

# Use of del Nido Cardioplegia Solution for Different Age Groups (Pediatric/Adult) in Cardiovascular Surgery

Kalp ve Damar Cerrahisinde Farklı Yaş Gruplarında (Pediatrik/Erişkin) del Nido Kardiyopleji Solüsyonunun Kullanımı

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## Abstract

The use of cardioplegia is an indispensable method of myocardial protection in surgical procedures with cardiac arrest in both pediatric and adult patients. In cardiac surgery, pharmacological arrest with cardioplegia solutions is the most prevalent and valid method for myocardial protection. Although in pediatric cardiac surgery, del Nido cardioplegia solution has been used for decades, its use in adult cardiac surgery is a relatively new phenomenon. More data are available due to its widespread use for many years in pediatric and infant patients; however, data on its use in adult patients are more limited. del Nido cardioplegia solution has been reported to be superior in several aspects in pediatric cardiac surgery. More evidence-based studies are needed to ensure optimal use of this myocardial protection technique for different age groups in a safer way. In this review, studies on the use of del Nido cardioplegia solution in different age groups are discussed.

**Key Words:** del Nido adult, del Nido pediatric, cardioplegia, myocardial protection

## Öz

Kardiyopleji, hem pediatrik hem de erişkin hastalarda kalbin durdurulmasıyla yapılan cerrahi prosedürlerde, miyokard korumasının ayrılmaz ve gerekli bir yöntemidir. Kalp cerrahisinde, miyokardın korunması için kardiyopleji solüsyonlarıyla uygulanan farmakolojik arrest en yaygın ve geçerli yöntemdir. del Nido kardiyopleji solüsyonu pediatrik kalp cerrahisinde onlarca yıldır kullanılmasına rağmen, yetişkin kalp cerrahisinde kullanımı nispeten yeni bir olgudur. Pediatrik ve infant hastalarda uzun yıllardır yaygın olarak kullanılması nedeniyle daha fazla veri mevcuttur; ancak erişkin hastalarda kullanımına dair veriler daha sınırlıdır. del Nido kardiyopleji solüsyonunun pediatrik kardiyak cerrahide çeşitli yönlerden daha üstün olduğu raporlanmıştır. Bu miyokard koruma tekniğinin farklı yaş gruplarında daha güvenli bir şekilde optimal kullanımını sağlamak için daha fazla kanıta dayalı çalışma gerekmektedir. Bu derlemede farklı yaş gruplarında del Nido kardiyopleji solüsyonunun kullanımı ile ilgili yapılan çalışmalar ele alınmıştır.

**Anahtar Kelimeler:** del Nido yetişkin, del Nido pediatrik, kardiyopleji, miyokardiyal koruma

## Introduction

Myocardial protection is the most important issue of all modern era cardiac surgery procedures. Although myocardial protection is often referred to as "cardioplegia", these terms should not be used interchangeably. Myocardial protection includes the preoperative process, selection of optimal

cardiopulmonary bypass techniques, anesthetic agents, topical cooling, avoidance of distension, surgical repair, and management of hemodynamic parameters (1). Myocardial protection is a complex process involving all actors in the operating room, including anesthesiologist, surgeon and perfusionist (2). Cardioplegia is a basic cardioprotective pharmacological treatment for electromechanical cardiac arrest during cardiac surgery (3,4).

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In the myocardial protection technique, the applied elements which are designed to quickly arrest the heart in diastole, create an immobile working area, and provide reliable protection against ischemia-reperfusion injury (5). del Nido cardioplegia solution is considered to be economically and clinically effective. Therefore, the relevance in this myocardial protection method is constantly increasing (6). In this review, current studies on the use of del Nido cardioplegia solution in different age groups are summarized.

### Myocardial Protection and Cardioplegia

In the last century, the surgical repair of congenital anomalies has evolved. In the 1950s, the studies of Kirklin, Lillehei, Bigelow, and Gibbon have reformed cardiac surgery safer (3,7). The science of myocardial protection began in the 1950s and has developed since then. In the 1980s and 1990s, the cornerstones of the cardioplegia strategy have been reshaped (crystalloid or blood, hot, warm or cold, continuous or intermittent, antegrade or retrograde cardioplegia) (8). In recent years, the mortality rate has decreased significantly in consequence of the use of new cardioprotective strategies and technologies as well as basic practice (9).

The idea of myocardial preservation in the perioperative period was first mentioned by Bigelow in a review published in 1950. Bigelow proved that myocardial preservation is possible with hypothermia method in dogs. Later, it was reported by Melrose in 1955 that reversible cardiac arrest could be achieved chemically. Bretschneider defined a low sodium and calcium free cardioplegia solution in his study in 1964. Another cardioplegia, St. Thomas solution was described in 1975 (10). This solution was used in St. Thomas hospital (11). Follette et al. (12) in the late 1970s, he introduced the use of blood cardioplegia to induce myocardial arrest (3). In the early 1990s, a new formulation, del Nido cardioplegia solution, was improved for myocardial protection (13).

Diastolic arrest is an obligation in all cases that require cross-clamping of the aorta during the operation. The purpose of cardioplegia is to limit reperfusion injury and maintain myocardial function during ischemic arrest. The most important factors contributing to myocardial protection are temperature of cardioplegia, chemical components of cardioplegia and delivery method (antegrade/retrograde). To prevent intracellular calcium accumulation and to optimize myocardial energy production during warming and reperfusion, acid buffering and myocardial edema should be managed by minimizing free oxygen radicals and achieving substrate supplementation (13-16). Clamping the aorta cut-off the blood flow to the coronary arteries. The role of cardioplegia is to reduce the undesirable effects of cardiac ischemia. The optimal cardioplegia solution should rapidly arrest the myocardium, reduce myocardial energy demand, preserve intracellular electrolytes during

the ischemic period and stop electromechanical activity (3). Immature myocardium of infant and newborn patients includes anatomical, physiological, structural and functional changes compared to adult myocardium. Therefore, myocardial protection requires a different strategy (1). Today, cardioplegia solutions; are divided into two groups as blood and crystalloid cardioplegia (Table 1). Crystalloid formulations are divided into two groups, intracellular and extracellular, according to their ionic components (8).

### del Nido Cardioplegia Solution

Cardioplegia solution is an indispensable and required myocardial protection method for patients of each ages in all cardiac surgical interventions that achieve cardiac arrest. In the early 1990s, under the leadership of Pedro del Nido, Hung Cao-Dan, K. Eric Sommers, and Akihiko Ohkado improved a new formulation for myocardial protection at the University of Pittsburgh (Pittsburgh, PA). The original solution has been modified, eventually known as del Nido cardioplegia in the literature and clinical practice. del Nido cardioplegia solution has a unrivaled formulation of four units of crystalloid for one unit of whole blood and is usually used as a single dose. Despite the formulation was improved firstly for use in pediatric patients, its use in adult cardiac surgery is as well increasing (13).

del Nido Cardioplegia solution contains a base solution (Plasma-Lyte A) with an electrolyte composition similar to the extracellular fluid content. Electrolyte concentrations in this solution at pH 7.4; 140 mEq/L sodium, 5 mEq/L potassium, 98 mEq/L chloride, 3 mEq/L magnesium, 23 mEq/L gluconate and 27 mEq/L acetate. For cardioplegia, the ingredients added to this base solution are listed in Table 2. In this formulation, one unit of highly oxygenated whole blood of the patient is added to four units of base solution. This blood is usually obtained from the

**Table 1: Classification of cardioplegia**

Crystalloid cardioplegia		Blood cardioplegia	
Intracellular	Extracellular	Blood amount	Temperature
- Bretschneider HTK	- St. Thomas - Celsior - Plegisol - del Nido	- With hemodilution - Only blood	- Cold - Warm - Hot

**Table 2: Contents of del Nido cardioplegia solution (13)**

Contents	Volume (mL)
Plasma-Lyte A	1000
Mannitol 20%	16.3
MgSO <sub>4</sub> 50%	4
NaHCO <sub>3</sub> 8.4%	13
KCl (2 mEq/mL)	13
Lidocaine 1%	13

bypass circuit. The calcium concentration of this cardioplegia can be defined as trace amounts, as 20% of it contains blood in the muscle. Trace calcium has been shown to be preferable over acalcemic or normal levels (17-21).

del Nido cardioplegia solution is usually given as a single dose (20 mL/kg). The maximum cardioplegia dose for patients over 50 kg is usually limited to one liter. Additional cardioplegia volume can be applied in conditions such as hypertrophic hearts, aortic regurgitation, and known coronary disease. For procedures requiring shorter cross-clamp time (<30 minutes), the cardioplegia dose of 10 mL/kg can be used. The delivery temperature is 8-12 °C. Cardioplegia dose is usually given as 20 mL/kg with a system pressure of 100-200 mmHg in 1-2 minutes. This method is performed with a cardioplegia conduction flow rate of 10-20 mL/kg/min for pediatric patients (13).

### Use of del Nido Cardioplegia in Pediatric Patients

del Nido cardioplegia solution has been widely used in pediatric cardiac surgery. Cardioplegia is initially the same for infant and pediatric patients; The volume is simply adjusted for flow and pressure (13). The advantages of the single-dose cardioplegia strategy are the avoidance of disruption to the surgical procedure and an importantly reduction in cross-clamp time. As an extracellular cardioplegic solution, del Nido solution meets these goals and has been successfully used in pediatric cardiac surgery (22).

O'brien et al. (23) showed that pediatric patients had reduced troponin T release compared to those receiving adult cardioplegia solution. They evaluated pediatric cardioplegia delivery (del Nido) and standard adult cardioplegia (modified Buckberg) in rat cardiomyocytes in their study and compared them with short-term outcomes in pediatric cardiac surgery patients.

In North America, reports from pediatric cardiothoracic surgeons have expressed that a single dose del Nido cardioplegia solution is the most used myocardial protection strategy (38%), regardless of cross-clamp duration (24).

Charette et al. (25) were grouped thirty-four pediatric patients with aortic cross-clamp times greater than 90 minutes with multi-dose modified adult solution and del Nido single-dose solution. They found that there were significant differences between the groups in perioperative glucose levels and the number of cardioplegia doses. Buel et al. (26) conducted a study in pediatric patients comparing the defibrillation rates of St. Thomas and del Nido cardioplegia solutions after cross-clamping. They showed that patients in all weights in the del Nido group had a reduction in defibrillation rates after cross-clamp removal.

The study consisted of 100 pediatric patients younger than 12 years who underwent elective surgical repair for ventricular

septal defects and tetralogy of Fallot. They reported that the duration of mechanical ventilation, hospital and intensive care unit stay periods were significantly lower in the del Nido group. In addition, del Nido group has been shown to have lower Troponin-I release at 24-hour intervals (27).

Gorjipour et al. (28) compared inflammatory responses between patients who received del Nido and multiple doses of St Thomas cardioplegia solution in cardiopulmonary bypass surgery for repair of tetralogy of Fallot in a randomized clinical trial. They showed that the anti-inflammatory cytokine response was significantly better in the St Thomas group than in the Del Nido group. They concluded that this effect may be due to the shorter application intervals of St Thomas cardioplegia solution, which prevents increased metabolic demand, myocardial rewarming, and hypoxia.

### Use of del Nido Cardioplegia in Adult Patients

In pediatric cardiac surgery, del Nido cardioplegia solution has been commonly used for almost 20 years (29). Although del Nido cardioplegia solution has been used in pediatric cardiac surgery for decades, its use in adult cardiac surgery is relatively new (30).

Considering the ease of administration, avoiding surgical procedure interruption and cost reduction potential, interest in del Nido solution is increasing in the adult heart surgery (31). The use of del Nido cardioplegia has become widespread in adult cardiac surgery centers in recent years and successful results have been obtained (13). Considering the ease of management and longer recovery interval, there is increasing interest in the use of del Nido cardioplegia in adult cardiac surgery patients (30). O'blenes et al. (21) evaluated that cardioplegic solution used for pediatric hearts (del Nido cardioplegia) may also be beneficial for elderly patients, as aged hearts and immature cardiomyocytes have similar properties. They compared its effect on the membrane potential of cardiomyocytes in aging rat hearts with standard cardioplegic solution. They used a newly isolated cardioplegic arrest and reperfusion cell model. In conclusion, del Nido cardioplegia preventing Ca<sup>2+</sup>-induced hypercontraction during early reperfusion has the potential to provide superior myocardial protection in aging hearts.

Govindapillai et al. (32) was evaluated recovery rates in isolated cardiomyocytes from aged rats (approximately 24 months) after 60-minute cardioplegic arrest with del Nido cardioplegia. del Nido cardioplegia has been shown to prevent spontaneous contractions during arrest and reduce troponin release in isolated elderly hearts. In isolated aged rat hearts, the del Nido cardioplegia strategy has been shown to be associated with less spontaneous activity during functional recovery compared to the standard multiple-dose 4:1 blood cardioplegia strategy and reduced myocardial damage during arrest.

del Nido and St. Thomas solutions were compared in studies on adult patients. In a study that included 100 patients who underwent valve replacement or coronary artery bypass grafting, it was shown that bypass times and cross-clamp times were less in the del Nido group. It was also shown that postoperative ejection fraction was better in the del Nido group (33). Redo surgeries generally require long and cardiopulmonary bypass and cross-clamp times. Sorabella et al. (34) investigated the use of del Nido cardioplegia and blood cardioplegia in reoperative aortic valve surgery (113 adult patients). It was reported that there was no difference between the two groups in terms of cross-clamp time, bypass time, postoperative complication rate, or patient outcomes (34).

Loberman et al. (35) compared both del Nido and whole blood cardioplegia groups in their study (coronary artery bypass grafting + valve patients) and reported similar clamping and cardiopulmonary bypass times. Higher CK-MB levels were observed at 24 hours in the del Nido group; however, they revealed that the incidence of postoperative atrial fibrillation is lower.

In adult isolated mitral or aortic valve surgeries, del Nido cardioplegia solution is relatively safe for use mainly. There are advantages such as reduced probability of surgical procedural interruption, lower fluctuations in intraoperative blood glucose levels, less need for postoperative insulin use, reduction in surgical time and lower cost in some surgical approaches (31).

Ota et al. (29) retrospectively evaluated the short-term (in-hospital) clinical outcomes of using del Nido cardioplegia solution in patients undergoing aortic valve replacement surgery. They compared these results with patients using conventional blood cardioplegia. del Nido cardioplegia technique could have enhanced the surgery by eliminating repeated cardioplegia dosing and retrograde cannulation and has been associated with shorter cross-clamp times (29).

Valooran et al. (22) published a review article on the use of del Nido cardioplegia in adult cardiac surgery. It has been revealed that intraoperative peak glucose levels and insulin requirement reduce with del Nido cardioplegia, which may have prognostic value. It has been reported that the incidence of atrial fibrillation and the number of defibrillations are lower with the use of this technique. As a result, they reported that there are no prospective randomized trials and a protocol-based approach is needed for its use in adults.

Ziazadeh et al. (36) compared the efficacy and results of a single dose del Nido cardioplegia with standard blood cardioplegia in minimally invasive aortic valve surgery. Their study included 178 non-randomized, single-center patients. In minimally invasive aortic valve surgery, del Nido has facilitated the cardioprotective regimen and reduced the aortic cross clamp time. Provided myocardial protection and clinical outcomes

equivalent to blood cardioplegia. As a result of the study, del Nido associated it with reduced cardiopulmonary bypass time and glucose levels.

Guajardo Salinas et al. (37) compared the outcomes of all patients using 4:1 blood cardioplegia with a single dose of 1:4 del Nido cardioplegia in 40 patients undergoing coronary artery bypass surgery. They concluded that a single dose of del Nido cardioplegia can be used in coronary surgery with good results.

In another study, the clinical results of del Nido and blood cardioplegia for cardiac protection in adult coronary artery bypass grafting patients were compared. Both cardioplegia have been reported to provide equivalent myocardial protection and clinical outcomes. del Nido has been associated with lower cardiopulmonary bypass time and glucose levels (38).

Ramanathan et al. (39) retrospectively reviewed 142 adult patients (valvular, aortic, and bypass procedures) using del Nido and Buckberg cardioplegia. They showed that less cardioplegia dose was used and less defibrillation was recorded in the del Nido group. However, no significant difference was observed in the incidence of postoperative events (39).

## Discussion

There are some vague concerns that need to be addressed before the routine adoption of del Nido cardioplegia use in adult cardiac surgery. Although the benefits of del Nido cardioplegia are attractive, the lack of a well-established protocol for its use is a major limitation of its routine use, as noted in recent studies. Despite being quite cost-effective, evidence for the use of del Nido cardioplegia in adults is relatively scarce (22). Despite the large number of unpublished cases of its use in adults in some centers, published clinical and animal data are few (31).

According to Sanetra et al. (6) of del Nido cardioplegia solutions; there are only a few randomized studies in pediatric patients and no randomized studies in adult patients. They reported that prospective, randomized studies should be conducted to prove the hypothesis of the feasibility or superiority of del Nido cardioplegia solution over other cardioplegia solutions in terms of myocardial protection (6). In our clinic, we lately use del Nido solution to take the advantages of the effects, such as, the ease of administration, avoiding surgical procedure interruption and cost reduction potential. In the early period we get good results, but we need comparative randomized studies to give precise and numerical results.

## Conclusion

del Nido Cardioplegia solution provides comfort without any interruption for cardioplegia delivery during the procedure and is associated with less cross-clamp time. Furthermore,



preparation and storage of del Nido cardioplegia is easy. Data on the use of del Nido cardioplegia solution differ for different age groups. Although there are more data due to its widespread use in pediatric and infant patients for a long time, data on its use in adult patients are limited. Although this cardioplegia solution is considered as pediatric cardioplegia, its clinical efficacy in protecting mature myocardium needs to be further determined. Despite being quite cost-effective, evidence for the use of del Nido in adults is relatively scarce. More evidence-based studies are needed to ensure safer and optimal use of this myocardial protection technique in different age groups.

## Ethics

### Authorship Contributions

Concept: O.D., N.D., E.Ö., E.İ., Design: O.D., N.D., E.Ö., E.İ., Analysis or Interpretation: O.D., N.D., E.Ö., E.İ., Literature Search: O.D., N.D., E.Ö., E.İ., Writing: O.D., N.D., E.Ö., E.İ.

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