The application of del Nido cardioplegia for myocardial protection in adult coronary artery bypass grafting: a cohort study

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Background: Del Nido cardioplegia is widely used in adult cardiopulmonary bypass surgery and has a satisfying cardioprotective effect for about 90 minutes by single dose, but the effect in patients with coronary heart disease remains confused. The purpose of this study was to examine the cardioprotective effect of del Nido cardioplegia in adult multivessel coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB).

Methods: This retrospective comparative analysis included 124 consecutive patients undergoing isolated on-pump CABG performed by a single surgeon between January 2017 and December 2020. The demographic characteristics and medical history of the included patients were collected. The included patients were divided into two groups: a del Nido cardioplegia (DN) group and a conventional multidose blood cardioplegia (BC) group. Perioperative, intraoperative, and postoperative indicators and complications were compared.

Results: Compared with the BC group, CPB and aortic cross-clamp time were significantly shorter in the DN group. In the early postoperative period, the hemoglobin concentration in the DN group was significantly higher than that in the BC group (P<0.05).

Conclusions: This study demonstrated that the application of del Nido cardioplegia in adult on-pump CABG could lead to a significantly shorter aortic cross-clamp and CPB time, as well as a higher hemoglobin concentration in the early postoperative period. The myocardial protective effect of del Nido cardioplegia is not inferior to that of conventional blood perfusion in adult on-pump CABG.

Keywords: del Nido cardioplegia; coronary artery bypass grafting (CABG); myocardial protection

Introduction

Cardioplegia is widely used in cardiopulmonary bypass (CPB) cardiac surgery. It can protect the myocardium, maintain cardiac arrest, provide myocardial metabolic substrates, and create a clear field for surgeons. There are various types of cardioplegia available for cardiac surgery. Cardioplegia can be divided into crystalloid cardioplegia and blood-containing cardioplegia according to its composition. Blood cardioplegia is more in line with a basic physiological condition and can provide energy and substrate to the myocardium, thereby providing better myocardial protection. Therefore, an intermittent warm blood cardioplegia strategy has widely applied in on-pump coronary artery bypass grafting (CABG) (1). The del Nido cardioplegia solution (DNS) was first developed for pediatric cardiac surgery (2). Previous reports have demonstrated the favorable myocardial protection of the DNS in adult

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valve surgery (3,4). In terms of myocardial protection, the currently widely used model is K$^+$ induced cardiac arrest. The theoretical basis is that high concentration of K$^+$ causes cell membrane depolarization and induces cardiac arrest in diastole. Different kinds of substrates provide several functions. For example, the dehydration effect of mannitol can prevent cardiomyocytes from hypertonic myocardial edema and damage caused by reactive oxygen species, while magnesium can competitively inhibit the influx of calcium ions which causes muscle contractions, thereby improving the function of cardiac muscles. Lidocaine, as an improved depolarizing agent, can reduce sodium and calcium ion influx by inhibiting sodium ion channels. To prevent the accumulation of calcium ions, DNS can also reduce the toxic reaction of hyperkalemia to cardiomyocytes. Finally, sodium bicarbonate is included to maintain the cell acid–base balance, effectively neutralize the acid substance produced by ischemic cardiomyocytes, reduce the times of myocardial perfusion, and prevent myocardial injury caused by prolonged cardiac arrest. Therefore, DNS allows surgeons to provide longer cardioprotective duration with a single dose of perfusion solution. However, myocardial protection for the patients with coronary artery disease is more challenging due to coronary stenosis, ventricular hypertrophy, and myocardial ischemia. DNS has a clear advantage in cardioprotective duration, but whether it is equally effective in patients with coronary heart disease is less certain. Therefore, the purpose of the present study was to investigate the myocardial protective effect of DNS and conventional blood cardioplegia (blood: crystalloid solution =4:1) in patients undergoing isolated on-pump CABG. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1965/rc).

Methods

Patients

Isolated on-pump CABG was performed in the 124 patients by a single surgeon at the department of Cardiovascular Surgery in the Nanfang Hospital of Southern Medical University from January 2017 to December 2020. In our institution, we switched our cardioplegia protocol from blood cardioplegia to del Nido cardioplegia in June 2018. Between January 2017 and May 2018, a total of 78 consecutive patients undergoing CABG using blood cardioplegia solution were included in the "BC group",

including 60 males and 28 females. Between June 2018 and December 2020, 46 consecutive patients undergoing CABG with DN cardioplegia solution were included in the "DN group", including 36 males and 10 females. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Nanfang Hospital (No. NFEC-2020-045). Individual consent for this retrospective analysis was waived.

Inclusion and exclusion criteria

The inclusion criteria for patients in this study who were older than 18 years old, diagnosed with coronary atherosclerotic heart disease in our institution, and who were undergoing isolated on-pump CABG for the first time.

The exclusion criteria for patients in this study were those who required emergency surgery; required fewer than 3 grafts; underwent cardiac surgery; required preoperative positive inotropic drug support; underwent preoperative mechanical circulatory support; had implanted pacemakers or implantable cardioverter defibrillators; had severe renal failure, liver failure, pulmonary disease, or malignancies; and those whose perioperative data were missing.

Study methods

Anesthesia and CPB

All patients were treated with general intravenous-inhalation combined anesthesia. After anesthesia, median sternotomy was routinely performed on patients so that on-pump CABG could be performed. During the operation, del Nido cardioplegia was applied in the DN group, and the traditional hyperkalemia cardioplegia (blood cardioplegia) was used in the BC group (blood: crystalloid solution =4:1). Intraoperative myocardial perfusion was performed by anterograde perfusion of the aortic root. In the DN group, del Nido cardioplegia was mixed with the patient's blood in a ratio of 1:4 and was perfused at 20 mL/kg, with the total amount not exceeding 1,000 mL. Cardioplegia was be added unless the duration of myocardial ischemia exceeded 90 minutes or cardiac electrical activity was detected during aortic cross-clamp. In the BC group, the high-potassium crystalloid solution was mixed with the patient's blood in a ratio of 1:4 and was perfused at 20 mL/kg, with the total amount not exceeding 1,000 mL, an additional half-volume of potassium ion cardioplegia (300–500 mL) was added at

30-minute intervals. After CPB, protamine was given to neutralize heparin before release of the aortic cross-clamp. Cannulae were removed and the patients were subsequently returned to the intensive care unit (ICU).

Observation indicators

We used a cohort study design to compare baseline, intraoperative, and postoperative data and complications between two groups of patients. Medical history data were extracted through a case management system and included the following: perioperative data, such as gender, age, height, and weight; preoperative complications, such as diabetes, hypertension, chronic kidney disease, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD); preoperative left ventricle ejection fraction (LVEF); preoperative serum creatinine (Scr) level; intraoperative data , such as CPB time, aortic cross-clamp (ACC) time, operation time, times of cardioplegia perfusion, total perfusion volume, and spontaneous heart rate; postoperative data, such as Scr level, hemoglobin concentration (Hb), and troponin T (cTnT), before operation (T0), immediately after ICU entry (T1), and 24 hours after operation (T2); total blood transfusion volume; ventilation time, ICU stay time; and postoperative complications. The indicators we used to assess the myocardial protection function included cardiac troponin T, postoperative complications, including ventilation time, acute kidney injury, postoperative atrial fibrillation and IABP requirement.

Statistical analysis

All statistical analyses were conducted using SPSS (version 25.0, IBM Corp., Armonk, NY, USA). Normal distribution tests, correlation, and parametric and nonparametric analyses were performed on the samples. Continuous variables are expressed as a mean ± SD. An independent samples *t*-test was performed for normal distribution analysis of continuous variables. For comparisons between the two groups, the Pearson chi-square test and Fisher's exact test were used for categorical variables. P values <0.05 were considered statistically significant.

Results

Preoperative clinical baseline data

There was no significant difference in preoperative clinical baseline data between the BC and DN groups, with comparable mean age (58.82 *vs.* 61.28 years, respectively),

preoperative EuroSCORE (European System for Cardiac Operative Risk Evaluation; 3.13 *vs.* 2.91, respectively), preoperative creatinine (103.77 *vs.* 103.76 mmol/L, respectively), pre-CPB LVEF (59.15% *vs.* 57.11%, respectively), and cTnT (0.28 *vs.* 0.21 ng/mL respectively; *Table 1*).

Intraoperative observation indicators

CPB time, ACC time, and perfusion time was significantly lower in the DN group than in the BC group (P<0.05). No significant difference was found between the groups in terms of blood products requirement, hematocrit (Hct) level before the termination of CPB, and spontaneous returned heart rate (P>0.05). The intraoperative data of both groups are presented in *Table 2*.

Postoperative and prognostic indicators

The postoperative and prognostic indicators of both groups are shown in *Table 3*. No significant difference was observed between the groups with regard to the ICU stay time, ventilation time, postoperative Scr, cTnT, LVEF, complications, or mortality (P>0.05), However, the hemoglobin level of the patients at T1 (immediately after ICU entry) and T2 (24 hours after surgery) in the DN group was significantly higher than that in the BC group. The adverse events in this study were in-hospital mortality and postoperative complications, including neurological complication, acute renal dysfunction, atrial fibrillation, IABP requirement, re-exploration for bleeding and poor wound healing. No significant difference was observed in both groups with regards to in-hospital mortality [1 patient (2.2%) in DN group versus 2 patients (2.6%) in BC group]. Furthermore, no significant difference was found in both groups in terms of the incidences of postoperative complications including neurological complication, acute renal dysfunction, atrial fibrillation, IABP requirement, re-exploration for bleeding and poor wound healing.

Discussion

Open-heart surgery often requires the heart to maintain a state of arrest, and cardioplegia is a mixed solution that changes the electrolyte environment to depolarize the cell membrane, induce cardiac arrest, and maintain a diastolic state. After years of extensive clinical application, DN cardioplegia has been extended from early pediatric cardiac

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Table 1 Baseline preoperative characteristics and comorbidities of both groups

Variable	All (N=124)	BC group (N=78)	DN group (N=46)	P value
Age (years)	59.73±9.19	58.82±8.38	61.28±10.34	0.150
BMI (kg/m^2)	19.65±2.92	20.09±3.04	19.69±2.73	0.465
Male (n)	96	60	36	0.863
LVEF (%)	58.39±9.35	59.15±9.27	57.11±9.45	0.243
Diabetes mellitus	56	30	26	0.051
Hypertension	76	49	27	0.649
Peripheral arterial disease	17	13	4	0.213
Cerebrovascular disease	21	13	8	0.917
COPD	11	8	3	0.704
Scr (mmol/L)	103.77±80.68	103.77±79.43	103.76±83.64	1.000
HGB (g/L)	128.39±18.52	126.81±18.07	131.07±19.17	0.218
cTnT (ng/mL)	0.26±0.52	0.28±0.44	0.21±0.69	0.467
EuroSCORE	3.05±2.08	3.13±2.10	2.91±2.06	0.580

BC, blood cardioplegia; DN, del Nido cardioplegia; BMI, body mass index; LVEF, left ventricle ejection fraction; COPD, chronic obstructive pulmonary disease; Scr, serum creatinine; HGB, hemoglobin; cTnT, cardiac troponin T.

Table 2 Comparison of the intraoperative observation indicators between the two groups

Variable	All (N=124)	BC group (N=78)	DN group (N=46)	P value
CPB time (min)	136.74±27.99	140.3±31.49	130.59±19.57	0.035
ACC time (min)	59.38±14.99	61.68±16.74	55.48±10.48	0.012
Perfusion times	1.51±0.58	1.76±0.56	1.09±0.29	<0.001
Transfused ES (mL)	166.13±224.38	175.64±217.39	150.00±237.35	0.541
Transfused FFP (mL)	30.08±101.57	37.66±115.89	17.39±70.88	0.231
Transfused albumin (mL)	10.08±31.22	6.41±24.65	16.30±39.52	0.130
Hct before CPB shutdown (%)	26.98±3.56	27.14±3.37	26.67±3.89	0.483
Spontaneous returned heartbeat (%)	114 (91.9)	69 (87.3)	45 (97.8)	0.131

BC, blood cardioplegia; DN, del Nido cardioplegia; CPB, cardiopulmonary bypass; ACC, aortic cross clamp; ES, erythrocytes; FFP, fresh frozen plasma; Hct, red blood cell specific volume.

surgery to adult cardiac surgery due to its advantages of long duration in maintaining myocardial protection through single perfusion (5,6). DNS was first used in pediatric CPB surgery in the 1990's (2). Unlike children, adults with heart problems often face to more serious illnesses, myocardial aging, or heart enlargement, and thus adult myocardial protection is mired with challenges. In addition, renal function in adults is less tolerant of crystal load, thus limiting its use in adults. Early use of cardioplegia mostly involved a blood-free high-concentration potassium citrate crystal solution. However, due to its poor oxygen-carrying capacity, easy-to-induce focal myocardial necrosis, and coronary endothelial damage, among other drawbacks (7), it has gradually been replaced by blood cardioplegia. Blood cardioplegia can provide oxygen and metabolic substrates for the ischemic myocardium by virtue of its oxygen-carrying capacity for blood, although it alleviates ischemia-reperfusion injury through multiple mechanisms (8). Blood cardioplegia needs to be perfused every 20 minutes due to its short duration of cardioprotective effect, which

Table 3 Comparison of postoperative and prognostic indicators between the two groups

Variable	All (N=124)	BC group (N=78)	DN group (N=46)	P value
Heart rebeating (%)	114 (91.9)	69 (87.3)	45 (97.8)	0.131
LVEF	60.21±6.97	60.99±6.61	58.93±7.46	0.119
Scr (mmol/L)				
T1	105.17±76.53	108.63±80.73	99.30±69.28	0.514
T2	128.44±82.13	130.19±81.67	125.48±83.72	0.759
HGB (g/L)				
T1	110.93±16.89	108.18±16.19	115.59±17.22	0.018
T2	104.43±14.89	102.19±15.20	108.22±13.69	0.029
Hct (%)				
T1	0.33±0.05	0.32±0.05	0.34±0.05	0.004
T2	0.31±0.04	0.31±0.05	0.33±0.04	0.028
CTnT (ng/mL)				
T1	6.42±5.67	6.63±5.28	6.07±6.31	0.592
T2	3.35±3.67	3.44±3.87	3.20±3.32	0.726
ICU stay (d)	3.9±2.8	4±2.9	3.7±2.6	0.563
Ventilation time (d)	1.8±1.9	1.6±1.6	2.0±2.3	0.349
Neurological complications	4	2	2	0.475
Acute renal dysfunction	9	5	4	0.908
Atrial fibrillation	20	14	6	0.473
IABP requirement	9	5	4	0.908
Re-exploration for bleeding	10	7	3	0.886
Poor wound healing	14	9	5	0.909
In-hospital mortality	3	2	1	0.691

LVEF, left ventricle ejection fraction; Scr, serum creatinine; HGB, hemoglobin; Hct, red blood cell specific volume; cTnT, cardiac troponin T; ICU, Intensive Care Unit; IABP, intra-aortic balloon pump.

can lead to surgical interruption. Patients with coronary heart disease have poor vascular conditions, and most have atherosclerotic plaques. Moreover, repeat touching of the coronary artery opening may increase the risk of plaque shedding. Furthermore, substrates required for cell metabolism may be washed away due to repeated perfusion, which can affect the cardio protection (9). Therefore, a better strategy of myocardial perfusion during on-pump CABG is urgently required.

The del Nido solution is an extracellular cardioplegia based on a high-potassium environment. It uses compound electrolyte as the base solution and contains 10% potassium chloride, 25% magnesium sulfate, 5% sodium bicarbonate, 2% lidocaine, and 20% mannitol, and is mixed in crystal:blood ratio of 4:1. It can induce cardiac arrest by a high potassium environment, and the dehydration effect of mannitol can prevent cardiomyocytes from hypertonic myocardial edema and damage caused by reactive oxygen species, while magnesium can competitively inhibit the influx of calcium ions which causes muscle contractions. Lidocaine, as an improved depolarizing agent, can reduce sodium and calcium ion influx by inhibiting sodium ion channels. To prevent the accumulation of calcium ions, it can also reduce the toxic reaction of hyperkalemia to cardiomyocytes (2). Finally, sodium bicarbonate is included to maintain the cell acid-base balance. *In vitro* experimental

studies have found that DNS can prevent spontaneous contraction during arrest, reduce the release of troponin, and produce excellent myocardial function in isolated cardiomyocytes; moreover, previous animal experiments suggest that its myocardial protective effect can last for about 90 minutes (6,8,10). In terms of highlights of the present study, firstly, we collected the data of patients who undergoing surgery by the same surgeon, which may exclude possible biases by different surgeon. Secondly, we included the marker of myocardial injury (cTnI) and postoperative complications to fully demonstrate the safety and efficacy of DNS. Finally, another highlight of our manuscript was that we compared the cardioprotective effect of DNS with blood cardioplegia, the most mainstream cardioplegia used in CABG, thereby making our conclusion more suitable for clinical practice.

In the present study, the times of perfusions in the DN group were significantly shorter than those in the BC group. Most of the patients in the DN group only needed a single intraoperative perfusion (only 4 patients needed 2 perfusions), while about 69.2% patients in the BC group need more than 2 perfusions. In addition, the ACC time (61.679±16.739 *vs.* 55.478±10.477; P<0.05) and CPB time (140.372±31.486 *vs.* 130.587±19.573; P<0.05) of the DN group were significantly shorter than those of the BC group. In the BC group, longer reperfusion and graft perfusion duration, as well as, the interruption of the procedure might have increased the operation time. Reducing the operating time may not only mitigate myocardial damage to a certain extent, but may also improve the efficiency of operating room usage and reduce the costs of hospital management (5,11-14). O'Donnell and colleagues found reported the requirement for defibrillation in a DN group to be significantly less than that a BC group (33.3% in the BC group *vs.* 13.0% in the DN group) (15). Therefore, reducing defibrillation appear to be highly conducive to postoperative myocardial recovery (16).

In this study, there was no significant difference between the two groups in the occurrence of spontaneous returned heartbeat or early postoperative troponin T levels, which might indicate that the myocardial protection effect of DNS is not inferior to that of blood cardioplegia. However, there may be selection bias due to the small sample size of this study. In addition, the process of CPB may cause coagulation disorders and blood cell destruction, which are mainly due to the effects of the interaction between heparin and protamine, compression damage of the pump, and inflammatory and oxidative stress reactions

(17-20). In the present study, we found that the level of hemoglobin and Hct in the DN group were higher than those in the BC group at the time of ICU admission and 24 hours after surgery. However, no significant difference was observed between the two groups with regard to the level of hemoglobin and Hct before the termination of CPB. This interesting phenomenon may be due to the shortened CPB and ACC duration, which can improve the coagulation function. Compared with that in the BC group, the incidence of postoperative bleeding in the DN group was lower, which reduced the loss of blood cells. Anemia has been shown to be closely related to early postoperative complications and mortality (21). Previous studies have shown that when Hct drops to 22% during CPB, the incidence of postoperative complications, such as stroke, myocardial infarction, low cardiac output, sudden arrest, kidney injury, prolonged ventilation time, pulmonary edema, sepsis, and multiple organ failure, obviously increase (22). Red blood cells participate in the oxygen-carrying process *in vivo*. Therefore, there is a risk of insufficient oxygen supply when the hemoglobin concentration drops significantly, which may lead to increased mortality. Blood transfusion, as a treatment for anemia, can increase the level of hemoglobin, but it is often associated with serious postoperative complications. The increased amount of blood transfusion in patients after cardiac surgery may increase the risk of various postoperative complications. In addition, there are increased risks of the spread of immunosuppressed infectious diseases and immune blood transfusion reactions (23-25). Therefore, it is critical that the abnormal coagulation function caused by prolonged CPB time be improved to better prevent complications after cardiac surgery. Furthermore, drainage volume and coagulation function indicators which may directly reflect the bleeding after CPB have not been included in our study and should thus be further explored in our subsequent research.

Compared with conventional multidose blood cardioplegia, the advantages of DNS can be stated as followed. Firstly, DNS can provide a 90-minute static and bloodless environment for surgeons with only a single dose, which can avoid surgical interruption and significantly shorten CPB time. Secondly, less precharge volume can be achieved in the DNS protocol, thereby avoiding hemodilution during the initial stage of CPB. On the other hand, the limitations of DNS shouldn't be ignored. In the DNS protocol, more crystalloid will be used during perfusion, which may aggravate the hemodilution

and increase volume load during the process of cardiac arrest. Furthermore, another dose of DNS may be needed after the first 90-minute cardiac arrest, but the optimal cardioprotective period of the second dose DNS still remains unclear.

This study had a few limitations which should be noted. First, this study was the retrospective nature of the data collection and the relatively small sample sizes. In order to exclude possible biases caused by different surgeons, all patients included in this study were operated on by the same surgeon, but this may have introduced patient selection biases. Second, some clinical and laboratory markers of myocardial injury were not collected to assess the severity of myocardial injury. Finally, the postoperative follow-up was relatively short. To further explore the cardioprotective effect of the DNS on CABG, it is necessary to conduct a more in-depth and sufficient large-sample multicenter prospective study.

Conclusions

This study revealed that the cardioprotective effect of Del Nido cardioplegia is not inferior to that of traditional blood cardioplegia in OPCABG. The application of del Nido cardioplegia in the OPCAB significantly shortens CPB time and ACC time due to the reduction of perfusion times and maintenance of the fluency of operations, thereby leading to a greater degree of myocardial protection.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1965/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1965/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1965/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Nanfang Hospital (No. NFEC-2020-045). Individual consent for this retrospective analysis was waived.

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(English Language Editor: J. Gray)