Original article

Analogy of Del Nido and conventional cardioplegia in patients undergoing isolated mitral valve replacement surgery: A single-center retrospective study

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ABSTRACT

Objective: The objective of this study was to assess the postoperative outcomes after utilizing the Del Nido cardioplegia as compared to conventional cardioplegia, in patients undergoing isolated mitral valve replacement surgery.

Methods: This was a single-center retrospective study conducted with the data from 80 patients with mitral valve disease, who underwent cardiopulmonary bypass. The outcome assessments of the Del Nido group (n = 40) was compared with that of the non-Del Nido group (n = 40). Various time factors were analyzed as end points that included cardiopulmonary bypass time aortic cross clamp time, duration of mechanical ventilation, need for postoperative inotropic support, volume of packed red blood cells (RBCs) transfusion, length of ICU and hospital stay, among others.

Results: The current study showed that the mean cardiopulmonary bypass time and aortic cross-clamp time were significantly shorter in the Del Nido group when compared to the non-Del Nido group (P < 0.05). The mean number of packed red blood cell pints administered in the Del Nido group was fewer than the non-Del Nido group (P < 0.05). No significant differences found in other outcome measures.

Conclusion: The use of the Del Nido cardioplegia technique did significantly reduce the aortic cross-clamping time and cardio-pulmonary bypass time. The present study did also show a marked reduction in the amount of packed RBCs transfusion in the Del Nido group as compared to non-Del Nido conventional cardioplegia. Rigorous, adequately scrutinized randomized control trials are required to reiterate these findings in-order to enable us to extrapolate their benefits to a larger population.

Introduction

The concept of cardioplegia was introduced by Melrose to arrest the heart electively in the year 1955.¹ Eventually, in 1973, Gay and Ebert came up with the new formula of crystalloid CP with much lesser concentration of Potassium Chloride (KCl), just enough to electromechanically stop the heart.² These studies subsequently led to the clinical use of St. Thomas solution in 1976. In early 1990, researchers at The University of Pittsburgh found out a novel solution for myocardial protection. The team, led by Dr. Pedro J DEL NIDO, Hung Cao-Danh, K. Eric

Sommers, and Akihiko Ohkado, subsequently patented this solution, which is currently called the Del Nido cardioplegia.³

Conventional CP for infants and pediatric were similar to those used in patients except for the adjustment in volume, flow and pressure.^{4,5} A more recently developed cardioplegia solution, viz. Del Nido cardioplegia, which remained to protect infants and pediatric myocardium alike, could be of benefit for adult population, due to the similarities that immature and senescent hearts share with respect to their increased tendency for myocyte injury during ischemia and reperfusion.

In spite of a proven benefit in the usage of Del Nido cardioplegia in

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pediatric population, surgical units for decades, have not tested its efficacy in adult cardia. Antegrade Single-dose, Del Nido cold blood CP could be used for antegrade delivery. Due to the ease of its administration and increased periods of redosing, Del Nido CP usage has been the rise in adult cardiac setup.^{6,7} This present study was aimed at comparing the Del Nido and conventional cardioplegia techniques in an attempt to find a feasible alternate for myocardial preservation, which may help to alleviate peri-operative ischemic injury/reperfusion injury and help to cut-short post-operative recovery period and hospital stay.

Methods

The study was conducted at a tertiary care hospital utilizing the clinical data of adult patients who underwent isolated mitral valve replacement for mitral stenosis (MS) or mitral insufficiency (MI). The study population was dichotomized into two groups based on the type of cardioplegia administered during the surgery; i.e. conventional cardioplegia (non-Del Nido group) (n = 40) and Del Nido cardioplegia (Del Nido) (n = 40). This was an observational retrospective study conducted between 2014 and 2017. The study included a total sample size of 80 patients based on the convenience sampling method and the samples who were eligible based on the inclusion criteria for the study were included. Patients in cardiogenic shock, following a concomitant cardiac surgical procedure or having active endocarditis were excluded from this study. The variables analyzed were peri-operative cardiopulmonary bypass time, aortic cross clamp time, duration of mechanical ventilation, and volume of packed red blood cells transfusion, length of ICU and hospital stay. Institutional Research Committee and Institutional Ethical Committee clearance were obtained prior to conducting the study.

The cardioplegia delivery method was mainly antegrade through the aortic route. Del Nido solution was a mixture of 4 parts of crystalloid solution to 1 part of oxygenated blood drawn from the oxygenator. The composition of the cardioplegic in the crystalloid part is given in the table below (Table 1). This cardioplegia is given as a single induction dose of 1 L which is cold (temperature of around 6–8 °C), this does not require re-dosing for up to a period 60–80 min. Re-dosing, if needed after 60–80 min, can be given by a maintenance dose which will be half the volume of the induction dose. Ultrafiltration performed in all patients in Del Nido group.

Conventional cardioplegia, alternatively, is a mixture of 1 part of crystalloid solution with 4 parts of oxygenated blood drawn from oxygenator. A comparative between the compositions of cardioplegia in the crystalloid part between the two groups is given in Table 1. In this technique, the cardioplegia is given in an induction dose of 1 L, which is cold, and temperature is maintained in the range of 5–8 °C and maintenance dose was repeated every 20 min with half the induction dose.

SPSS (version 16) package was used for data analysis. All quantitative data were coded and transformed to an excel master sheet for computer programming. Descriptive statistics were used to report all outcome variables. Chi-square test was done to assess the categorical data. For continuous data independent *t*-test was used as data were

normally distributed. For all data analyses, $p < 0.05$ was considered as statistically significant.

Results

Preoperative patient characteristics are presented in Table 2. There was no statistical significance, in terms of characteristics between two groups. The mean age of patients was 67.65, and the indications for surgery were mitral stenosis N = 53 (66.25%) and or mitral regurgitation N = 27 (33.75%). All mitral surgeries were completed with standard general anesthesia, employing cardiopulmonary bypass with trivial systemic hypothermia (30–34 °C) thorough the median sternotomy approach.

Cardiopulmonary bypass time in the Del Nido cardioplegia was significantly lesser than patients in the conventional cardioplegia 60 ± 10.5 mins and 90 ± 13.5 mins respectively with $P < 0.05$. Aortic cross-clamp time was also relatively lesser in the Del Nido group 50 ± 15.5 and 70 ± 20.5 as compared to the conventional group.

The conventional group significantly had higher volume of initial dose of cardioplegia solution compared to the Del Nido group. Additional doses of cardioplegia administered were 1.0 ± 0.4 patients and 3.2 ± 1.3 patients respectively in the Del Nido and the conventional group. The total volume of solution administered in the Del Nido group was very less than in the conventional group with the statistical significance ($P = 0.001$) (Table 3).

Inotropic support was required for 26 (65%) patients in the Del Nido group and for the conventional group 28 (70%) patients ($p = 0.152$). Use of dosages of postoperative inotropes used were same between the groups. None of the patient required a postoperative intra-aortic balloon pump. Vasoactive inotropic score did not show any statistically significant disparity.

In terms of duration of mechanical ventilation, this was almost identical in the two groups ($p = 0.373$). There was no statistical significance ($p = 0.033$ with respect to total PRBC transfusion units (mean) between the Del Nido group (1.3 ± 1.5) and the conventional group (2.3 ± 2.4) were administered in the intra- and/or postoperative period (Table 4). There was no postoperative cerebrovascular accident and mortality occurred in either group. There was no statistically significant difference in the duration of intensive care unit stay and the number of days of stay in the hospital between the two groups.

Discussion

Even though the Del Nido cardioplegia has been in use for pediatric heart surgery for decades, its use in adult surgery is comparatively a developing concept. The conventional cardioplegia technique has been widely used in adult cardiac surgery as a standard for myocardial

Table 1
Composition of cardioplegia solutions.

Composition	del Nido cardioplegia	Conventional cardioplegia
Carrier	1 L plasmalyte base solution with pH 7.4	1 L Ringer Lactate
Blood: Clear	1: 4	4: 1
KCl	26 mmol (13 ml)	16 mmol (1.19 g)
NaHCO ₃	26 mmol (13 ml)	20 mEq (20 mmol)
Mannitol	16.3 ml	20 ml
Lidocaine 2%	6.5 ml	–
MgSO ₄	8 mmol (4 ml)	16 mmol (3.25 g)
Procaine hydrochloride	–	1 mmol (0.27 g)

Table 2
Preoperative patient demographics.

N = 80					
Characteristics	del Nido group (n = 40)		Conventional Group (n = 40)		p value
Age (mean $\pm$ SD years)	66.6 $\pm$ 13.5		68.7 $\pm$ 11.7		0.47
	Frequency	Percentage	Frequency	Percentage	
Gender					
Male	30	75	26	65	0.32
Female	10	25	14	35	
Comorbidityr					
Hypertension	34	85	32	80	0.55
Diabetes	22	55	18	45	
Indications for operation					
Mitral stenosis	29	72.5	24	60	0.23
Mitral regurgitation	11	27.5	16	40	

Table 3
Operative and perfusion data.

N = 80				
Outcome measures	del Nido group (n = 40)	Conventional group (n = 40)	t value	p value
Cardiopulmonary bypass time (mean $\pm$ SD minutes)	60 $\pm$ 10.5	90 $\pm$ 13.5	11.09	0.001
Cross-clamp time (mean $\pm$ SD minutes)	50 $\pm$ 15.5	70 $\pm$ 20.5	4.92	0.001
Cardioplegia Volume				
Total initial dose (ml)	954 $\pm$ 235	1062 $\pm$ 198	11.09	0.021
Antegrade-initial (ml)	944 $\pm$ 230	786 $\pm$ 295	2.67	0.001
Number of additional doses	1.0 $\pm$ 0.4	3.2 $\pm$ 1.3	10.23	0.001

Table 4
Postoperative outcomes.

N = 80			
Outcomes	del Nido group (n = 40)	Conventional group (n = 40)	p value
Postoperative inotropic support	26 (65%)	28 (70%)	0.152
Number of inotropes	1.9 $\pm$ 1	2.0 $\pm$ 0.9	0.449
Nor adrenaline dose (μ /min)	4.0 $\pm$ 2.6	3.6 $\pm$ 2.7	0.592
adrenaline dose (μ /min)	2.4 $\pm$ 1.5	2.7 $\pm$ 1.5	0.600
Ventilation duration (hours)	5.6 $\pm$ 1.7	6.8 $\pm$ 2.2	0.373
Total PRBC Transfusion (mean) (units)	1.3 $\pm$ 1.5	2.3 $\pm$ 2.4	0.033
ICU stay (mean $\pm$ SD days)	1.99 $\pm$ 0.9	1.87 $\pm$ 0.8	0.530
Postoperative hospital stays (mean $\pm$ SD days)	5.05 $\pm$ 2.3	4.1 $\pm$ 1.9	0.472
Intra-aortic balloon pump	0 (0%)	0 (0%)	0
In-hospital mortality	0 (0%)	0 (0%)	0

protection with good clinical outcome. Administration of cardioplegia and frequency may vary widely between centers. Some studies have demonstrated good safety even with a single dose of cardioplegia thus reducing the cross-clamping time in order to advance surgical outcomes.

Our study main findings were that: the Del Nido cardioplegia use was associated with shorter cardiopulmonary bypass and cross clamping times, there was no any cerebrovascular accident and mortality during the post-operative period in both the Del Nido and conventional group, during an operation myocardial protection as evidenced by requirement for inotropes for circulatory support was equal in both the groups, and the Del Nido solution usage decreases the volume of packed red blood cell pints transfusion. The findings of our study are in line with previously conducted study which states that cardiopulmonary bypass time was statistically significantly shorter in the del Nido group and Del Nido cardioplegia is safe and can be used efficiently in isolated valve replacement surgery.^{17–19} Our study findings are also supported by recently published systematic review and meta-analysis on del Nido versus blood cardioplegia in adult cardiac surgery.²⁰

A previous study reported that decreased administration for patients receiving the Del Nido cardioplegia¹⁶ which was inconsistent with this study as we found there was no significant statistical association between the type of cardioplegia and the possibility of receiving the RBCs transfusion. We suggest use of ultrafiltration decreases red blood transfusion when high crystalloid-based solution is used.

The myocardium of adult patients behaves differently when compared to myocardium of pediatric patients during ischemia and are often not protected well by some of the cardioplegia solutions. This may be the reason why adult patients subjected to cardiac surgical procedures have decreased recovery of ventricular function and the lesser chance of survival.^{8,9} The mechanism accountable for an intolerance to

ischemia seems to be connected to faster buildup of intracellular Ca²⁺.^{9–11} The strategies to decrease the buildup of intracellular Ca²⁺ in adult hearts would therefore advance the regaining of ventricular function after the ischemia.⁷

The lidocaine, which is existing in the Del Nido solution, is a common chemical but the mechanism of action is not evidently understood. Likelihoods include coronary vasodilation to advance delivery of cardioplegia solution, prevention of arrhythmias due to reperfusion, and decrease of Na⁺ influx via the gap current through the arrest. During the cardioplegic arrest, membrane potential steadies at a comparatively depolarized level at which a trivial tonic inward Na⁺ current is active. This window current is connected to a trivial proportion of the voltage gated Na⁺ networks that are existing, open, and in the full of life state.^{12–14} This is a potential disadvantage of depolarizing cardioplegic arrest since Na⁺ influx is understood to be the key driver of Ca²⁺ excess.¹⁵

With an intention to optimize the potential of the Del Nido cardioplegia solution formulation, we endorsed that lidocaine moves the activation and in-activation curves for Na⁺ networks in a way that decreases the possible for Na⁺ window current. This may signify an imperative mechanism of benefit with the Del Nido formulation, and the lidocaine concentration in the present preparation seems to be enough.

The Del Nido cardioplegia formulation also comprises a little excess magnesium and potassium compared to the standard cardioplegia, leading in additional pronounced depolarization of membrane. This dyselectrolyemia also could contribute to a more efficient arrest. Decreased spontaneous activity in the ischemic period must bound the development of intracellular acidosis, which energies the Na⁺, and later Ca²⁺ influx, that leads to reperfusion ischemic injury.

The two distinct advantages of the Del Nido cardioplegia over the conventional cardioplegia are seeming from this study data. First, surgeries using the Del Nido were shorter, despite similar pre surgery risk factors, which we attribute to the condensed time needed for administration of cardioplegia. With the Del Nido formulation, the disturbance of repetitive cardioplegia administering was avoided. Repetitive administration can be cumbersome, can intrude the flow of the surgery, and could be tough to time correctly. In this setting, a single-dose agent is extremely desirable. Furthermore, the condensed cross-clamp (ischemic time) can demonstrate to have positive effects on clinical outcomes.

Conclusion

This study demonstrated that use of the Del Nido cardioplegia solution decreased the cardiopulmonary bypass and cross clamp time also the necessity for repetitive doses of cardioplegia administration. Furthermore, the additional advantage of maintaining continuity of the surgery without the necessity for recurrent cardioplegia administration cannot be ignored. The Del Nido cardioplegia solution relates to the less spontaneous action during the arrest, decreased the myocardial injury, and enhanced the functional recovery.

Recommendations

Single dose of Del Nido cardioplegia is reliable and acceptable for use, with exceptional postoperative outcomes, in mitral valve surgery. The limitations of this study are descriptive and retrospective in nature, and a small cohort size. Additional prospective long-term research studies should be carried out to discover the applications of the Del Nido cardioplegia solution and to validate this study findings.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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