Propensity Matched Analysis of del Nido Cardioplegia in Adult Coronary Artery Bypass Grafting: Initial Experience With 100 Consecutive Patients

Tomasz Timek, MD, Charles Willekes, MD, Olivia Hulme, BS, Ben Himelhoch, BS, Daniel Nadeau, MD, Andrew Borgman, MS, Jeff Clousing, CCP, Dick Kanten, CCP, and Joe Wagner, CCP

Division of Cardiothoracic Surgery, Meijer Heart and Vascular Institute at Spectrum Health, Michigan State University College of Human Medicine, Anesthesia Practice Consultants, DeVos Cardiovascular Research Program, and Van Andel Institute/Spectrum Health, Grand Rapids, Michigan

Background. **Del Nido cardioplegia (DC) offers prolonged cardiac protection with single-dose administration and has had a long safety record in pediatric cardiac surgery. However, its application in the adult population has thus far been limited. We evaluated the efficacy of cardiac protection and clinical outcomes of DC vs blood cardioplegia (BC) in adult coronary artery bypass graft (CABG) patients.**

Methods. **Clinical outcomes of 100 consecutive isolated CABG patients who received DC (May to September 2014) were compared with the previous 100 consecutive isolated CABG patients receiving BC (December 2013 to April 2014). Propensity matching yielded 82 pairs. The same surgeons operated on all patients. Clinical patient characteristics and data were extracted from our local The Society of Thoracic Surgeons database and the electronic medical record.**

Results. **Preoperative characteristics were similar between BC and DC patients before and after propensity matching. BC patients received anterograde and retrograde cardioplegia, whereas DC was delivered anterograde, with 92 of 100 patients receiving a single dose only. Inotropic support upon arrival to the recovery unit did not differ between BC and DC (0.28 ± 0.11 vs 0.27 ± 0.11 μg/kg/min milrinone [$p = 0.8$] and 0.05 ± 0.03 vs 0.05 ± 0.03 μg/kg/min norepinephrine [$p = 0.7$]), nor did postoperative troponin T levels (0.56 ± 0.48 vs 0.70 ± 1.27 ng/mL; $p = 0.3$). The peak intraoperative glucose level was higher in BC (209.8 ± 40.4 mg/dL) than in DC (161.4 ± 42.3 mg/dL) patients ($p < 0.001$). No patients died in either group, and the postoperative incidence of atrial fibrillation, stroke, reoperation for bleeding, and prolonged intubation did not differ between the groups before and after matching. There was also no difference in the postoperative ejection fraction between the groups (0.51 ± 0.13 vs 0.47 ± 0.13 for BC and DC, respectively; $p = 0.17$).**

Conclusions. **In our initial experience, DC provided equivalent myocardial protection and clinical outcomes to BC in adult isolated CABG patients. DC was associated with lower cardiopulmonary bypass glucose levels than BC and demonstrated the feasibility of single-dose administration for routine coronary operations.**

(Ann Thorac Surg 2016;101:2237–42)

Reliable myocardial protection is central to safe performance of any cardiac operation requiring cardiac standstill, yet there is no agreement in the published literature or clinical practice about the superiority of one cardioplegic solution over another [1]. Buckberg cardioplegic solution [2] in a 1:4 dilution with whole blood has formed the basis for myocardial protection as blood cardioplegia (BC) at our institution for several years; however, it requires a high volume of solution, cumbersome delivery modes, and significantly perturbs intraoperative glucose management.

Del Nido cardioplegia (DC) [3] has demonstrated a long safety record in pediatric cardiac operations, with single-dose administration for more than 90 minutes of cardioplegic arrest [4]. The solution is based on Plasma-Lyte A (Baxter Healthcare, Deerfield, IL), which has an electrolyte milieu similar to extracellular fluid, with the addition of mannitol, magnesium sulfate, sodium bicarbonate, potassium chloride (26 mEq), and lidocaine. There is no calcium in the base solution or as an additive [3].

Although a few centers [5] have used del Nido solution in adult cardiac operations, there is paucity of data on the efficacy and safety of DC in the adult population.

Accepted for publication Dec 23, 2015.

Address correspondence to Dr Timek, Division of Cardiothoracic Surgery, Meijer Heart and Vascular Institute at Spectrum Health, Grand Rapids, MI 49506; email: tomasz.timek@specctrumhealth.org.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2015.12.058

Recently, DC has been shown to be safe in reoperative aortic valve operations [5] and in coronary artery bypass grafting (CABG) after infarction [6]. It also offers equivalent myocardial protection in patients undergoing isolated valve operations, with potential for operative time and cost savings [7]. There are, however, no reports on the clinical use of del Nido solution in routine adult CABG operations. We set out to investigate the safety and efficacy of del Nido solution vs BC in adult patients undergoing coronary revascularization. We hypothesized that DC would provide myocardial protection equivalent to our standard BC while simplifying the cardioprotective regimen.

Patients and Methods

This study was approved by the Spectrum Health Institutional Review Board and was in full compliance with its policies and procedures. We reviewed the clinical outcomes of the first 100 patients who underwent isolated CABG at our center using DC. From May to September 2014, 100 consecutive patients undergoing isolated CABG received DC for intraoperative myocardial protection. Emergency and resternotomy operations were included in the study group. To minimize selection bias for the operating surgeons, DC was the only type of cardioplegia used during this portion of the study period. The control group comprised the previous 100 consecutive isolated CABG patients operated on by the same surgeons from December 2013 to April 2014 when only BC was used.

DC was delivered in anterograde fashion in a 1:4 dilution with blood predominantly as a single dose of 1,000 mL at 4°C. DC redosing was planned at 60 minutes after the initial dose if the total aortic cross-clamp time was anticipated to exceed 90 minutes. Myocardial temperature was not measured, and no topical hypothermia was used.

BC was administered in a 4:1 blood dilution and given as initial anterograde or retrograde, or both, bolus of 1,000 to 2,000 mL at 4°C to achieve a myocardial temperature of less than 10°C. Subsequently, retrograde delivery was repeated every 15 to 20 minutes and monitored by myocardial temperature in most cases. A 500 mL warm shot was delivered retrograde in most patients pending surgeon preference.

Systemic hypothermia was not used routinely in either group, and body temperature was allowed to drift during the procedure. Volume and mode of cardioplegia delivered and intraoperative hemoglobin, glucose, and potassium values were obtained from the electronic perfusion record. Level of inotropic support before leaving the operating room and initial levels in the recovery unit were recorded in the patient's electronic medical record. Troponin T levels were drawn on all patients 16 hours after the operation in accordance with temporal peak troponin T levels in patients with myocardial infarction [8].

Preoperative clinical characteristics, perioperative deaths, and 30-day events were queried directly from The Society of Thoracic Surgeons database. Available postoperative echocardiographic studies for assessment of left ventricular function were retrieved from the electronic medical record.

All data are reported as mean ± 1 standard deviation. Data were compared using the Student t test for independent observations, with the level of statistical significance set at a p value of less than 0.05. The Fisher exact test was used where appropriate.

Propensity score matching was performed using R 3.2.0 software (The R Foundation for Statistical Computing, http://www.r-project.org/foundation/), making use of the MatchIt 2.4-21 package [9]. The following variables were included in a logistic regression model to estimate the propensity scores: age, sex, number of diseased vessels, history of myocardial infarction, history of diabetes, left ventricular ejection fraction, history of chronic obstructive pulmonary disease, last creatinine level, and weight. Nearest-neighbor matching without replacement was used to match BC and DC patients using linear propensity scores. An optimal caliper size of 0.23 was determined by minimizing the total absolute standardized mean difference between groups for all matching variables across a range of caliper sizes. The analysis excluded 1 BC patient and 4 DC patients who were missing data for some baseline matching criteria. The matched cohort contained 82 patients in the BC and DC groups.

Results

The Society of Thoracic Surgeons risk score for the BC and DC patients was 1.2% ± 1.2% and 1.6% ± 2.2%, respectively, and did not differ significantly ($p = 0.11$). The number of grafted vessels also did not differ between the groups (3.3 ± 0.8 vs 3.1 ± 0.9 for BC and DC, respectively; $p = 0.20$). Table 1 summarizes the preoperative characteristics of the two groups before and after propensity matching. Pertinent cardiopulmonary bypass (CPB) data are presented in Table 2. BC patients required much higher volume and multiple doses of cardioplegia, whereas 92 of 100 DC patients received a single dose for the entire operative procedure. These findings were confirmed in the propensity-matched cohort. Of the remaining 8 patients, 6 received a second dose of 500 mL and another 2 received additional 1,000 mL and 1,500 mL of cardioplegia in divided doses, respectively. Two of these 8 patients were complex redo patients.

Blood glucose management was facilitated by administration of DC. Defibrillation after cardioplegic arrest was needed in 11 of 100 DC patients. All patients were routinely weaned from CPB with norepinephrine and milrinone according to the standard protocol, with the occasional addition of epinephrine. The last recorded dose of inotropic agents before leaving the operating room did not differ between the two groups (0.33 ± 0.13 vs 0.31 ± 0.15 μg/kg/min milrinone [$p = 0.2$] and 0.05 ± 0.03 vs 0.04 ± 0.03 μg/kg/min norepinephrine [$p = 0.5$], for BC and DC, respectively). In both groups, 6 of 100 patients required the addition of epinephrine, without a difference in the mean dose.

Table 1. Preoperative Characteristics

Variable[a]	Unmatched			Matched		
	BC	DC	*p* Value	BC	DC	*p* Value
Patient age, y	65.1 ± 10.7	66.4 ± 9.5	0.357	65.6 ± 10.3	65.3 ± 9.4	0.862
Ejection fraction	0.514 ± 0.126	0.511 ± 0.143	0.839	0.511 ± 0.131	0.511 ± 0.145	0.986
Pre-op creatinine, mg/dL	1.1 ± 0.63	1.2 ± 1.4	0.371	1.1 ± 0.68	1.1 ± 0.63	0.856
Diabetes	47/100	42/100	0.569	38/82	36/82	0.875
COPD	10/100	13/100	0.851	8/82	9/82	0.901
Myocardial infarction	37/100	48/100	0.152	36/82	39/82	0.754

[a] Continuous variables are presented as mean ± standard deviation and categoric variables as number of patients/total number of patients.

BC = blood cardioplegia; COPD = chronic obstructive pulmonary disease; DC = del Nido cardioplegia.

Upon leaving the operating room, the level of insulin infusion was significantly higher in BC than in DC patients (4.7 ± 4.5 vs 2.8 ± 3.1 U/h; $p = 0.0006$). Initial inotropic support in the recovery unit also did not differ between BC and DC (0.28 ± 0.11 vs 0.27 ± 0.11 μg/kg/min milrinone [$p = 0.8$] and 0.05 ± 0.03 vs 0.05 ± 0.03 μg/kg/min norepinephrine [$p = 0.7$]). Mean troponin T level drawn 16 hours after the operation was 0.56 ± 0.48 ng/mL in BC patients and 0.70 ± 1.27 ng/mL in DC patients ($p = 0.3$).

No patients died, and the incidence of postoperative adverse events or intensive care unit and hospital stay did not differ between the two groups before or after propensity matching, as reported in Table 3. Follow-up echocardiography was available for 35 of 100 BC patients at 4.1 ± 4.3 months and for 41 of 100 DC patients at 4.0 ± 3.5 months. The preoperative ejection fraction was 0.45 ± 0.13 for BC patients and 0.43 ± 0.15 for DC patients and did not differ significantly ($p = 0.51$). There was also no difference in the ejection fraction after CABG between the two patient groups (0.51 ± 0.13 vs 0.47 ± 0.13 for BC and DC, respectively, $p = 0.17$). At the last follow-up in October 2015, 2 patients had died in the DC group and 1 in the BC group.

The current cost of DC at our institution is $48.00 per 1,000 mL whereas BC costs $141.00 per 1,000 mL. As determined from the total cardioplegia dose and dilution of blood, the average BC patient received 662 mL of undiluted cardioplegia, and each DC patient received 870 of undiluted solution. Both solutions are packaged in 1,000-mL bags, and each patient in both groups required an average of 1 bag of solution for completion of the procedure. The cost saving with the use of DC was thus $9,300, a sum that does not include the cost of the retrograde cardioplegia catheter ($72 per catheter) that was used in most of the BC patients.

Comment

Optimal cardioplegic protection of the heart continues to be debated, but a standardized solution is yet to be accepted. The current study demonstrated equivalent myocardial protection in routine CABG patients with DC vs BC in a series of 100 consecutive patients. In a propensity-matched analysis, postoperative outcomes did not differ with the two different modes of myocardial protection. There was also no difference in postoperative myocardial function as assessed by transthoracic echocardiography.

Safety and efficacy of DC has recently been reported for patients undergoing routine isolated valve operations [7],

Table 2. Cardiopulmonary Bypass Data

Variable	Unmatched			Matched		
	BC (Mean ± SD)	DC (Mean ± SD)	*p* Value	BC (Mean ± SD)	DC (Mean ± SD)	*P* Value
Cardioplegia volume, mL	3,307 ± 1,193	1,091 ± 231.5	<0.001	3,307 ± 1171	1,090 ± 231.4	<0.001
Doses, No.	4.8 ± 2.2	1.1 ± 0.48	<0.001	4.8 ± 2.2	1.1 ± 0.52	<0.001
Pre-CPB glucose, mg/dL	118 ± 37.7	123.1 ± 35.2	0.316	117.1 ± 39.1	126 ± 36.8	0.133
Highest CPB glucose, mg/dL	209.8 ± 40.4	161.4 ± 42.3	<0.001	207.8 ± 37.4	164.5 ± 44	<0.001
Post-CPB						
Glucose, mg/dL	164.4 ± 35.9	152.8 ± 40.6	0.032	163.3 ± 34.6	155.3 ± 42.4	0.188
Hemoglobin, g/dL	11.2 ± 1.6	11.1 ± 1.6	0.934	11.1 ± 1.5	11.2 ± 1.6	0.839
K^+, mEq/L	4.4 ± 0.71	4.8 ± 4.1	0.311	4.4 ± 0.7	4.9 ± 4.5	0.299
CPB time, min	93.2 ± 24.1	86.6 ± 28.1	0.076	91.9 ± 24.7	88.5 ± 28.9	0.417
Cross-clamp time, min	74.9 ± 20.3	68.7 ± 22.5	0.04	74.2 ± 20.9	70.5 ± 22.8	0.288

BC = blood cardioplegia; CPB = cardiopulmonary bypass; DC = del Nido cardioplegia; SD = standard deviation.

Table 3. Postoperative Events

	Unmatched[b]		Matched[b]	
Variables[a]	BC	DC	BC	DC
Mortality	0/100	0/100	0/82	0/82
Cerebrovascular accident	2/100	1/100	1/82	1/82
Hemodialysis	5/100	1/100	5/82	1/82
Atrial fibrillation	26/100	35/100	22/82	26/82
Reoperation for bleeding	0/100	2/100	0/82	1/82
Prolonged intubation	5/100	3/100	5/82	3/82
Length of stay				
Hospital, d	7.2 ± 5.8	7.3 ± 4.3	7.3 ± 6.3	7.3 ± 4.6
Intensive care unit, h	37.2 ± 51.1	34.2 ± 36.5	39 ± 54.6	32.2 ± 33.4

[a] Categoric variables are shown as number of patients/total number of patients and continuous variables as mean ± standard deviation. [b] The *p* values between the groups were not statistically significant.

BC = blood cardioplegia; DC = del Nido cardioplegia.

with no difference in postoperative troponin levels or inotropic support between DC and BC patients. Our study corroborates these results in patients with coronary artery disease undergoing surgical intervention with similar mode of cardioplegia delivery. Postoperative troponin levels and inotropic agent infusions did not differ between our DC and BC patients. Yerebakan and colleagues [6] reported similarly encouraging results in high-risk CABG patients who underwent operations after acute myocardial infarction with DC or whole blood cardioplegia. Their study revealed equivalent clinical outcomes with predominantly anterograde delivery as a single dose, although 20% of the patients received a retrograde dose. This study was, however, limited by relatively low number of patients and lack of postoperative troponin measurements.

The Columbia group [5] reported similar results in aortic valve reoperations. Approximately 75% of these patients had previous CABG operations, and single-dose DC was used up to cross-clamp times of 90 minutes.

Although the literature on the use of DC in adult cardiac operations is only beginning to surface, evidence is growing that DC may provide efficacious myocardial protection for routine cardiac procedures. Current data suggest the feasibility of single-dose administration for routine coronary procedures.

In the pediatric population, single-dose administration of DC has been used for aortic cross-clamp times exceeding 90 minutes [4], but extrapolation to the adult population needs to be done with caution because associated coronary artery disease and myocardial hypertrophy that is often seen in adult disease may affect cardioplegia delivery and distribution. Isolated heart studies in senescent rats [10], however, revealed superior myocardial function and reduced troponin release with single-dose DC vs multidose BC after a 60-minute cardiac arrest in a Langendorff preparation. This experimental study lends support to efficacious myocardial protection of the aged heart with DC, which is corroborated by the current data.

In our study, a single dose of DC provided good myocardial protection for a mean arrest time of approximately 70 minutes, yet for anticipated aortic cross-clamp times of 90 minutes or longer, cardioplegia was redosed. On the basis of this initial series and the published literature, we currently use a single cold anterograde 1,000-mL dose for CABG patients and repeat the dose with 500 mL at 60 minutes if the aortic cross-clamp time is expected to be more than 90 minutes.

In the clinical setting of CABG operations, DC also offers potential benefits over BC. Single-dose DC administration permits uninterrupted performance of the operation and enhances the "flow" of the procedure. Although DC can be delivered retrograde, we found anterograde delivery was reliable in the absence of significant aortic insufficiency, thus obviating the need for retrograde catheter placement and potential injury to the coronary sinus. As such, use of DC facilitated "decluttering" of the operative filed by removing the retrograde catheter, temperature probe, and topical cooling, while permitting expeditious performance of the planned procedure.

Because DC is not glucose based, intraoperative glucose management may be expected to be easier with this solution than with BC. Similar to the Cleveland Clinic group [7], we observed significantly higher peak CPB glucose levels as well as higher levels of insulin infusion after cessation of CPB. Because intraoperative glucose management may portend subsequent outcomes, [11] better glycemic control with DC could have real clinical significance.

DC is also associated with potential cost savings because the cost of cardioplegia solution alone in our study provided a cost saving of almost $9,300 per 100 patients. We perform more than 400 isolated CABG procedures annually, which represents significant cost savings.

Limitations

The results of this clinical study must be interpreted in light of several important limitations. This was a single-center nonrandomized study, and extrapolation of these results must be interpreted in that context. The total number of patients in the study group was relatively low, and therefore, the possibility of a type II error cannot be completely excluded. The preoperative clinical characteristics of the operated-on patients were quite similar, and all patients underwent isolated CABG, thus providing a relatively homogenous patient cohort. Propensity matching was further used to minimize the influence of any differences in baseline preoperative characteristics. This was not a concurrent series, but all patients were operated on within 1 year, and therefore, the effect of changes and advances in surgical care in this short interval on operative outcomes can be considered minimal, especially because our center heavily relies on

standardized protocols that were not altered for the purpose of this study.

Because this was a nonrandomized study, there is inherent selection bias in the study design, which we attempted to minimize by including consecutive patients in each group and using only one cardioplegia solution for the respective time interval of BC or DC treated patients. We must emphasize that most patients in the study had normal preoperative myocardial performance and were considered to be of routine risk. Extrapolation of DC efficacy in complex, elderly patients with moderately or severely reduced left ventricular function may require adjustment of dose, mode of delivery, and dosing intervals and should be performed with caution.

The cost analysis may not be extrapolated to all centers because local pricing and packaging/additives of cardioplegic solutions may significantly affect price of the "standard" center solution. However, this comparison is a useful guide for potential cost savings.

Conclusion

Our clinical series of 100 consecutive patients revealed that DC delivered predominantly as a single anterograde dose provided equivalent myocardial protection to standard BC in patients undergoing isolated coronary revascularization. The del Nido solution permitted improved intraoperative glycemic control, simplified the cardioplegic regimen, and established feasibility of single-dose administration. The optimal dosing interval and mode of delivery of DC in adult patients remains to be clearly established, and generalization of these results to more complex patients requires further clinical experience and should be performed with caution.

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INVITED COMMENTARY

The fundamental principles of myocardial protection during surgically produced ischemia are to minimize energy demand by induced cardiac arrest and hypothermia. The methods commonly used to achieve these goals have relied on perfusion of the heart via coronary arteries (antegrade) or coronary veins (retrograde) with a cold solution containing a high concentration of potassium. Topical cooling, or insulation of the heart from surrounding tissues, is frequently utilized to maintain hypothermia, and repeat administration of the solution also has been shown to be effective in maintaining hypothermic myocardial temperatures. Beyond these basic tenets efforts to further enhance myocardial preservation have included cardioplegia additives that aim to provide substrates for the heart for energy production, primarily based on oxidative phosphorylation. Thus red blood cells in high concentration (1 part crystalloid to 4 parts whole blood), and high glucose concentration form the basis of blood cardioplegia as described by Buckberg over 35 years ago [1]. An alternative pathway for energy production is the less efficient but likely adequate glycolytic pathway that utilizes endogenous glycogen stores for substrate. To promote this pathway during ischemia an absence of exogenous glucose and proton buffering are required [2]. pH buffering can be achieved with a number of different additives such as histidine (present in Custodiol, Essential Pharmaceuticals, Ewing, NJ) or by the carbonic anhydrase enzyme present in high levels within red blood cells. Buffering with red blood cells only requires a low red cell concentration, such as with 4 parts crystalloid to 1 part whole blood. This latter approach forms the basis for the del Nido formulation along with lidocaine as a sodium-channel blocker for prolonged hyperpolarizing arrest.

Experience with del Nido cardioplegia in adults is evolving as surgeons extend its use to procedures where

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.01.095