomized controlled trial (RCT) that included primarily low risk patients with first-time coronary artery bypass grafting and/or first-time single valve procedures. In this RCT, Ad and associates found several advantages with use of DNC which has led them to prematurely end the study after the data safety interim analyses. They found a higher return to spontaneous rhythm (97.7% vs 81.6%; $P = .023$) and fewer patients required inotropic support (65.1% vs 84.2%; $P = .050$), with the use of DNC. They also found a trend of lower Troponin levels with DNC which did not reach a statistical significance ($P= .04$). In their study, an alpha level of $P < .001$ was determined to be required for statistical significance because of the effect of early ending of study on alpha level.[12]

In another RCT which also included relatively low risk patients, Sanerta and coauthors randomized 150 patients who underwent isolated aortic valve replacement to DNC or cold blood cardioplegia. They also found a trend of lower Troponin values in the DNC that did not reach a statistical significance. Their study however was not powered to detect such a difference.[13]

Similarly, safety and potential advantages of DNC in adult cardiac surgery has been reported in several observational studies.[5-11] In a large systematic review and meta-analysis included more than 2000 patients (mostly isolated CABG and single valve procedures), An et al found no difference between DNC and BC in mortality or major morbidity. However, DNC reduced cardioplegia volume requirements ($P < 0.001$), aortic cross-clamp ($P < 0.001$), and CPB times ($P = 0.03$). Likewise, and similar to our findings, DNC was associated with reduced Troponin release (P = 0.001).[19]

In contrast to aforementioned studies that included mostly low risk and relatively simple adult cardiac surgery procedures. Reports on use of DNC for more complex procedures have been limited.[14,15] deLenoir and associates[20] compared DNC to blood cardioplegia in 283 patients undergoing complex aortic root procedures. Similar to our findings and findings of others, aortic cross-clamp and CPB times were shorter with DNC (P=0.006). Interestingly, in contrast to findings by us and others, they found a non-significant trend toward higher troponin T levels with DNC (P=0.07) and in patients with myocardial ischemia longer than 180 minutes, median CK-MB was higher in DNC group (75.1 (59.3-300) µg/L than in BCS 60.5 (16.5-116) µg/L (P=0.01). In view of findings by deLenoir and colleagues, we performed a post-hoc sub-group analyses to examine the trend in postoperative Troponin T levels in patients with ischemia time longer than 180 minutes (n= 32) and we found a trend of lower peak Troponin T level in the DNC group that did not reach a statistical significance with the limited sample size (1.5 ± .8 ng/ml vs. 1.8 ± .7 ng/ml, P = 0.2).

Similar to our findings, Hamad and associates [15]compared DNC to blood cardioplegia in patients undergoing combined CABG and aortic valve replacement and found that postoperative creatine kinase, MB isotype (P = 0.011) and troponin T levels \sout(P = 0.028) were significantly lower in the DNC group compared to BC. Additionally, our findings regarding lower Troponin T level is in line with findings from a recent important meta-analysis by Gambardella and associates.[21]

In conclusion, DNC was associated with significantly shorter CPB and cross clamp time, significantly lower post-operative troponin release and shorter duration of inotropic support and ICU length of stay. These benefits were observed for all categories of adult cardiac surgery including high risk procedures.

Limitations

This is an observational single center retrospective study which makes it susceptible to inherent selection and information biases. However, the prospective nature of the data collection and the very low rate of missing data add strength to the internal validity of the study. Likewise, since all procedures were performed by a single surgeon, bias from difference in surgical and myocardial protection techniques is minimized. Importantly, the findings from our study must be interpreted and compared to previous and future studies in the context of the large heterogeneity in cardioplegia practice with regard to composition, temperature, additives and adjuncts for myocardial protection. These factors are important confounders that must be evaluated when comparing different studies of cardioplegia. Finally, we reported only short-term outcomes and weather DNC is associated with any potential long-term benefits is unknown.

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Disclosures

None

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Table 1. Demographics and baseline clinical profile

Variable	**BC**
No. of patients	(74)

Age (y)	58 (
BSA	1.88
BMI	30.5
Female	37.8
Euro Score ES II	3.7
Diabetes mellitus	50 (
Hypertension (%)	58.3
Creatinine (mg/dl)	101
Operation Category	
Isolated CABG	35.1
Isolated Valve(s)* AVR(r) MVR(r) TVR(r) MVR(r) + TVR(r) AVR(r) + MVR(r) AVR(r)+MVR(r)+TVR(r) Other	48.6
Combined CABG + Valve(s)*	13.5
Others*	2.7
Preoperative MI (%)	5.5
Atrial Fibrillation (%)	24.7
Ejection Fraction	49.1
Redo surgery (first & multiple) (%)	6.8
Preoperative stroke (%)	4.1
Creatinine Clearance	95.4
Systolic PAP (mmHg)	43.3
Hemoglobin (mg/dl)	11.9
Hematocrit	0.38
Baseline hs-cTnT (ng/ml)	0.07

BC, Blood Cardioplegia; DNC, del Nido Cardioplegia; BSA, body surface area; BMI, body mass index; MI, myocardial infarction; LVEF, left ventricular ejection fraction; hs-cTnT, high sensitivity troponin T.* This includes single, double or triple valves repair and/or replacements. Others include aortic root replacement, ascending aorta or aortic arch interventions such as type A dissection repair, post-myocardial VSD closure and LV aneurysm repair among others.

Table 2. Operative profile and postoperative outcomes

Variable	**BC (n = 74)**	**DNC (n = 231)**	**P value**
Intraoperative Variables			
Duration of CPB (min)	178 ± 60	150 ± 51	<.001
Clamp time (min)	143 ± 60	118 ± 42	<.001
Cardioplegia volume (ml)	3348 ± 932	1458 ± 447	<.001
Number of cardioplegia doses	5.5 ± 2	1.8 ± .7	<.001
Postoperative Outcomes			
Operative mortality* (%)	1.4 (1)	.4 (1)	.43
Postoperative ECMO (%)	0 (0)	.9 (2)	.42
Perioperative MI (%)	5.4 (4)	2.6 (6)	.26
Stroke (%) Ischemic stroke Early stroke+	1.4 (1) 1.4 (1) 1.4 (1)	1.7 (4) 1.7 (4) .9 (2)	.82
IABP	4.1 (3)	3.9 (9)	.95

New atrial fibrillation	17.6 (13)	14.7 (34)	.56
PRBC transfusion	75.7 (56)	76.6 (177)	.87
FFP transfusion	68.9 (51)	67.5 (156)	.82
Platelets transfusion	73 (54)	68.4 (158)	.46
AKI requiring dialysis	2.7 (2)	1.7 (4)	.60
Deep Sternal infection	1.4 (1)	.9 (2)	.71
Ventilation time (hours)	12.5 (9.5-21)	11.7 (7-18)	.22
ICU length of stay (d)	4 (2-6)	3 (2-5)	.047
Hospital length of stay (d)	11 (7-19)	9 (7-14)	.10

*Operative mortality is defined as any in-hospital death.+Early stroke is defined as stroke that is diagnosed on awakening from anesthesia. Delayed is stroke that happens after normal wakening from anesthesia. BC, Blood cardioplegia; DNC, del Nido Cardioplegia; ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass; MI, myocardial infarction.

Table 3 : Predictors of Postoperative Peak Troponin T Level with Linear Regression

Univariable	**Univariable**	**Univariable**	**Univariable**	**Univariable**	**Univariable**	**Univariable**	**Univariable**	**Univariable**	**Multivariable**	**Multivariable**	**Multivariable**	**Multivariable**	**Multivariable**
Variable	RS	RS	F	β	t	P	P			RS	F	β	t
DNC	DNC	.048	14.7	-.22	-3.8	-3.8	<.001			.21	12.8	-.21	-3.5
Clamp	Clamp	.066	18.5	.26	4.3	4.3	<.001					.24	3.9
Time*	Time*	.07	20.1	.26	4.5 -.5	4.5 -.5	<.001					.22	3.6
B-	B-	.001	.25	-.029	1.1 -.5	1.1 -.5	.62						
Troponin*	Troponin*	.004	1.2	.06	-1 -.97	-1 -.97	.30						
Age*	Age*	.001	.27	-.03	1.5	1.5	.60						
Gen-	Gen-	.004	1.03	-.06	-.65	-.65	.31						
der	der	.003	.95	-.057	-.52	-.52	.33						
BSA*	BSA*	.007	2.1	.09			.14						
HTN	HTN	.001	.42	-.04			.52						
DM	DM	.001	.27	-.03			.61						
Creatinine*	Creatinine*												
Hb*	Hb*												
LVEF*	LVEF*												

*These variables are treated as continuous covariates in the univariable and multivariable linear regression analysis. DNC, del Nido Cardioplegia (reference group is blood cardioplegia); B-Troponin, baseline troponin level; BSA, body surface area; HTN, systemic hypertension; DM, diabetes mellitus; Hb, hemoglobin (g/dl); LVEF, left ventricular ejection fraction. RS, R square. Variance Inflation factor (VIF) for all variables included in the model is <1.5.

Figure 1. Troponin T level (ng/ml) by cardioplegia type.

Change in Troponin T levels at baseline, peak and trough stratified by cardioplegia type (del Nido Cardioplegia (DNC) and blood cardioplegia (BC)). The estimated marginal means with 95% CI for baseline, peak and trough troponins are depicted in the figure. Repeated measures analysis was adjusted for age and Cross Clamp Time. Age: F = 0.39, P = 0.5; cross clamp time: F = 10.8, P = 0.001; Cardioplegia Type: F = 14.3, P < 0.001.

Figure 2. Graphical summary of Del Nido cardioplegia (DNC) compared to blood cardioplegia (BC) in

various categories of adult cardiac surgery procedures. Both techniques had equivalent mortality and major morbidity. DNC was associated with lower postoperative troponin release (P<.001), lower duration of inotropic support (P=.02) and shorter intensive care unit stay (P=.04)".