J Extra Corpor Technol. 2020;52:272–8
The Journal of ExtraCorporeal Technology

Use of del Nido Cardioplegia for Adult Heart Surgery: How Long Is Not Too Long?

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Abstract: The most apparent practical advantage of del Nido cardioplegia (DNC) is that it allows the surgeon a longer arrest period before a subsequent dose is needed, as opposed to the conventional St. Thomas' cardioplegia solution where the recommended ischemic time is ~15–20 minutes. In this study, we explored the incidence of arrhythmia after cross-clamp removal as a surrogate for a safe myocardial ischemic time with the use of DNC in adult heart surgery. A total of 113 patients who had undergone heart valve repair and/or replacement surgery at the National University Hospital, Singapore, were investigated. This single-center retrospective study was conducted on a population where DNC had been used for myocardial protection between January 2017 and April 2019. Cardioplegia ischemic time interval groups were not significant predictors of postoperative arrhythmia, defibrillation, and intraoperative intra-aortic balloon pump usage. Crude comparison of postoperative outcomes showed no significant differences in any other postoperative variables, including mortality and total hospital stay. From the results of the present study, it appears that there is no optimal ischemic time interval for the administration of DNC within a 120-minute time period. It is likely that DNC has a redosing interval of, and may provide adequate myocardial protection, for up to 120 minutes. **Keywords:** cardioplegia, ischemia/reperfusion, arrhythmia, defibrillation, statistics/regression analysis, del Nido, dosing, timing. *J Extra Corpor Technol. 2020;52:272–8*

Cardioplegia serves a critical role in inducing electromechanical quiescence of the heart during cardiac surgery because it depolarizes the extracellular membrane potential and lowers the resting potential of ventricular myocytes (1). A noncontracting heart, coupled with cross-clamping of the aorta that limits continuous coronary blood flow, offers surgeons an enhanced surgical field (2). These advantages conferred by cardioplegia have been heavily used in cardiac surgery since Gerbode and Melrose discovered the ability of potassium citrate to arrest the human heart in diastole in 1958 (3).

Del Nido cardioplegia (DNC), developed by Dr. Pedro del Nido (4) from the University of Pittsburgh in the 1990s, is composed of extracellular solution and autologous blood derived from the extracorporeal circuit, forming a crystalloid: blood ratio of 4:1 (5). A single dose (20 mL/kg) of DNC provides adequate myocardial protection for ~90 minutes and reduces the myocardial temperature to less than 15°C, minimizing oxygen consumption (5).

A single dose of DNC is recognized as a viable alternative to multi-dose conventional cardioplegia (6). The non-inferiority of DNC compared with conventional cardioplegia has also been tested (7,8), but the presumed

Received for publication April 14, 2020; accepted October 6, 2020.
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The senior author has stated that the authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

duration of safe myocardial protection varies widely (6,9). The choice of safe duration is determined by the operating surgeon or by the institutional protocol (10). There is no general consensus about the safe duration of DNC, despite its suitability for long duration use, and remarkably no redosing rationale to DNC has been clearly demarcated.

However, because the focus of the existing literature has been on the suitability of DNC in replacing conventional blood cardioplegia and DNC's inherent benefits in terms of efficacy, clinical outcomes, and cost-effectiveness, the most apparent practical advantage of DNC in allowing a longer redosing interval has yet to be extensively explored. To our knowledge, there has not been a comprehensive study comparing DNC dosing intervals and its impact on clinical outcomes in adult or pediatric heart surgery. Therefore, this study aimed to investigate the optimal ischemic time interval when administrating DNC before the removal of aortic cross-clamp (AXC) in adult heart surgery.

METHODS

This single-center retrospective study collected the data of 177 patients who had undergone heart valve repair and/or replacement surgery at the National University Hospital, Singapore, between January 2017 and April 2019. This study was approved by the Domain Specific Review Board (DSRB) under the National Healthcare Group, Singapore (Application Number: #2019/00554). From this initial group of 177 patients, those with multi-dose DNC administered during surgery were excluded, leaving 113 single-dose DNC patients for inclusion into the present study.

DNC Ischemic Time Interval Groups

To assess the ideal ischemic time interval for DNC, the cardioplegia ischemic intervals were divided into four groups: <60 minutes, 60–89 minutes, 90–120 minutes, and >120 minutes.

Main Outcomes Assessed

Besides demographic data such as age, gender, patients' pre-existing health status, operative and postoperative outcomes were analyzed. The primary outcomes were incidence of arrhythmia (ventricular tachyarrhythmia in the form of ventricular tachycardia (VT)/ventricular fibrillation (VF)) after aortic artery cross-clamp release and defibrillation requirement, whereas the secondary outcomes were cardiopulmonary bypass (CPB) time, AXC time, length of stay, patient status at discharge and at 30 days, and postoperative stay in days.

Statistical Analysis

Data were analyzed using SPSS 25.0 (IBM Corp., Armonk, NY) software (11). Where appropriate, continuous data were expressed as mean (SD) when the data followed a normal distribution and as median (minimum-maximum) when the data were skewed. Categorical variables, including nominal and ordinal variables, were presented as frequency (percentage). The significance level used across all data analyses was .05.

When comparing the means of baseline patient characteristics between the ischemic time interval groups, the ANOVA test was carried out when comparing continuous data that were normally distributed. The alternative non-parametric Kruskal–Wallis test was performed to compare the difference between skewed continuous data in mean ranks. Nominal and ordinal data were compared using Pearson's $\chi 2$-square test. When the number of cells with an expected count less than five was >0, Fischer's exact test was used instead.

Ordinal and binomial regression analyses were carried out to assess the relationship between dependent variables and several independent covariates when controlling for other variables. Regression models were used to predict the dependent variable, dichotomous in binomial regression and non-dichotomous in ordinal regression, from predictor covariates. The main dependent variables assessed were the incidence of postoperative arrhythmia and defibrillation rates, as well as intraoperative intra-aortic balloon pump (IABP) usage. The independent covariates used in each regression models were intraoperative potassium after del Nido cardiolegia administration, post-operative potassium, lactate on CPB, as well as AXC time, CPB time, and IABP usage (for postoperative arrhythmia and defibrillation).

RESULTS

Patient Baseline Characteristics

Of the 113 patients who underwent surgery with single-dose DNC, most baseline characteristics compared among the four DNC ischemic time interval groups did not show any significant differences. There were significant differences between the groups in frequencies of aortic incompetence (p = .004), mitral incompetence (p = .018), and mitral stenosis (p = .047) (Table 1).

Perioperative Characteristics

All 113 patients underwent a variety of procedures including valve repair and/or replacement procedures, coronary artery bypass graft (CABG), and complex surgeries from January 2017 to April 2019. Comparison of perioperative characteristics showed significant differences among the four groups (Table 2) in type of procedure (p = .038), minimally invasive surgery (p = .004), AXC time ($p < .0001$), CPB time ($p < .0001$), and length of procedure ($p < .0001$). Mean AXC time was 47.62 (9.34) minute in the <60-minute group, 74.65 (8.26) minute in the 60– to 89-minute group, 104.88 (8.28) minute in the 90– to 120-minute group, and 128.50 (7.45)

Table 1. Baseline characteristics of patients in each cardioplegia ischemic time interval group.

Patient Characteristic	Cardioplegia Ischemic Time Interval Groups (frequency [%], mean [SD], median [range], n = 113)				*p*-Value
	<60 minutes	60–89 minutes	90–120 minutes	>120 minutes	
	n = 26	n = 55	n = 26	n = 6	
Gender (male)	14 (53.8)	36 (65.5)	18 (69.2)	3 (50.0)	.590
Age (years)	54.15 (13.82)	57.91 (13.37)	61.85 (12.93)	55.00 (7.67)	.200
Height (cm)	163.42 (9.36)	163.25 (11.27)	165.20 (11.31)	172.40 (14.52)	.347
Weight (kg)	65.40 (15.66)	64.34 (14.16)	65.64 (15.34)	72.35 (11.85)	.654
Never smoked	22 (84.6)	36 (65.5)	18 (69.2)	3 (50.0)	.020
Diabetes mellitus	7 (26.9)	8 (14.5)	5 (19.2)	3 (50.0)	.212
Cardiomegaly	12 (46.2)	30 (54.5)	16 (61.5)	2 (33.3)	.522
Congestive heart failure	6 (24.0)	21 (38.2)	8 (30.8)	3 (50.0)	.499
Preoperative heart rhythm					.225
Sinus rhythm	20 (76.9)	40 (72.7)	13 (50.0)	3 (50.0)	
Atrial fibrillation/flutter	5 (19.2)	13 (23.6)	10 (38.5)	1 (16.7)	
Other abnormal rhythm	1 (3.8)	2 (3.6)	2 (7.7)	2 (33.3)	
Ventricular fibrillation	0 (.0)	0 (.0)	0 (.0)	0 (.0)	
Complete heart block/pacing	0 (.0)	0 (.0)	0 (.0)	0 (.0)	
Ejection fraction (%)	55.58 (11.60)	56.77 (12.73)	57.23 (7.91)	54.20 (9.26)	.916
Aortic incompetence (severe)	5 (19.2)	2 (3.6)	4 (15.4)	0 (.0)	.004
Mitral incompetence (severe)	7 (26.9)	40 (72.7)	15 (57.7)	1 (16.7)	.018
Tricuspid incompetence (severe)	2 (7.7)	3 (5.5)	5 (19.2)	0 (.0)	.405
Aortic stenosis (severe)	3 (11.5)	5 (9.1)	2 (7.7)	1 (16.7)	.550
Mitral stenosis (severe)	2 (7.7)	0 (.0)	4 (15.4)	2 (33.3)	.047
Tricuspid stenosis (none)	26 (100.0)	55 (100.0)	26 (100.0)	6 (100.0)	1.000
Pulmonary stenosis (none)	26 (100.0)	55 (100.0)	26 (100.0)	6 (100.0)	1.000
Chronic lung disease (none)	14 (100.0)	31 (96.9)	16 (100.0)	4 (100.0)	.691
Hypertension	12 (46.2)	28 (50.9)	12 (46.2)	3 (50.0)	.970
Peripheral vascular disease	1 (3.8)	1 (1.8)	26 (100.0)	6 (100.0)	.653
Previous CV intervention	1 (3.8)	2 (3.6)	2 (7.7)	1 (16.7)	.629
ASA class III	20 (76.9)	37 (67.3)	19 (73.1)	5 (83.3)	.411
Redo surgery	1 (3.8)	2 (3.6)	2 (7.7)	1 (16.7)	.629
Operative urgency (elective)	24 (92.3)	44 (80.0)	18 (69.2)	5 (83.3)	.145
EuroSCOREII	1.10 (.64, 5.53)	1.61 (.50, 13.33)	2.55 (.50, 10.17)	2.72 (2.08, 9.04)	.104
Logistic EuroSCORE	2.27 (1.49, 8.96)	3.74 (.88, 43.05)	3.46 (1.51, 22.96)	1.54 (.74)	.144

ASA, American Society of Anesthesiologists; CV, cardiovascular.

minute in the >120-minute group, with a significant difference in means, $p < .0001$. Mean CPB time was 137.54 (66.13) minute in the <60-minute group, 178.4 (86.7) minute in the 60– to 89-minute group, 210.73 (72.11) minute in the 90– to 120-minute group, and 306.50 (115.22) minute in the >120-minute group, with a significant difference in means, $p < .0001$. There was also a significant difference in the mean length of the procedure between the groups ($p < .0001$) with a mean total operative time of 240.96 (48.24) minute in the <60-minute group, 278.84 (53.13) minute in the 60– to 89-minute group, 290.69 (50.00) minute in the 90– to 120-minute group, and 339.50 (78.96) minute in the >120-minute group (Table 2).

Analyzing defibrillation rates, we observed that one shock for defibrillation was required in three (12.0%) patients in the <60-minute group, one (1.8%) patient in the 60– to 89-minute group, two (7.7%) patients in the 90– to 120-minute group, and one (16.7%) patient in the >120-minute group. Two shocks for defibrillation were required in one (4.0%) patient in the <60-minute group, seven (12.7%) patients in the 60– to 89-minute group, and two (7.7%) patients in the 90– to 120-minute group, whereas four shocks were required in one (16.7%) patient in the >120-minute group. There was no statistically significant difference in overall defibrillation rates among the groups, $p = .190$ (Table 2).

Intraoperative Characteristics

In terms of intraoperative characteristics, we observed statistically significant differences between the ischemic time interval groups when comparing postoperative lactate ($p = .014$), cell saver volume ($p = .001$), and cannulation method ($p = .048$) (Table 3). The average postoperative lactate levels were 3.04 (1.44) mmol/L, 2.60 (1.10, 10.20) mmol/L, 3.40 (1.70, 10.80) mmol/L, and 6.70 (3.80, 9.60) mmol/L for the <60-minute, 60– to 89-minute, 90– to 120-minute, and >120-minute groups, respectively. The average cell saver volume was 398.00 (139.00–1,010.00) mL for the <60-minute group, 664.71 (190.56) mL for the 60– to 89-minute group, 791.75 (288.22) mL in the 90– to 120-minute group, and 1,019.00 (253.14) mL in the >120-minute group (Table 3).

In terms of the delivery mode of DNC, antegrade cardioplegia (ACP) delivery was performed in a majority of

Table 2. Perioperative characteristics of patients.

Patient Characteristic	Cardioplegia Ischemic Time Interval Groups (frequency [%], mean [SD], median [range], n = 113)				*p*-Value
	<60 minutes	60–89 minutes	90–120 minutes	>120 minutes	
	n = 26	n = 55	n = 26	n = 6	
Operative procedures					.038
Valve only	13 (50.0)	32 (58.2)	12 (46.2)	3 (50.0)	
Valve + other	3 (11.5)	12 (21.8)	13 (50.0)	2 (33.3)	
CABG + valve	3 (11.5)	6 (10.9)	1 (3.8)	0 (.0)	
CABG + other	1 (3.8)	2 (3.6)	0 (.0)	0 (.0)	
CABG + valve + other	0 (.0)	1 (1.8)	0 (.0)	1 (9.1)	
CABG only	2 (7.7)	2 (3.6)	0 (.0)	1 (9.1)	
Others (multiple procedures)	4 (15.4)	0 (.0)	0 (.0)	1 (16.7)	
CABG category					.101
Nonisolated CABG	6 (60.0)	15 (71.4)	6 (100.0)	–	
On-pump isolated	4 (40.0)	6 (28.6)	–	–	
Minimally invasive cardiac surgery (MICS)	19 (73.1)	36 (65.5)	8 (30.8)	2 (33.3)	.004
IABP usage					.546
Intraoperative	1 (3.8)	1 (1.8)	2 (7.7)	0 (.0)	
Postoperative	1 (3.8)	0 (.0)	0 (.0)	0 (.0)	
AXC time (min)	47.62 (9.34)	74.65 (8.26)	104.88 (8.28)	128.50 (7.45)	<.0001
CPB time (min)	137.54 (66.13)	178.4 (86.7)	210.73 (72.11)	306.50 (115.22)	<.0001
Defibrillation					.190
Spontaneous	21 (84.0)	47 (85.5)	21 (80.8)	4 (66.7)	
DC X 1	3 (12.0)	1 (1.8)	2 (7.7)	1 (16.7)	
DC X 2	1 (4.0)	7 (12.7)	2 (7.7)	0 (.0)	
DC X 3	0 (.0)	0 (.0)	0 (.0)	0 (.0)	
DC X 4	0 (.0)	0 (.0)	0 (.0)	1 (16.7)	
Length of procedure (min)	240.96 (48.24)	278.84 (53.13)	290.69 (50.00)	339.50 (78.96)	<.0001

patients, with 24 (92.3%) patients in the <60-minute group, 44 (80.0%) patients in the 60– to 89-minute group, 22 (84.6%) patients in the 90– to 120-minute group, and four (66.7%) patients in the >120-minute group. ACP and coronary ostial delivery was performed in eight (14.5%) patients in the 60– to 89-minute group, four (15.4%) patients in the 90– to 120-minute, and two (33.3%) patients in the >120-minute group. Retrograde cardioplegia (RCP) with coronary ostial delivery was carried out in one (1.8%) patient in the 60– to 89-minute group. ACP delivery and RCP delivery were carried out in one (3.8%) patient in the <60-minute group and two (3.6%) patients in the 60– to 89-minute group. ACP, RCP, and coronary ostial delivery were carried out in only one (1.8%) patient in the <60-minute group. There was no significant difference in the cardioplegia delivery mode among the groups, $p = .232$ (Table 3).

Postoperative Outcomes

For all 113 patients, four (15.4%) patients in the <60-minute group, eight (14.5%) patients in the 60– to 89-minute group, four (15.4%) patients in the 90– to 120-minute group, and one (16.7%) patient in the >120-minute group developed a postoperative arrhythmia. Only one (3.8%) patient in the 90– to 120-minute group passed away. The average length of total hospital stay was 8.00 (2.83), 13.00 (5.00, 63.00), 26.50 (8.00, 101.00), and 12.00 (9.00, 15.00) days in the <60-minute, 60– to 89-minute, 90– to 120-minute, and >120-minute groups, respectively. There were no significant differences in postoperative arrhythmia, patient status at discharge, patient status at 30 days, operative mortality, and total hospital stay in days, among the four groups (Table 4).

Binomial and Ordinal Regression Analyses

A binomial logistic regression analysis was carried out to predict the incidence of arrhythmia using cardioplegia ischemic time interval groups. Potassium after DNC administration, postoperative potassium, lactate on CPB, as well as CPB time, AXC time, and IABP usage were used as predictors. The data of patients with pacemakers were excluded from this analysis.

The results showed that the odds of developing postoperative arrhythmias in patients with administration of DNC for the different ischemic time interval groups were similar, and that none of the four cardioplegia ischemic time interval groups were significant predictors of postoperative incidence of arrhythmia. We also observed that potassium after DNC administration, postoperative potassium, lactate on CPB, as well as CPB time, AXC time, and IABP usage were also not significant predictors of rates of postoperative arrhythmia (Table 5).

Following this, an ordinal logistic regression analysis was performed to predict defibrillation rates using the same variables (as in the binomial regression) as predictors. The data of patients with pacemakers were excluded from this analysis as well. The results demonstrated once again that the odds of defibrillation requirement were similar across

Table 3. Intraoperative characteristics of patients in different groups.

Patient Characteristic	Cardioplegia Ischemic Time Interval Groups (frequency [%], mean [SD], median [range], n = 113) <60 minutes n = 26	60–89 minutes n = 55	90–120 minutes n = 26	>120 minutes n = 6	p-Value
Cannulation method					.048
Femoral artery and femoral/ jugular vein	15 (57.7)	30 (54.5)	6 (23.1)	1 (16.7)	
Aorta and atrial/caval	11 (42.3)	23 (41.8)	17 (65.4)	4 (66.7)	
Aorta and femoral/jugular vein	0 (.0)	0 (.0)	0 (.0)	0 (.0)	
Femoral artery and atrial/caval	0 (.0)	1 (1.8)	0 (.0)	1 (16.7)	
Other	0 (.0)	1 (1.8)	1 (3.8)	0 (.0)	
Patient cooled down temperature (°C)	32.80 (1.36)	31.70 (1.63)	32.60 (1.19)	31.00 (3.46)	.016
Volume of first dose of del Nido (mL**)**	843.12 (201.44)	860.42 (172.12)	838.23 (169.23)	928.33 (228.51)	.715
Volume of first dose (mL/kg)	13.11 (2.23)	13.76 (2.75)	13.38 (3.99)	12.49 (2.14)	.661
Volume at which heart was arrested (mL)	166.00 (80.00, 480.00)	209.21 (103.59)	201.76 (86.59)	170.00 (132.00, 570.00)	.874
Cardioplegia delivery mode					.232
ACP	24 (92.3)	44 (80.0)	22 (84.6)	4 (66.7)	
ACP + coronary ostial	0 (.0)	8 (14.5)	4 (15.4)	2 (33.3)	
RCP + coronary ostial	0 (.0)	1 (1.8)	0 (.0)	0 (.0)	
ACP + RCP	1 (3.8)	2 (3.6)	0 (.0)	0 (.0)	
ACP + RCP + coronary ostial	1 (3.8)	0 (.0)	0 (.0)	0 (.0)	
K + pre-CPB (mmol/L)	3.79 (.35)	3.66 (.41)	3.59 (.48)	3.68 (.26)	.320
K + after del Nido (mmol/L)	4.22 (.57)	4.25 (.700)	4.24 (.60)	4.28 (.43)	.982
K + postoperative (mmol/L)	4.03 (.45)	3.90 (.46)	3.96 (.39)	3.77 (.36)`	.460
Lactate on CPB (mmol/L)	2.88 (1.05)	3.10 (1.24)	2.64 (1.81, 10.37)	4.03 (2.60, 5.45)	.078
Lactate postop (mmol/L)	3.04 (1.44)	2.60 (1.10, 10.20)	3.40 (1.70, 10.80)	6.70 (3.80, 9.60)	.014
Hemofilter used	10 (38.5)	30 (54.5)	15 (57.7)	2 (33.3)	.370
Hemofilter volume (mL)	1,500.00 (800.00, 3,900.00)	1,600.00 (300.00, 5,200.00)	2000.00 (500.00, 5,500.00)	2,500.00 (919.24)	.831
Cell saver (mL)	398.00 (139.00, 1,010.00)	664.71 (190.56)	791.75 (288.22)	1,019.00 (253.14)	.001
Donor blood given (mL)	392.00 (153.91)	633.53 (306.88)	604.50 (279.16)	571.50 (13.44)	.333

the four groups, and none of the groups were significant predictors of defibrillation rates. Potassium after DNC administration, postoperative potassium, lactate on CPB, as well as CPB time, AXC time, and IABP usage were again not significant predictors of rates of postoperative arrhythmia as well (Table 5).

A binomial regression analysis was also carried out to evaluate predictors for rates of intraoperative IABP usage. We noted that cardioplegia ischemic time intervals, as well as all other predictors used in the regression model, were not significant predictors of intraoperative IABP usage (Table 5).

Table 4. Postoperative outcomes of patients.

Patient Characteristic	Cardioplegia Ischemic Time Interval Groups (frequency [%], mean [SD], median [range], n = 113) <60 minutes n = 26	60–89 minutes n = 55	90–120 minutes n = 26	>120 minutes n = 6	*p*-Value
Arrhythmia	4 (15.4)	8 (14.5)	4 (15.4)	1 (16.7)	.326
Patient status at discharge					.623
Alive	26 (100.0)	54 (98.2)	25 (96.2)	6 (100.0)	
Alive with minor disability	0 (.0)	1 (1.8)	0 (.0)	0 (.0)	
Alive with major disability	0 (.0)	0 (.0)	0 (.0)	0 (.0)	
Dead	0 (.0)	0 (.0)	1 (3.8)	0 (.0)	
Patient status at 30 days					.396
Alive	26 (100.0)	55 (100.0)	25 (96.2)	6 (100.0)	
Dead	0 (.0)	0 (.0)	1 (3.8)	0 (.0)	
Operative mortality	0 (.0)	0 (.0)	1 (3.8)	0 (.0)	.396
Total hospital stay (days)	8.00 (2.83)	13.00 (5.00, 63.00)	26.50 (8.00, 101.00)	12.00 (9.00, 15.00)	.293

Table 5. Multiple regression analysis

Binomial Regression Analysis of Incidence of Arrhythmia				
Cardioplegia ischemic time interval groups (minutes)	β	Odd ratio	*p*-value	95% CI
<60	–	–	.526	–
60–89	.889	2.433	.476	(.211, 28.077)
90–120	<.0001	1.000	1.000	(.014, 73.209)
>120	.967	2.629	.752	(.007, 1,049.261)
K+ after del Nido	.384	1.468	.369	(.635, 3.393)
K+ postoperative	–.219	.804	.750	(.209, 3.088)
Lactate on CPB	–.177	.838	.496	(.504, 1.394)
CPB time	–.001	.999	.885	(.992, 1.007)
AXC time	.010	1.010	.767	(.943, 1.083)
IABP use				
None	–	–	.209	–
Intraoperative	2.094	8.115	.077	(.798, 82.488)
Postoperative	–18.191	<.0001	1.000	–
Ordinal regression analysis of defibrillation requirement				
Cardioplegia ischemic time interval groups (minutes)	β	Odd ratio	*p*-value	95% CI
<60	–1.226	.294	.686	(.001, 110.692)
60–89	–.322	.725	.878	(.012, 43.985)
90–120	–1.081	.339	.429	(.023, 4.934)
>120	0[a]	1	–	–
K+ after del Nido	.511	1.667	.225	(.730, 3.805)
K+ postoperative	–.301	.740	.665	(.189, 2.891)
Lactate on CPB	–.120	.887	.584	(.578, 1.362)
CPB time	–.002	.998	.593	(.991, 1.005)
AXC time	.010	1.010	.779	(.943, 1.082)
IABP use	1.089	2.970	.267	(.435, 20.280)
Binomial regression analysis of incidence of intraoperative IABP usage				
Cardioplegia ischemic time interval groups (minutes)	β	Odd ratio	*p*-value	95% CI
<60	–	–	.447	–
60–89	–4.398	.012	.133	(.000, 3.825)
90–120	–6.657	.001	.191	(.000, 27.892)
>120	–8.291	.000	.252	(.000, 361.433)
K+ after del Nido	–1.795	.166	.140	(.015, 1.804)
K+ postoperative	–1.280	.278	.396	(.014, 5.343)
Lactate on CPB	.408	1.504	.189	(.818, 2.767)
CPB time	.002	1.002	.743	(.988, 1.017)
AXC time	.121	1.129	.182	(.945, 1.349)

DISCUSSION

From the results of our study, we observed that none of the cardioplegia ischemic interval groups were significant predictors of both postoperative arrhythmia and defibrillation rates. Given that the odds of postoperative arrhythmia and defibrillation were similar even in groups with ischemic time interval lengths of close to or even more than 120 minutes, it would seem reasonable to conclude that the dosing interval of DNC may potentially last for up to 120 minutes. Considering that DNC has been described to last for around 90 minutes, this is an interesting finding, given that the intuitive view on cardioplegia administration has been that shorter ischemic time intervals are more likely to lead to better myocardial protection, and that shorter redosing intervals and multi-dose cardioplegia are the current "gold standard." However, whether DNC can ensure adequate myocardial protection beyond 120 minutes is difficult to determine because the longest ischemic time interval recorded in our present study was 141 minutes, and only a sample size of six patients were included in the >120-minute group, which was unlikely to be representative of a larger patient cohort.

Although we observed no influence of cardioplegia ischemic time interval on defibrillation rates, evidence from the current literature have demonstrated that the use of DNC was associated with less defibrillation requirement than conventional St. Thomas' cardioplegia solution in adult patient cohorts (12). Hence, although there might not be a benefit in terms of reduction in defibrillation requirement associated with the use of shorter or longer dosing intervals of DNC, it remains that the use of DNC may still provide the potential benefit of a lower risk of the need for defibrillation.

At the same time, from the results of our regression analysis, cardioplegia ischemic time intervals were not significant predictors of intraoperative IABP requirement. No significant differences between the DNC cardioplegia ischemic time interval groups were detected in other major secondary outcomes, including patient status at discharge and at 30 days, operative mortality, and total hospital stay in days, highlighting the safety profile of DNC. These results are consistent with a previous meta-analysis published comparing the clinical outcomes of DNC with St. Thomas cardioplegia solutions, which concluded that the use of DNC led to similar clinical outcomes in in-hospital mortality and incidence of IABP usage in adult patients (13). Our results also reiterate DNC's superior or equivalent efficacy compared with conventional cardioplegia in the existing literature (6,14–17).

To the best of our knowledge, there have been no studies to date that examined the optimal ischemic time interval for DNC, or guidelines published on how long the ischemic time interval should be to ensure myocardial protection. With the results of our study, it would appear that there is no optimal ischemic time interval within a time period of up to 120 minutes. It seems that single-dose DNC was able to provide adequate myocardial protection and good postoperative outcomes, regardless of the dosing time interval within a 120-minute time period.

Limitations

The main limitation of the present study was its retrospective nature, which carries with it an inherent bias. In addition, the number of patients receiving administration of DNC for each of the four ischemic time interval groups could not be controlled, resulting in discrepancies among the groups. Finally, because of a lack of data on myocardial temperature, we were unable to ascertain that the temperature of DNC was kept below 15° in all cases. However, given that there were no severe postoperative outcomes, such as perioperative myocardial infarctions, we assumed that the temperature of DNC was maintained at an adequate temperature during surgery.

Future Perspectives

More randomized controlled trials with larger patient cohorts are needed in the future to verify the optimal ischemic time interval for superior myocardial protection with the use of DNC.

CONCLUSION

From the results of the present study, it appears that there is no optimal ischemic time interval for the administration of DNC within a 120-minute time period, with all four ischemic time interval groups of <60 minutes, 60–89 minutes, 90–120 minutes, and >120 minutes demonstrating similar rates of intraoperative IABP usage, postoperative arrhythmia, and defibrillation requirement. It is likely that DNC has a redosing interval of, and may provide adequate myocardial protection, for up to 120 minutes.

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