Experience in the Use of del Nido Cardioplegia in Ramathibodi Hospital

Narongrit Kantathut MD*, Chaliow Shaishana CCP*,
Wanrudee Thongcherd CCP*, Wilailak Sornprasit CCP*,
Sumethee Jiraratkul CCP*, Suthit Vilaikan CCP*, Panwasa Krailest CCP*,
Parinya Leelayana MD*, Piya Cherntanomwong MD*, Siam Khajarern MD*

** Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

Background: *del Nido cardioplegia is an extracellular, single-dose, non-calcium cardioplegic solution that has been increasing in popularity for the last decade. Plasma-Lyte A, the main base solution is not available in Thailand. We hypothesized that lactated Ringer solution can safely replace Plasma-Lyte A as the main carrier for del Nido cardioplegia.*
Objective: *To report early results using lactated Ringer solution as a main carrier for del Nido cardioplegia.*
Material and Method: *All patients undergoing cardiac surgery with del Nido cardioplegia between December 2016 and May 2017 were reviewed. Preoperative, intraoperative, and postoperative outcomes were collected and analyzed.*
Results: *Mean age was 51.48±20.58 years, and 57.14% were male. Mean STS score was 3.01±3.10. Total cardioplegia use was 1,207.43±380.93 ml. Number of cardioplegia given was 1.66±0.72 times. Aortic cross clamp time and total bypass time were 108.51±48.60 mins and 145.63±55.63 mins, respectively. Ventricular fibrillation after aortic cross clamp removal occurred in four patients (11.43%). ICU stay and hospital stay were 1.94±1.15 days and 8.06±7.57 days, respectively. New onset of atrial fibrillation occurred in six patients (17.14%). Complications occurred in one patient (2.86%) (acute kidney injury). There was one case of mortality (2.86%) was observed.*
Conclusion: *Lactated Ringer solution can be used safely to replace the crystalloid component of del Nido cardioplegia, Plasma-Lyte A, with an acceptable result.*

Keywords: *del Nido cardioplegia, Lactated ringer solution, Myocardial protection*

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del Nido cardioplegia has been used exclusively in the pediatrics cardiac centers for myocardial protection during cardiac surgery[1]. The single-dose, cold blood cardioplegia, can be safely delivered antegrade or retrograde for longer redosing interval. There is increasing in popularity in the adult cardiac surgery due to its cost-effectiveness and excellent myocardial protection[2-11]. Unfortunately, its use is nearly impossible for the countries where Plasma-Lyte A, the main carrier for del Nido cardioplegia, is not available.

With this limitation, our intention was to find a good substitute for Plasma-Lyte A. Although the crystalloid component of del Nido cardioplegia was designed to have no calcium, lactated Ringer solution can safely replace Plasma-Lyte A and be administrated with an excellent result in some cardiac centers (by direct communication with Dr. Pedro del Nido who developed this solution).

Our goal was to report early results using lactated Ringer solution as a main carrier for del Nido cardioplegia.

Correspondence to:
Khajarern S, Cardiovascular and Thoracic Surgery, Department of Surgery, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.
Phone: +66-2-2011315, Fax: +66-2-2011316
E-mail: siam.kha@mahidol.ac.th

Material and Method

Patient population and study design

Between December 2016 and May 2017, 35 patients that underwent cardiac surgery using lactated Ringer solution as a main carrier for del Nido cardioplegia were included in this study. Patient characteristics included age, gender, body surface area, preoperative comorbidities (diabetes, hypertension, hyperlipidemia, prior stroke, atrial fibrillation, chronic kidney disease with baseline creatinine greater than 2.0 mg/dL, chronic obstructive pulmonary disease (COPD), cirrhosis), New York Heart Association functional classification, Society of Thoracic Surgeon predicted risk of mortality score (STS score), prior cardiac surgery, type of operation and the outcomes

included total cardioplegia volume, number of cardioplegia doses, retrograde/antegrade cardioplegia use, total aortic cross clamp time, total bypass time, ventricular fibrillation after aortic cross clamp removal, length of stay in the ICU, post-operative hospital stay, new onset of atrial fibrillation, acute kidney injury, respiratory complication, and stroke, mortality were collected prospectively under protocol approved by Institutional Review Board of Ramathibodi Hospital, Mahidol University. This descriptive, non-comparison study was designed to describe the composition and delivery methods of del Nido cardioplegia using lactated Ringer solution as a main crystalloid component, and to report early outcomes.

Composition of del Nido cardioplegia

A comparison of del Nido cardioplegia components is shown in Table 1. The cardioplegia is sterilely prepared by Ramathibodi Hospital's pharmacist in clean room class 100 (ISO class 5-International Organization of Standardization). It is kept in refrigerator with temperature 2 to 8°C and will be used within 24 hours. It is delivered 1: 4 with 1 part of oxygenated pump blood to 4 parts of cardioplegia solution.

Cardioplegia administration

del Nido cardioplegia can be delivered antegrade through Aortic root catheter, directly through the coronary ostia, or retrograde via coronary sinus, depending on the type of operation and degree of aortic valve insufficiency. Our protocol is to administer as a single dose 20 mL/kg with maximum dose of 1,000 mL for patients larger than 50 kg. After 90 minutes of aortic cross clamp time, the surgeon decides how much subsequent doses needs to be administered[1,12]. In our circuit, del Nido cardioplegia passes through a cardioplegia set with coil heat exchanger and the delivery temperature is at 4°C. It is generally given over one to two minutes with system pressure 100 to 200 mmHg (Fig. 1).

Table 1. Composition of del Nido cardioplegia solutions

Components	del Nido cardioplegia	Modified
Base solution (1 L)	Plasma-Lyte A	Lactated ringer solution
Sodium Bicarbonate 1 mEq/mL	13 mL	13 mL
Mannitol (20%)	16.3 mL	16.3 mL
Magnesium Sulfate (50%)	4 mL	4 mL
Lidocaine (1%)	13 mL	13 mL
Potassium Chloride 2 mEq/mL	13 mL	13 mL

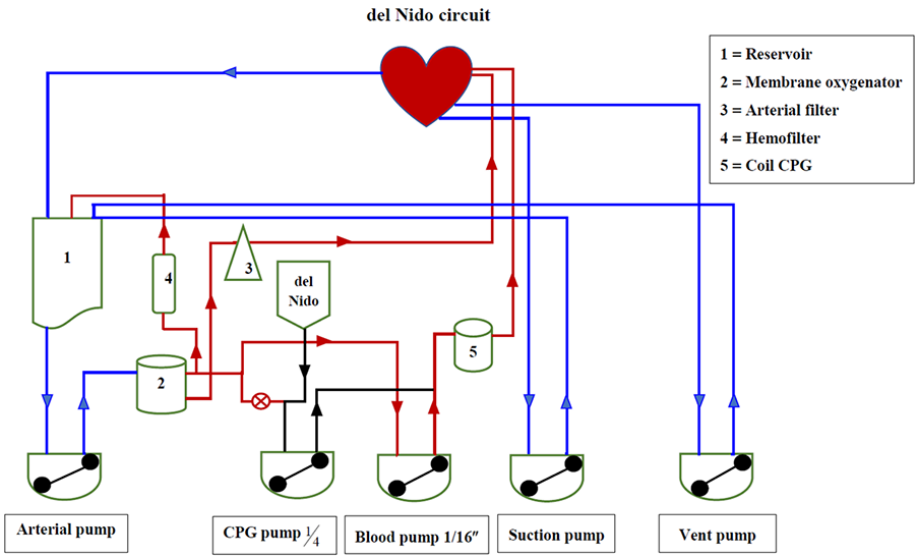

Fig. 1 Cardiopulmonary bypass circuit for del Nido cardioplegia (Coil CPG: Cardioplegia set with coil heat exchanger).

Statistical analysis

Data were analyzed using STATA version 14 (Texas, USA). Continuous variables were reported as mean and standard deviation. Categorical variables were reported as frequency and percentage.

Results

Patient demographics

The baseline patients' characteristics are summarized in Table 2. Mean age was 51.48±20.58 years (range 6 to 81, 95% CI 44.38 to 58.59). Twenty patients (57.14%) were male. The types of operations are summarized in Table 3. Mean STS score was 3.01±3.10% (n = 26, range 0.50 to 13.82, 95% CI 1.75 to 4.26). We could not calculate STS mortality score for all patients because it is not available for the patients with congenital heart disease.

Intraoperative variables

Intraoperative outcomes are summarized in Table 4. Mean cardioplegia use was 1,207.43±380.93 ml (range 250 to 2,000, 95% CI 1,076.57 to 1,338.28). Mean number of cardioplegia given was 1.66±0.72 (range 1 to 4, 95% CI 1.41 to 1.91). Mean aortic cross clamp time was 108.51±48.60 minutes (range 26 to 205, 95% CI 91.82 to 125.21). Mean total bypass time was 145.63±55.63 minutes (range 47 to 271, 95% CI 126.52 to 164.74). Four patients (11.43%) had ventricular fibrillation after aortic cross clamp removal.

Postoperative outcomes

Postoperative outcomes are summarized in Table 5. Mean ICU stay was 1.94±1.15 days (n = 34, range 1 to 6, 95% CI 1.54 to 2.34). Mean hospital stay was 8.06±7.57 days (n = 34, range 4 to 42, 95% CI 5.41 to 10.70). Six patients (17.14%) had new onset of atrial fibrillation. One patient (2.86%) had acute kidney injury. There was no respiratory complication and stroke. One case mortality occurred in our study (2.86%).

Discussion

Numerous of cardioplegic solutions, the solution that used to arrest and protect the heart during cardiac surgery, is available worldwide. del Nido cardioplegia is an extracellular cardioplegia that has a unique feature. Its action is to hyperpolarize the myocyte membranes during the ischemic arrest causing reduction of myocardial metabolic requirement and enhancing myocardial protection. Lidocaine, a sodium channel blocker induces hyperpolarization. Magnesium

Table 2. Patient characteristics

Variable	Total (n = 35)	95% CI	Range
Age, mean (SD)	51.48 (±20.58)	44.38 to 58.59	6 to 81
Height (cm), mean (SD)	158.30 (±12.25)	154.09 to 162.51	111 to 170
Weight (kg), mean (SD)	59.11 (±15.66)	53.73 to 64.49	18 to 87.7
BSA (m^2), mean (SD)	1.60 (±0.26)	1.51 to 1.69	0.77 to 2.03
STS score (%), mean (SD), n = 26 (74.29%)	3.01 (±3.10)	1.75 to 4.26	0.50 to 13.82
EF(%), mean (SD)	55.43 (±14.51)	50.44 to 60.42	27 to 76.40
Gender, n (%)			
Male	20 (57.14)		
Female	15 (42.86)		
DM, n (%)	12 (34.29)		
HT, n (%)	20 (57.14)		
DLP, n (%)	18 (51.43)		
CKD (creatinine >2 mg/dL), n (%)	6 (17.14)		
COPD, n (%)	1 (2.86)		
Cirrhosis, n (%)	0		
Atrial fibrillation, n (%)	6 (17.14)		
Prior stroke, n (%)	3 (8.57)		
NYHA, n (%)	35 (100)		
Class 1	5 (14.29)		
Class 2	23 (65.71)		
Class 3	3 (8.57)		
Class 4	4 (11.43)		

sulfate, a calcium antagonist affects the reduction of intracellular calcium accumulation. These are the unique properties of del Nido cardioplegia as well as Mannitol for scavenging of free radicals, reduction of myocardial cell swelling, and Sodium Bicarbonate for buffering[1].

Originally, del Nido cardioplegia was designed to have no calcium by using Plasma-Lyte A as the base solution, but the final calcium concentration in this cardioplegia can be considered as trace after mixing with one part of oxygenated pump blood and four parts of the solution[1]. Therefore, Calcium level is another concern in our cardioplegia regimen. Lactated Ringer

Table 3. Type of operations

Type of operation	Total (n = 35)
Closure of atrial septal defect	4
Repair of sinus venosus defect	1
Total correction of Tetralogy of Fallot	1
Redo Pulmonary valve replacement	3
Coronary artery bypass grafting	11
Coronary artery bypass grafting, left atrial appendage excision and pulmonary vein isolation	1
Mitral valve replacement	2
Mitral valve replacement, tricuspid valve repair	1
Mitral valve replacement, tricuspid valve replacement and left atrial appendage excision	1
Mitral valve replacement, tricuspid valve repair, coronary artery bypass grafting and left atrial appendage excision	1
Aortic valve replacement	2
Aortic valve replacement, mitral valve replacement	1
Aortic valve replacement, mitral valve repair	1
Redo aortic root replacement (Bentall)	1
Aortic valve replacement, coronary artery bypass grafting	1
Mitral valve repair	1
Mitral valve repair, coronary artery bypass grafting	2

Table 4. Intraoperative outcomes

Variable	Total (n = 35)	95% CI	Range
Total cardioplegia use, mean (SD)	1,207.43 (±380.93)	1,076.57 to 1,338.28	250 to 2,000
Number of doses, mean (SD)	1.66 (±0.72)	1.41 to 1.91	1 to 4
Cross clamp time, mean (SD)	108.51 (±48.60)	91.82 to 125.21	26 to 205
Total bypass time, mean (SD)	145.63 (±55.63)	126.52 to 164.74	47 to 271
Ventricular fibrillation after aortic cross clamp removal, n (%)	4 (11.43)		

Table 5. Postoperative outcomes

Variable	Total (n = 35)	95% CI	Range
ICU stay (day), mean (SD), n = 34	1.94 (±1.15)	1.54 to 2.34	1 to 6
Hospital stay (day), mean (SD), n = 34	8.06 (±7.57)	5.41 to 10.70	4 to 42
New onset of atrial fibrillation, n (%)	6 (17.14)		
Acute kidney injury, n (%)	1 (2.86)		
Respiratory complication, n (%)	0		
Stroke, n (%)	0		
Mortality, n (%)	1 (2.86)		

solution usually has calcium ion between 2 to 3 mEq/L. The final calcium concentration in our cardioplegia regimen may be higher, however the results are acceptable.

Mortality occurred in one patient (2.86%). The patient had triple vessel disease with severe mitral valve insufficiency and severe left ventricular dysfunction with 28% of left ventricular ejection fraction. The patient underwent four vessel coronary artery bypass grafting and mitral valve repair with very long 200 minutes of aortic cross clamp time. The patient was weaned off and transferred to the intensive care unit with low dose of inotrope. The post-operative course was complicated by early severe left ventricular dysfunction requiring intra-aortic balloon pump insertion and then ECMO cannulation. Later, we lost this patient due to multiorgan failure. Postoperative left ventricular dysfunction in this patient may result from administration of our cardioplegia regimen with very long aortic cross clamp time or underestimation of preoperative severe left ventricular dysfunction without viability test. However, overall mortality rate in our study were comparable with calculated STS mortality score.

Although del Nido cardioplegia is exclusively use in pediatrics cardiac center, its use has been recently increasing in popularity into the field of adult cardiac surgery[2-11]. Types of operation in our study vary from surgical treatment for congenital heart disease to complex adult cardiac surgery. Our study demonstrates that del Nido cardioplegia can be used safely in any type of cardiac surgery. In patients with concern of coronary artery distribution, such as patients with coronary artery stenosis or patients with aortic valve insufficiency, the delivery method must be cautious, either antegrade or retrograde. Our study demonstrated that del Nido cardioplegia can be used safely in isolated coronary artery bypass grafting and in the patients with aortic valve disease with excellent results. Safety and feasibility of direct administration through coronary ostia and by retrograde fashion was also demonstrated.

Since there is no standard protocol for del Nido cardioplegia, the number of doses and volume of cardioplegia use for redosing vary based on surgeon's decision. As single dose basis of del Nido cardioplegia, the optimal timing described by many authors[2-12] is usually less than 90 minutes of aortic cross-clamp time, but some authors[3,5,7,13] re-dose after 90 minutes if a further ischemic period is required. Therefore, with longer period of redosing interval and lower total volume of cardioplegia, aortic cross-clamp time and hemodilution may be reduced as demonstrated in previously published studies[3,4,7,13]. The number of doses and total cardioplegia use in our study varied upon the complexity of operation. Our protocol is to re-dose after 90 minutes and the volume of cardioplegia use depends on how long the rest of the operation is expected to be. Aortic cross-clamp time can be safely extended to 205 minutes with our protocol.

Lower incidence of ventricular fibrillation after aortic cross clamp removal and lower incidence of postoperative atrial fibrillation were also reported in recent studies[10,11]. In our study, 11.43% of patients had ventricular fibrillation and 17.14% of patients had postoperative atrial fibrillation. These finding seem to be lower than in general but the lack of comparative group in this study precluded us from the conclusion.

Limitation

As descriptive basis, lack of cohort to compare the results is the main limitation of our study. Although, the early results were very promising, a large, prospective, randomized trial must be designed to investigate the application of lactated Ringer solution as a carrier for del Nido cardioplegia and to validate our current finding.

Conclusion

Lactated Ringer solution can be used safely to replace the crystalloid component of del Nido cardioplegia, Plasma-Lyte A, with an acceptable result. However, without multicenter study, the use should be limited in the countries where Plasma-Lyte A is not provided.

What is already known on this topic?

The efficacy of del Nido cardioplegia has been proven for myocardial protection during cardiac surgery. However, Plasma-Lyte A, the main base solution is not available in Thailand. This precludes its application in the most cardiac centers.

What this study adds?

Lactated Ringer solution can safely replace Plasma-Lyte A as a main base solution for del Nido cardioplegia with an acceptable result.

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Potential conflicts of interest

None.

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ประสบการณ์การใช้น้ำยาหยุดการเต้นของหัวใจชนิด del Nido ในการผ่าตัดหัวใจในโรงพยาบาลรามาธิบดี

ณรงค์ฤทธิ์ ขันธทัต, เฉลียว ชัยชนะ, วรรณฤดี ทองเชิด, วิไลลักษณ์ ศรประสิทธิ์, สุเมธี จิระรัตนกุล, สุทิตย์ วิลัยการ, พรรวสา ไกรเลิศ, ปริญญา ลีลายนะ, ปิยะ เชิญฉนอมวงศ์, สยาม ค้าเจริญ

ภูมิหลัง: del Nido cardioplegia คือ สารละลายที่ใช้หยุดหัวใจในขณะที่ทำการผ่าตัดโดยวิธีการให้เพียงครั้งเดียว ซึ่งได้รับความนิยมมากขึ้นเรื่อย ๆ ในช่วงสิบปีที่ผ่านมา เนื่องจากตัวทำละลายหลัก คือ Plasma-Lyte A ไม่จำหน่ายในประเทศไทย ผู้นิพนธ์จึงนำ lactated Ringer solution มาใช้แทน โดยตั้งสมมติฐานว่าจะได้ผลใกล้เคียงกัน

วัตถุประสงค์: เพื่อรายงานผลการรักษาเบื้องต้นของการใช้ lactated ringer solution เป็นส่วนผสมหลักใน del Nido cardioplegia

วัสดุและวิธีการ: ศึกษาโดยการเก็บข้อมูลจากผู้ป่วยที่มารับการผ่าตัดหัวใจในโรงพยาบาลรามาธิบดีโดยใช้ del Nido cardioplegia ตั้งแต่เดือนธันวาคม พ.ศ. 2559 ถึง เดือนพฤษภาคม พ.ศ. 2560 วิเคราะห์จากข้อมูลก่อนการผ่าตัด, ระหว่างการผ่าตัดและหลังผ่าตัด

ผลการศึกษา: อายุเฉลี่ยของผู้ป่วยคือ 51.48±20.58 ปี โดย 57.14% เป็นเพศชาย, STS score เฉลี่ยของผู้ป่วยคือ 3.01±3.10 ปริมาณของน้ำยาที่ใช้เฉลี่ย 1,207.43±380.93 ml, จำนวนครั้งของการให้ cardioplegia คือ 1.66±0.72 ครั้ง เวลาของ Aortic cross clamp และ Total bypass คือ 108.51±48.60 นาที และ 145.63±55.63 นาที ตามลำดับ, ผู้ป่วย 4 คน (11.43%) เกิด Ventricular fibrillation หลังจากที่คลาย Aortic cross clamp, จำนวนวันที่อยู่ใน ICU และจำนวนวันที่นอนโรงพยาบาล คือ 1.94±1.15 วัน และ 8.06±7.57 วัน ตามลำดับ, ผู้ป่วย 6 คน (17.14%) เกิด Atrial fibrillation, มีภาวะแทรกซ้อนเกิดขึ้น 1 ราย (2.86%) (ภาวะแทรกซ้อนทางไต) และมีการตายเกิดขึ้น 1 ราย (2.86%)

สรุป: การนำ lactated ringer solution มาใช้แทน Plasma-Lyte A เพื่อเป็นส่วนผสมหลักของ del Nido cardioplegia สามารถทำได้โดยปลอดภัย และได้ผลการรักษาเป็นที่น่าพอใจ