Safety and Efficacy of Del Nido Cardioplegia Compared with Conventional Blood Cardioplegia in Isolated Coronary Artery Bypass Surgery – A Retrospective Study in a Tertiary Care Academic Centre in Kerala, India

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ABSTRACT

BACKGROUND

The del Nido cardioplegia was devised and introduced as a single dose cardioplegia for myocardial protection in congenital heart surgery by Petro del Nido and team. The most commonly used cardioplegia in adult cardiac surgery was multidose blood cardioplegia which has to be repeated every 25 to 30 minutes to maintain cardiac arrest. For this, the surgery has to be interrupted leading to prolonged cardiopulmonary bypass and aortic cross clamp time. With promising results of del Nido cardioplegia in adult cardiac surgery, more and more centres adopted this single dose cardioplegia in adult cardiac surgery. We retrospectively analysed the safety and efficacy of del Nido cardioplegia and compared them with those of conventional blood cardioplegia in isolated coronary artery bypass surgery.

METHODS

We have been using multidose conventional blood cardioplegia (CBCP) solution for all our cardiac surgeries. We changed the cardioplegia protocol to single dose del Nido cardioplegia (DNCP) solution in October 2016. We collected the preoperative, intraoperative and post-operative data of 100 patients in each group, who underwent elective isolated coronary artery bypass surgery.

RESULTS

The baseline demographic features, pre- and post-operative cardiac function, number of coronary arteries involved, and comorbidities were similar in both groups. There was a statistically significant reduction in cardiopulmonary bypass time (77.16 ± 13.13 minutes vs. 121.69 ± 28.18 minutes, P-value < .00001) and aortic cross clamp time (57.71 ± 10.6 minutes vs. 77.26 ± 20.29 minutes, p value < .00001) in the DNCP group. The total dose of cardioplegia solution required was significantly less in DNCP group (1000 mL vs. 2393.56 ± 592.42 mL, P-value < .00001). The mean post-operative hospital stay in DNCP group was 7.87 ± 1.25 days as compared to 12.49 ± 1.29 days in CBCP group with a P-value < .00001.

CONCLUSIONS

The del Nido cardioplegia solution is associated with shorter cardiopulmonary bypass and aortic cross clamp time, less volume of cardioplegia solution and shorter mean hospital stay. The del Nido cardioplegia can be used in adult cardiac surgery with the same safety of conventional blood cardioplegia in adult isolated coronary artery bypass surgery.

KEYWORDS

Del Nido Cardioplegia, Isolated Coronary Artery Bypass Surgery, Myocardial Protection, Cardiopulmonary Bypass Time, Aortic Cross Clamp Time

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BACKGROUND

Most adult cardiac surgeries are performed in patients suffering from heart arrest, which provides a motionless and blood less surgical field. Myocardial protection during open heart surgery has been the focus of clinical research for many decades. The concept of cardioplegia, a method to reduce global myocardial ischemic damage by inducing immediate cessation of electromechanical activity came in late 1950s.[1] The word 'cardioplegia' was introduced by Lam in 1957. The search for an ideal cardioplegia solution is still continuing since the beginning of cardiac surgery.

Several cardioplegic techniques with different chemical composition are used in cardiac surgery. The most widely used blood cardioplegia is a mixture of subject's oxygenated blood with a crystalloid solution in the ratio 4:1. The greatest disadvantage of conventional blood cardioplegia is that it has to be repeated every 25 - 30 minutes to maintain the diastolic cardiac arrest. For this the surgical procedure has to be interrupted leading to long myocardia ischemic time and cardiopulmonary bypass time. The del Nido cardioplegia[2] was introduced for paediatric cardiac surgery at the University of Pittsburgh by Pedro Del Nido and team in the early 1990s. With encouraging results of del Nido cardioplegia in adult cardiac surgery,[3] more and more centres started using del Nido cardioplegia in adults.[4]

This study was conducted to know the effectiveness of del Nido cardioplegia compared to blood cardioplegia in adult isolated coronary artery bypass surgery.

METHODS

This retrospective cohort study was conducted in a single tertiary care academic centre, Govt. T.D. Medical College, Alappuzha, Kerala using the clinical and operative data of patients who underwent isolated coronary artery bypass surgery from January 2011 to October 2018. The study protocol was approved by institutional research committee and institutional ethics committee. In October 2016, we changed the cardioplegia strategy from conventional blood cardioplegia to del Nido cardioplegia in all coronary artery bypass surgeries. The study population was organised into two groups based on the type of cardioplegia administered during surgery: group I intermittent conventional cardioplegia used in patients from January 2011 to September 2016, group II del Nido cardioplegia used in patients from October 2016 to October 2018. We selected consecutive first 100 patients in each group and data was collected from the case records of the patients in the medical records library.

Inclusion Criteria

All elective isolated coronary artery bypass surgeries performed using cardiopulmonary bypass and cardioplegia – either conventional blood cardioplegia or del Nido cardioplegia were included.

Exclusion Criteria

Emergency surgery, off pump coronary artery bypass surgery, non-coronary artery bypass grafting (CABG) cardiac surgeries, combined surgeries and surgeries using cardioplegia other than blood cardioplegia and del Nido cardioplegia were excluded from the study.

Cardioplegia

The conventional cardioplegia was prepared by adding 30 ml of potassium chloride (2 mEq / ml), 62.5 ml of 20 % mannitol and 30 ml of 8.4 % sodium bicarbonate to 1000 ml of 5 % dextrose and diluting it with the subjects heparinised oxygenated blood from the extracorporeal circuit in the ratio 1:4 (crystalloid: blood), cooled to 4^0 C and administered antegrade into the aortic root. The initial dose was 20 ml / kg and repeated every 25 - 30 minutes with a dose of 10 ml / kg.

The del Nido cardioplegia was prepared by adding 13ml of potassium chloride (2 mEq / ml), 16.3 ml of 20 % mannitol, 13 ml of 8.4 % sodium bicarbonate, 4 ml of 50 % magnesium sulphate, and 13 ml of 1 % lidocaine to 1000 ml of Plasma-Lyte A and diluting it with subjects heparinised oxygenated blood from the extracorporeal circuit in the ratio 4:1 (crystalloid: blood), cooled to 4^0 C and administered antegrade into the aortic root. Initial dosing was 1000 ml and redosing was considered when aortic cross clamp time reached 90 minutes.[2]

Data Collection

Specific pre-operative, intraoperative and post-operative variables were collected using structured proforma. Pre-operative patient demographics collected are detailed in Table I. The intraoperative and the post-operative variables collected are detailed in Table II.

Statistical Analysis

The data were collected and entered in Microsoft Excel and analysed using Statistical Package for the Social Sciences (SPSS). Independent samples t-test and chi-square test were used for testing level of significance where applicable. All P-values ≤ 0.05 were considered significant.

RESULTS

A total of 200 patients were studied; 100 in the conventional blood cardioplegia (CBCP) group and 100 in the del Nido cardioplegia (DNCP) group. The preoperative patient demographics in two groups are presented in Table I. There was no statistically significant difference between two groups. The overall mean age was 57.3 ± 7.67 years; and the male female ratio was 88:12. The intra-operative and post-operative feature of the two groups presented are in Table II. The CPB time and aortic cross clamp time in two groups were analysed and del Nido cardioplegia group showed a statistically significant reduction in CPB time (77.16 ± 13.13 minutes vs. 121.69 ± 28.18 minutes, P-value

< .00001, two sample T test) and aortic cross clamp time (57.71 ± 10.6 minutes vs. 77.26 ± 20.29 minutes, P-value < .00001, independent sample T-test). The DNCP group showed a statistically significantly lower volume of cardioplegic solution compared to CBCP group (1000 mL vs. 2393.56 ± 592.42 mL, P-value < .00001, independent sample T test). The requirement and duration of inotropic supports in the post-operative period didn't show any statistically significant difference between two groups. The duration of post-operative hospital stay was significantly short in the DNCP group with early discharge to home (7.87 ± 1.25 days vs. 12.49 ± 1.29 days, P-value < .00001, independent sample T-test).

Sl. No.	Parameter	CBCP	DNCP	P-Value	
1	AGE	56.38 ± 7.44	57.96 ± 7.76	.2398	Independent sample T test
2	SEX	M: F 88:12	84:16	.4149	Chi-square test
3	BSA	1.71 ± 0.15	1.70 ± 0.15	.7247	Independent sample T test
4	LMCA disease	41	43	.7744	Chi-square test
5	Number of coronary arteries involved	2.81 ± 0.40	2.67 ± 0.58	.0863	Independent sample T test
6	DM	54	52	.7769	Chi-square test
7	HTN	56	59	.6678	Chi-square test
8	DLP	35	42	.3090	Chi-square test
9	Pre-operative EF	62.27 ± 11.17	61.50 ± 9.83	.3301	Independent sample T test

Table 1. Pre-Operative Parameters

BSA: Body Surface Area, LMCA: Left Main Coronary Artery, DM: Diabetes Mellitus, HTN: Hypertension, DLP: Dyslipidaemia, EF: Ejection Fraction

Sl. No	Parameter		CBCP	DNCP	P Value	
1	Number of grafts		3.51 ± 0.73	3.62 ± 0.78	.3974	Independent sample T test
2	CPB Time		121.69 ± 28.18	77.16 ± 13.13	< .0001	Independent sample T test
3	ACC Time		77.26 ± 20.29	57.71 ± 10.6	< .0001	Independent sample T test
4	Cardioplegia volume (mL)		2393.56 ± 592.42	1000 ± 0	< .0001	Independent sample T test
5	Number of doses of CP		2.67 ± 0.73	1 ± 0	< .0001	Independent sample T test
6	Inotropes	Dopamine	100	100		
		Adrenaline	100	100		
		Noradrenaline	59	64	.4674	Chi square test
7	Post-operative EF (%)		57.7 ± 7.5	56.38 ± 7.44	.1446	Independent sample T test
8	Post-operative hospital stay (days)		12.49 ± 1.29	7.87 ± 1.25	< .0001	Independent sample T test

Table 2. Intraoperative and Post-Operative Parameters

CPB: Cardiopulmonary Bypass, ACC: Aortic Cross Clamp, CP: Cardioplegia, EF: Ejection Fraction

DISCUSSION

During cardiac surgery, maintaining a motionless heart and myocardial protection are important for the safe and effective performance of cardiac surgery and post-operative recovery. Several cardioplegic solutions with different chemical composition have been developed since the origin of concept of cardioplegia. But there is no consensus on the best cardioplegic solution. Every attempt in modification of chemical composition is made to minimize the myocardial injury during the cardioplegic arrest.[5] Initially ischemic cardiac arrest was used to cardiac contraction during surgery, which was associated with myocardial necrosis and postoperative myocardial dysfunction leading to high mortality. In 1813 Ringer reported that high concentration of potassium can cause cardiac arrest.[6] Based on this report, Melrose and associates used hyperkalaemic solution prepared by adding potassium citrate to blood during CPB to arrest the heart. Later the term 'cardioplegia' was coined by Lam et al. in 1957.[7]

In early 1980s, Follette and colleagues formulated the concept of cold hyperkalaemic blood cardioplegia.[8] The advantages with blood as the carrier include; its buffering capacity, endogenous oxygen radical scavenging property, detoxifying action and superior oxygen transport capacity. The myocardial protection and cardioplegia techniques witnessed a dramatic improvement to overcome or minimise the adverse effects of cardioplegic arrest. This mainly focussed on the rapid chemical arrest to conserve high energy phosphate stores and reduce ischemia, hypothermia to reduce the metabolic rate, adjunctive agents to reduce the effects of ongoing ischemia, continuous or intermittent delivery to restore or maintain tissue oxygenation, identifying metabolic enhancements and buffers, managing Ca2 + accumulation and understanding the pathophysiology of ischemia and reperfusion.

The resting membrane potential of the myocardial cell varies from - 50 to - 95 mV depending upon the type of cell. It is mainly contributed by the potassium + (K) channels which maintains an outward potassium current. The cardiac action potential has five phases. Phase 0: the rapid depolarisation and overshoot is caused by a sudden increase in conductance of sodium + (Na) due to activation of voltage gated Na + channels leading to movement of Na + ions in to the cells down its electrochemical gradient and the membrane potential moves close to Na + equilibrium potential of + 60 mV. Once the equilibrium potential of Na + is reached, the number of Na+ ions leaving and entering the cell reaches a balance and no current flows. Phase 1: early rapid repolarisation is due to closure of voltage gated Na + channels and activation of 4 -aminopyridine sensitive outward K + current, 4 -aminopyridine resistant calcium ions (Ca2) + activated chlorine (Cl) - current and an outward movement of Na + by Na + / Ca2 + exchange. Phase 2: plateau phase is due to slower and prolonged opening of voltage gated Ca2 + channels and partially by inward sodium current by Na + / Ca2 + exchanger. Phase 3: rapid repolarisation is due to closure of Ca2 + channels preventing inward movement of Ca2 + and activation of various K + channels leading to outward movement of K +. Phase 4: diastolic depolarisation is due to selective permeability of membrane to K +. The Na + / K + adenosine triphosphate (ATPase) pump exchanges three Na + for tow K + leading to a negative intracellular potential.

The cardioplegia solutions are classified broadly in to blood cardioplegia and crystalloid cardioplegia solutions based on the base solution used to deliver cardioplegia solution. The increased oxygen carrying capacity of blood compared to crystalloid, helps to maintain oxygen delivery to arrested myocardial cells and repay oxygen debt. The buffering capacity of histidine moieties in blood helps maintain acid base balance and pH. The glucose and fatty

acids in blood provides nutrition to the myocardial cells. The oxygen free radical scavengers present in blood like glutathione, glutathione peroxidase and catalase helps to protect from free radical mediated tissue injury. Due to these factors blood is considered as the ideal vehicle to deliver cardioplegia solution. The blood cardioplegia maintains aerobic arrest and helps to minimise ischemia and reperfusion injuries. The cardioplegia solution is mixed with blood in different proportions, cooled and delivered to the myocardium either antegrade or retrograde. The hypothermia helps to bring down the metabolic rate and myocardial oxygen demand. Immediately after connecting to cardiopulmonary bypass and draining of blood, the oxygen demand of myocardium is reduced by approximately 40 %. Arresting the decompressed heart in diastole using cardioplegia reduces myocardial oxygen demand by approximately 80 to 90 %. Combining hypothermia with diastolic cardioplegic arrest will bring down the myocardial oxygen demand by 97 %. The greatest reduction in myocardial oxygen demand in arrested heart is observed between 37^{o} C and 25^{o} C.

The conventional blood cardioplegic solution uses 5 % Dextrose as the base solution and is prepared by adding 30 ml of potassium chloride (2 mEq / ml), 62.5 ml of 20 % mannitol and 30 ml of 8.4 % sodium bicarbonate to 1000 ml of 5 % Dextrose and diluting it with the subjects heparinised oxygenated blood from the extracorporeal circuit in the ratio 1:4 (crystalloid: blood). The del Nido cardioplegia solution contains Plasma-Lyte A and a crystalloid component. The base solution has an electrolyte composition similar to extracellular fluid and the crystalloid component contains mannitol, magnesium sulphate, sodium bicarbonate, potassium chloride and lidocaine. The del Nido cardioplegia solution is mixed with blood in 4:1 ratio.

The cardioplegia solution used in cardiac surgery targets various phases of myocardial action potential and excitation-contraction coupling. Most commonly used method is depolarising cardiac arrest. Increased concentration of potassium in the extracellular fluid will cause depolarising cardiac arrest. The increased concentration of potassium in the extracellular space leads to depolarisation of cardiac myocyte membrane potential. When the membrane voltage is approximately - 65 mV, the voltage dependent fast Na + channels are inactivated and this prevents Phase 0 of action potential. The advantages of depolarisation arrest are: the arrest is rapid and is associated with reliable recovery. The major disadvantage with depolarisation arrest is poor myocardial recovery. The major reasons for poor myocardial recovery are; decreased adenosine triphosphate (ATP), intracellular acidosis, intracellular accumulation of Na + and Ca2 + and wash out of potassium containing solution. In polarised cardiac arrest, the membrane potential of the myocardial cell is kept close to the resting membrane potential. This helps in reducing the ATP utilisation and prevents intracellular accumulation of Ca2 +. The most commonly used polarising agents are lidocaine, procaine, magnesium, adenosine and potassium channel openers. Combining polarising agents with lidocaine which will block the sodium channels and magnesium which will compete Ca2 + along with the depolarising hyperkalaemia will help to minimise the negative effects of depolarising arrest by keeping the cells polarised to some degree and this will prevent intracellular accumulation of Na + and Ca2 +.

The intracellular Ca2 + concentration is maintained low in normal myocardial cells by the voltage gated Ca2 + channels. The regulation of intracellular concentration of Ca2 + is closely associated with the intracellular concentration of Na +. Three mechanisms operate to maintain intracellular concentration of Na +. The first mechanism is Na + / K + ATPase pump which moves one Na+ out for one K+ in against their concentration gradient. Second mechanism is Na + / hydrogen (H) + exchanger which exchanges one Na+ for one H+ removed from cytosol. Third mechanism is Na + / Ca2 + exchanger which pumps out intracellular Ca2 + in exchange for Na + into the cell during diastole. During myocardial ischemia and reperfusion, there is disruption of this Na + and Ca2 + homeostasis leading to accumulation of Na + and Ca2 + with in the cell. During myocardial ischemia, myocardial cells will shift to anaerobic glycolysis which will produce only 2 ATPs / mole of glucose and a heavy load of H+ is generated during this process. This increased concentration of H + ions within the cells will stimulate Na + / H + exchanger leading to pumping out of H + in exchange for Na + which will result in increased intracellular concentration of Na +. The reduced availability of ATP due to anaerobic glycolysis will lead to decreased activity of Na + / K + ATPase resulting in intracellular accumulation of Na +. Accelerated accumulation of intracellular Ca2 + ions during the myocardial ischemia mediates the early myocardial injury that occurs during the reperfusion.[9] Lidocaine in the del Nido cardioplegia has membrane stabilising properties and is a Class I antiarrhythmic drug. Lidocaine directly blocks Na + channels in the phase 0 of action potential leading to increased refractory period of myocardial cells. Lidocaine has a relatively long half-life, which is prolonged in the absence of coronary circulation. Lidocaine blocks intracellular accumulation of Ca2 + by blocking the 'window' channel. Mg2 + acts as a calcium antagonist, blocks L-type Ca2 + channels in the phase 2 of action potential and helps to reduce the intracellular accumulation of Ca2 + and thereby reducing myocardial excitability, cellular metabolism and energy consumption.[10]

Reactive oxygen species are free oxygen radicals derived from oxygen and include superoxide anion (- O2) and hydroxyl anion. They are mainly produced in the mitochondria. Normally in low concentration, these free radicals help in body's defence mechanism against microorganisms and cardioprotective conditioning responses. A check is maintained in their level by the endogenous antioxidant mechanisms–superoxide dismutase, catalase, reduced glutathione, glutathione peroxidase and glutathione reductase. But during myocardial ischemia, these endogenous antioxidants are depleted leading to state that favours accumulation of oxygen free radicals. However, the supply of primary substrate for production of free radicals, oxygen, is limited during myocardial ischemia and hence the production of oxygen free radicals is mainly seen during reperfusion when oxygen is introduced into the myocardial circulation after a

period of ischemia and in the post-operative period. Intermittent perfusion of myocardium with cardioplegic solution in multidose cardioplegia strategy increases the production of oxygen free radicals compared to single dose cardioplegia strategy. The oxygen free radicals will cause tissue injury of peroxidation of lipid component of cellular membranes including sarcoplasmic reticulum and mitochondrial membranes leading to loss of membrane potential, metabolic activity and release of proapoptotic factors. In vascular endothelium free radicals will cause disruption of endothelia function leading loss of endothelial integrity, increased production of pro-inflammatory factors and vasoactive substances. All these mechanisms contribute to the post-ischemic myocardial dysfunction, dysrhythmia, myocardial necrosis and apoptosis. Mannitol in the del Nido cardioplegia acts as a free radical scavenger and helps to reduce myocardial oedema by its osmotic activity.

Sodium bicarbonate helps to maintain the intracellular pH. During cardioplegic arrest, the myocardial cells will shift to anaerobic glycolysis for ATP synthesis. Anaerobic glycolysis will lead to production and accumulation of more H+ ions which intern inhibit the anaerobic glycolysis. Sodium bicarbonate in del Nido cardioplegia helps to scavenge H + ions and maintains pH favourable for anaerobic glycolysis. The high concentration of carbonic anhydrase in the red blood cells (RBCs) in the blood component of del Nido cardioplegia scavenges H + ions more efficiently with bicarbonate producing carbon dioxide and water.

The present study evaluated the safety of del Nido cardioplegia in adult isolated coronary artery bypass surgery. The study showed a significantly lower dose of cardioplegic solution requiring only single dose in the del Nido cardioplegia group for procedure requiring less than 90 minutes, with a significantly reduced CPB time and aortic cross clamp time compared to conventional blood cardioplegia without affecting the post-operative outcome. In the paper ' Comparison of del Nido cardioplegia and St. Thomas Hospital solution – two types of cardioplegia in adult cardiac surgery' published by Prashant Mishra et al. in the Kardiochirurgia i Torakochirurgia Polska 2016, they concluded that the use of del Nido cardioplegia leads to shorter cross clamp and CPB times, reduces cardioplegia dosage, and provides potentially better myocardial protection in terms of left ventricular ejection fraction (LVEF) preservation, with a safety profile comparable to St. Thomas cardioplegia.[11]

The advantages of the del Nido cardioplegia are

1. Single dose application.
2. Low Ca2 + levels.
3. Glucose free ingredients.
4. Reduced CPB time and aortic cross clamp time.
5. Early myocardial recovery.
6. Shorter hospital stays and early discharge to home.

CONCLUSIONS

Our study showed that the del Nido cardioplegia is safe and effective in adult cardiac surgery as the conventional blood cardioplegia and is associated with reduced CPB time and aortic cross clamp time, less volume of cardioplegia solution and shorter post-operative hospital stay. Moreover, the cardiac surgery can be performed uninterrupted using the del Nido cardioplegia, unlike in conventional cardioplegia in which surgery has to be interrupted during repeated doses of cardioplegia. More studies are required to establish its safety, indications and optimal use.

Limitations of the Study

The present study was a retrospective single-centre study. There was no long-term follow-up data. Multicentre, prospective randomised controlled studies are required to establish best uses of del Nido cardioplegia.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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