The use of del Nido cardioplegia in adult cardiac surgery: A prospective randomized trial

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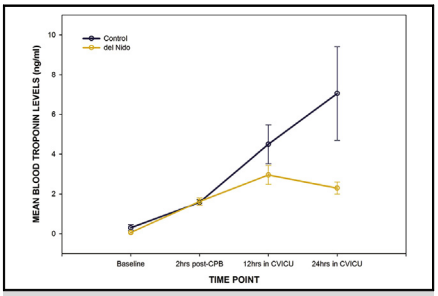
ABSTRACT

Objectives: The del Nido cardioplegia solution has been used extensively in congenital heart surgery for more than 20 years and more recently for adults. This randomized controlled trial examined whether expanding this technique to adult cardiac surgery confers benefits in surgical workflow and clinical outcome compared with blood-based cardioplegia.

Methods: Adult first-time coronary artery bypass grafting (CABG), valve, or CABG/valve surgery patients requiring cardiopulmonary bypass (CPB) were randomized to del Nido cardioplegia (n = 48) or whole blood cardioplegia (n = 41). Primary outcomes assessed myocardial preservation. Troponin I was measured at baseline, 2 hours after CPB termination, 12 and 24 hours after cardiovascular intensive care unit admission. Alpha was set at $P < .001$.

Results: Preoperative characteristics were similar between groups, including age, Society of Thoracic Surgeons risk score, CABG, and valve procedures. There was no significant difference on CPB time (97 vs 103 minutes; $P = .288$) or cross-clamp time (70 vs 83 minutes; $P = .018$). The del Nido group showed higher return to spontaneous rhythm (97.7% vs 81.6%; $P = .023$) and fewer patients required inotropic support (65.1% vs 84.2%; $P = .050$), but did not reach statistical significance. Incidence of Society of Thoracic Surgeons-defined morbidity was low, with no strokes, myocardial infarctions, renal failure, or operative deaths. For del Nido group patients, troponin levels did not increase as much as for control patients ($P = .040$), but statistical significance was not reached.

Conclusions: Evidence from this study suggests del Nido cardioplegia use in routine adult cases may be safe, result in comparable clinical outcomes, and streamline surgical workflow. The trend for troponin should be investigated further because it may suggest superior myocardial protection with the del Nido solution. (J Thorac Cardiovasc Surg 2017;■:1-8)



Mean troponin I levels by treatment group from pre-surgery to 24 hours after cardiovascular intensive care unit (CVICU) admission.

Central Message

Evidence from this initial randomized controlled trial suggests use of del Nido cardioplegia in routine adult cases may be safe, have comparable clinical outcomes, and streamline surgical workflow.

Perspective

The del Nido cardioplegia solution has been used extensively in congenital heart surgery for more than 20 years. Recent literature has suggested that del Nido solution may be administered safely in adult surgical procedures. Results of this randomized trial support previous studies on safety of del Nido solution and suggest comparable results for myocardial injury and potential benefits in surgical workflow.

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Optimal myocardial protection during cardiac surgery is a key component of a successful procedure.[1] Since the 1950s, research and strategies have been developed to continuously improve myocardial protection and prevent further ischemic injury.[2-4] The use of hypothermic and

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CPB = cardiopulmonary bypass
CVICU = cardiovascular intensive care unit
STS = Society of Thoracic Surgeons
TEE = transesophageal echocardiography

hyperkalemic cardioplegia solutions evolved to become the clinical standard in many cardiac surgery programs across the world.[5] Despite the multitude of reported cardioplegia systems, there is a lack of clear consensus on composition, route, and technique.[1,5,6]

A novel formula for cardioplegia was introduced in congenital heart surgery in 1995.[7] This formula was patented as a single dose and modified depolarizing solution. Now commonly referred to as del Nido solution, this blood and crystalloid mixed formula has been associated with a longer duration of safe myocardial ischemic arrest.[8,9] This solution has been purported to preserve intracellular high-energy phosphates and intracellular pH and reduce calcium ion influx during and after ischemic arrest and led to its increased use across pediatric congenital cardiac surgery programs.[10,11]

Multiple observational studies have suggested that the del Nido solution is associated with safety and efficacy in adult surgical procedures.[12-18] Despite these encouraging findings, adaptation of the protocol in treating adult ischemic myocardium has not been addressed by prospective randomized trials.[19] The purpose of this prospective randomized controlled trial was to compare the del Nido cardioplegia protocol with an existing whole blood-based cardioplegia strategy in routine coronary artery bypass grafting (CABG), valve, and CABG/valve surgery procedures.

METHODS

After obtaining institutional review board approval (study No.14-1653), adult patients presenting for first-time CABG or heart valve surgery requiring cardiopulmonary bypass (CPB) between February 2015 and April 2016 were eligible to participate (study No. NCT02442050). Inclusion criteria included adult patients aged 19 to 79 years; patients able to receive and provide informed consent; stable patients with surgical procedures requiring CPB and myocardial arrest; and isolated CABG surgery, isolated single-valve surgery, or concomitant CABG and single-valve surgery. Exclusion criteria included previous cardiac surgery, patients with preoperative inotropic pharmacologic support, patients receiving preoperative mechanical circulatory support, patients with an implanted pacemaker or implantable cardioverter-defibrillator, and patients undergoing cardiac surgical procedures outside of the inclusion criteria categories.

Patients completed written informed consent and were randomized to receive del Nido cardioplegia solution or whole blood cardioplegia. There were 2 arms for randomization in this trial to ensure equitable representation of surgical procedures in each treatment group: all eligible patients undergoing any heart valve surgical procedure with or without CABG surgery, and all eligible patients undergoing CABG surgery. Within each arm, patients were randomized to the intervention group (del Nido solution) or the control group (whole blood cardioplegia) using random number generation and blocked randomization with groups of 20. The randomization order was created before enrollment began and was then transferred to sealed consecutively numbered envelopes by a member of the study team who was not involved in patient enrollment. Of 99 patients who provided written informed consent and were enrolled in the study, 90 were randomized to a treatment group and 9 patients withdrew or had surgery canceled. Randomization occurred the day before the originally scheduled surgery date. One patient randomized to the control group was excluded because surgery was canceled. Therefore, 89 patients were included in these analyses (Figure 1) with 48 in the del Nido group and 41 in the control group.

Primary outcome measures assessed myocardial preservation by return to spontaneous rhythm; defibrillation requirement; inotropes; and troponin levels at 4 time points: baseline (at anesthesia induction), 2 hours after termination of CPB, 12 hours after admission to a cardiovascular intensive care unit (CVICU), and 24 hours after admission to a CVICU. Secondary outcomes assessed safety and workflow, including CPB and cross-clamp time, cardioplegia redosing, blood transfusion, and electrocardiogram changes 1 day after surgery. Postoperative clinical outcomes were defined by the Society of Thoracic Surgeons (STS) Adult Cardiac Surgical Database. Calculated ejection fraction was assessed using transesophageal echocardiography (TEE) before surgery and at the termination of CPB.

CPB and Cardioplegia Delivery

For these patients, CPB was conducted with the Terumo Advanced System I Extracorporeal Perfusion System (Terumo Cardiovascular Group, Ann Arbor, Mich). All CPB circuits consisted of a Terumo RX series oxygenator and hardshell reservoir, an AF-125 arterial filter, and Xcoating surface coating. Patients with a body surface area < 1.9 m^2 received a Terumo RX-15 oxygenator and 3/8-in arterial and venous tubing, whereas patients with a body surface area ≥ 1.9 m^2 were supported with a Terumo RX-25 oxygenator and 1/2-in venous tubing. Heparin dosing and anticoagulation was calculated using the Medtronic Hemostasis Management System (Medtronic, Minneapolis, Minn). Acute normovolemic hemodilution and retrograde autologous prime were performed on all patients deemed hemodynamically stable to donate and able to maintain a CPB hematocrit of at least 21%. Target hypothermic systemic temperatures on CPB support were maintained between 32°C and 35°C. The use of cardiotomy pump suction was limited to intracardiac blood collected during heart valve procedures. The Fresenius Continuous Autotransfusion System (CATS^{plus}; Fresinius KABI AG, Bad Homburg, Germany) was used to process surgical shed blood and residual CPB circuit volume after bypass was complete.

The del Nido and whole-blood cardioplegia formulas were delivered through the Quest Medical Myocardial Protection System II (Quest Medical Inc, Allen, Tex) (Table 1). Patients enrolled in the intervention group received 1.0 L del Nido cardioplegia after the aortic cross-clamp was applied to the ascending aorta (Central Admixture Pharmacy Services Inc., Bethlehem, Pa). An additional 500 mL was administered if left ventricular hypertrophy was present per the discretion of the attending surgeon. When a retrograde dose of cardioplegia through a coronary sinus catheter was requested by the surgeon, the calculated induction dose was equally split between antegrade and retrograde routes. Although not required for the study protocol, all patients received both antegrade and retrograde administration per standard of care. Subsequent doses of del Nido were not indicated unless the ischemic duration exceeded 90 minutes or there was spontaneous return of electrical activity during the aortic cross-clamp period. If a subsequent dose of del Nido was required, an additional 500 mL was administered. Delivery of del Nido solution was administered in a 1:4 ratio of blood to crystalloid at a temperature of 6°C to 10°C. Topical cooling was applied in all cases.

Patients enrolled in the control group received whole blood cardioplegia according to the institutional adult cardioplegia protocol. No additional