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Commentary: The role of del Nido cardioplegia in adult cardiac surgery: The jury is still out

Harold L. Lazar, MD

del Nido cardioplegia solution (DNS), administered as a single dose during aortic clamping, was initially developed for pediatric cardiac surgery to improve “surgical work flow” by limiting the need for multiple reinfusions.¹ It has since been adopted by cardiac surgeons to reduce crossclamp (XC) and cardiopulmonary bypass (CPB) times in an attempt to decrease perioperative morbidity and mortality. Retrospective studies involving coronary artery bypass graft procedures and isolated aortic valve replacements have demonstrated that DNS does significantly decrease XC and CPB times, but this has not resulted in any significant improvement in morbidity or mortality compared with traditional multidose blood cardioplegia techniques.²⁻⁵ Most of the studies have been retrospective and small in size, consisting of a cohort of stable, elective patients with minimal comorbidities, preserved left ventricular function without right ventricular dysfunction, undergoing noncomplex operative procedures, and with XC times <60 minutes. In fact, a prospective, randomized study in low risk patients undergoing coronary artery bypass graft procedures comparing DNC to multidose blood cardioplegia found no difference in postoperative morbidity or mortality.⁶ Furthermore, in that study, one-third of the DNS group patients actually received multiple doses of DNS.⁶

Lenoir and colleagues⁷ sought to enhance our knowledge of DNS use in adult cardiac surgery by reporting their results in patients undergoing complex procedures requiring prolonged periods of cardioplegic arrest. In 283 patients undergoing aortic root repairs using either a Ross or valve-sparing procedure, 110 patients were 1:1 propensity matched between DNS and multidose blood cardioplegia. The patient cohort consisted of young (average age, 48 years), elective

Harold L. Lazar, MD

CENTRAL MESSAGE

Prospective, randomized, multi-center studies are needed to further define the role of del Nido cardioplegia solution in adult cardiac surgery.

patients; predominately in New York Heart Association functional class I or II (88%), with minimal comorbidities (eg, 13% had diabetes) and average preserved left ventricular ejection fraction (59%). Few patients required additional concomitant procedures (eg, 5% underwent a coronary artery bypass graft procedure and 2% underwent a mitral procedure). The mean European System for Cardiac Operative Risk Evaluation II score was 1.56. DNS consisted of a single antegrade dose of 1250 mL at 4°C. After 60 minutes of XC, an additional 625 mL DNS was administered if the XC time was estimated to exceed an additional 90 minutes. In patients receiving multidose blood cardioplegia, an initial antegrade dose of 1000 mL was followed by 400 mL every 15 to 20 minutes. Topical cooling was not used and systemic hypothermia was used only for arch procedures. The majority of patients in both groups (54%), received an antegrade/retrograde delivery technique.

Patients protected with DNS had significantly decreased CPB (163 ± 5 min vs 181 ± 5 min; $P = .01$) and XC times (145 ± 5 min vs 161 ± 4 min; $P = .006$) compared with multidose blood cardioplegia patients. In both the matched and unmatched patients, there was no difference in postoperative morbidity or mortality, or the need for blood products or the use of intravenous insulin between the DNS and multidose blood cardioplegia patients. Although the incidence of myocardial infarction was twice as great in the DNS group compared with the multidose blood cardioplegia group (18% vs 9%), this was not statistically significant ($P = .16$). However, in patients with XC time >180 minutes, postoperative creatine kinase-MB levels were significantly higher in the DNS group compared

From the Division of Cardiac Surgery, the Boston University School of Medicine, Boston, Mass.

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Address for reprints: Harold L. Lazar, MD, Division of Cardiac Surgery, Boston University School of Medicine, 80 E Concord St, Boston, MA 02118 (E-mail: harold.l.lazar@gmail.com).

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with the multidose blood cardioplegia group (75.1 $\mu\text{g/L}$ vs 60.5 $\mu\text{g/L}$; $P = .047$) although there was no difference in postoperative morbidity or mortality. The immediate postoperative left ventricular ejection fraction was also similar between the groups.

As was the case in previous studies in patients protected with DNS, this study was retrospective and not randomized. The sample size was small due to propensity matching, which limited the statistical power. Not all patients were available to assess left ventricular ejection fraction at 1 year after the operation, so the long-term effects of the increase in cardiac enzymes is not known in all of the patients. The observed increase in creatine kinase-MB levels in this study was also noted by Yammine and colleagues⁵ in a retrospective, propensity-matched patient series undergoing adult cardiac surgery using DNS. Similar to the results reported by Lenoir and colleagues,⁷ Yammine and colleagues⁵ found that the elevated enzyme levels resulted in no difference in morbidity or mortality immediately following surgery and for 1 year postoperatively.

DNS appears to be safe for low risk, elective patients with minimal comorbidities undergoing isolated coronary artery bypass grafting and aortic valve replacement procedures where the XC time is anticipated to be no longer than 60 minutes. With the new guidelines recommending transcatheter aortic valve replacement for low-risk patients, many patients in need of aortic valve replacement will now undergo a percutaneous procedure. Patients undergoing surgical aortic valve replacement will have more complex anatomy that might require concomitant procedures and require longer XC times and the most optimal forms of myocardial protection. There are currently no data to suggest that DNS will provide adequate protection for those patients with right ventricular dysfunction and those with reduced ejection fraction who require longer XC times for more complex procedures. Patients with multivessel coronary disease and those with left ventricular hypertrophy in which the distribution of cardioplegia is not uniform may also not be good candidates for DNS. Rao and colleagues⁸ found that when thermographic imaging was used to assess cardioplegic distribution, patients undergoing coronary artery bypass grafting with multivessel disease protected with DNS required an average of 6 doses of cardioplegia to prevent increases in global myocardial temperature of 10°C or higher. During a mean XC time of 132 minutes, this required an average volume of 2710 mL DNS. Another area of concern with DNS is when and how much additional cardioplegia should be given if the XC time exceeds 60 minutes. Infusing multiple doses of DNS may be detrimental due to increased concentrations of lidocaine in the myocardium. A close relationship exists between lidocaine dose and toxicity, which can result in peripheral vasodilatation,

negative inotropy, ventricular arrhythmias, and central nervous system side effects such as seizures.⁹

Based on the results from their study, Lenoir and colleagues⁷ conclude that caution is warranted in adopting DNS in aortic surgery requiring long ischemic times and that further studies are required to establish the exact role of DNS in complex cardiac surgeries. They also propose that if patients require longer than expected ischemic times, surgeons should switch from DNS to multidose blood cardioplegia after 90 minutes of aortic XC rather than attempting to redose with DNS to avoid the potential for lidocaine toxicity. I wholeheartedly agree with these conclusions. Multidose blood cardioplegia has been the gold standard for achieving optimal myocardial protection in all types of adult cardiac surgery procedures. Before we adopt and endorse DNS, which may save 10 to 15 minutes of XC time—which has not translated into improved postoperative outcomes—more data are needed. Where will these data come from? Previously, I called for a multicenter Cardiothoracic Surgery Network-sponsored trial that would be prospectively randomized and adequately powered, including all types of adult cardiac surgery procedures (ie, both urgent and emergent cases) with established protocols for both DNS and multidose blood cardioplegia.¹⁰ Important end points should include not only XC and CBP times and operative mortality, but also need for inotropic support, number of blood transfusions, the incidence of perioperative myocardial infarction, changes in ejection fraction, and intensive care unit and hospital length of stay. It is important to remember that it is the quality of myocardial protection, and not necessarily the time during which myocardial protection is provided that will determine perioperative outcomes. The high quality data obtained from prospective, multicenter trials will help to determine whether DNS is effective in protecting all types of patients undergoing all types of adult cardiac surgery under all conditions. Until then, the jury is still out regarding the role of DNS in adult cardiac surgery.

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Commentary: Del Nido cardioplegic solution: Is it really better than any other?

Frank W. Sellke, MD

The del Nido cardioplegic solution (DNS) has recently received a large amount of attention as a method to improve myocardial protection for both pediatric and adult patients undergoing cardiac surgery. Although some have proposed that the myocardial protection afforded by DNS is actually superior to other commonly used solutions, the real benefit of DNS is as a way to speed up an operation by limiting the times a surgeon needs to deliver the cardioplegia. DNS was originally developed for pediatric cardiac surgery as a single-dose formula.¹ Although DNS has been studied in pediatric patients, its effectiveness in adults is still under investigation. DNS contains a base solution of Plasma-Lyte A (Baxter Healthcare Corp, Deerfield, Ill), which has an electrolyte composition similar to extracellular fluid. In the original formulation, the concentrations of electrolytes before the addition of cardioplegic additives are 140 mEq/L sodium, 5 mEq/L potassium, 3 mEq/L magnesium, 98 mEq/L chloride, 27 mEq/L acetate, and 23 mEq/L gluconate, but this has been modified by many clinicians, including the authors of the study under consideration. The formulation of both original and modified versions serves as the crystalloid component, which is mixed with blood at a ratio of 4 parts crystalloid to 1 part fully oxygenated patient whole blood. Of note, it is a potassium-rich, lidocaine-containing solution with a

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Address for reprints: Frank W. Sellke, MD, Alpert Medical School of Brown University, Rhode Island Hospital, MOC 360, 2 Dudley St, Providence, RI 02903 (E-mail: frank_sellke@brown.edu).

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Frank W. Sellke, MD

CENTRAL MESSAGE

Del Nido cardioplegic solution may improve myocardial protection and increase the speed of an operation. However, caution must be taken to maintain optimal protection during long operations.

lower hematocrit level than conventional blood-based cardioplegia and the only glucose and calcium in the delivered solution is from the patient blood mixed with the crystalloid component. The magnesium is a useful component to limit calcium influx and sequestration into cells.

Lenoir and colleagues² examine the effectiveness of DNS compared with traditional blood cardioplegia on myocardial protection and clinical outcomes in patients undergoing prolonged aortic root surgery. Both solutions were initially delivered at 4°C but with different volumes. In the DNS group, after 60 minutes, an additional volume was administered if the myocardial ischemic time was anticipated to exceed 90 minutes. In the blood cardioplegia group, the solution was readministered every 15 to 20 minutes. Myocardial protection was assessed by gathering the highest postoperative creatine kinase-MB isotype levels and troponin T levels at 1, 12, 24, and 48 hours after surgery. Both groups did well, but there was a trend toward higher troponin T levels in the DNS group compared with standard blood cardioplegia