Clinical Outcomes of Modified Del Nido Cardioplegia in Adult and Pediatric Cardiac Surgery; A Multicentered Cross Sectional Study

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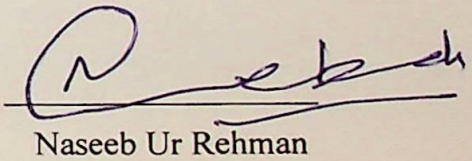
Student/Author Signature: 

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DEDICATION

This thesis is dedicated to my parents, whose unwavering support, unconditional love, and constant encouragement have been the foundation of my journey. Your sacrifices and belief in me have been my greatest strength.

To my family, thank you for being my pillars of support, for celebrating my successes, and for standing by me in times of struggle. Your presence has made this achievement all the more meaningful.

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LIST OF ABBREVIATIONS

ADP	Adenosine Diphosphate
AOR	Adjusted Odds Ratio
ASA	American Society of Anesthesiologists
CPB	Cardiopulmonary Bypass
CRT	Cardiac Resynchronization Therapy
DEL	Del Nido
ECG	Electrocardiogram
ICU	Intensive Care Unit

ABSTRACT

Introduction

Modified Del Nido cardioplegia is increasingly used in adult and pediatric cardiac surgery due to its potential to simplify intraoperative management and improve outcomes.

Objective: This multicenter cross-sectional study evaluates the clinical outcomes of modified Del Nido cardioplegia in adult and pediatric patients undergoing cardiac surgery.

Methods: A total of 200 patients (60.8% adults, 39.2% pediatrics) were included, analyzing demographic data, intraoperative parameters, and postoperative outcomes. Key metrics included CPB time, cross-clamp time, cardioplegia volume, left ventricular ejection fraction (LVEF) at discharge, and hospital stay.

Result

This study examined 200 patients (60.8% adults and 39.2% pediatrics) undergoing cardiac surgery, with adults having a mean age of 43.19 ± 17.65 years and pediatric patients averaging 6.51 ± 3.49 years (P = 0.001). Males were predominant in both cohorts (41.8% adults, 22.2% pediatrics; P = 0.06), with adults demonstrating greater weights (62.9 ± 15.9 kg vs. 16.6 ± 8.3 kg, P = 0.001) and body surface areas (1.63 ± 0.4 m^2 vs. 0.67 ± 0.2 m^2, P = 0.001). NYHA class I was notably more prevalent in the juvenile population (92.1% vs. 73.7%, P = 0.005), but a history of smoking was confined to adults (18.4%, P = 0.001). Intraoperatively, adults exhibited prolonged cardiopulmonary bypass (CPB) durations (103.2 ± 44.4 min vs. 73.53 ± 41.1 min, P = 0.001) and aortic cross-clamp intervals (67.5 ± 32.6 min vs. 52.2 ± 32.6 min, P = 0.002), alongside increased cardioplegia volume and duration (972.4 ± 427.5 ml vs. 393.7 ± 250.9 ml, P = 0.001; 62.9 ± 30.1 min vs. 48.5 ± 31.2 min, P = 0.001). Postoperatively, pediatric patients exhibited a higher left ventricular ejection fraction (LVEF) at discharge (62.5 ± 4.7% vs. 55.9 ± 9.1%, P = 0.001), but the duration of hospital stays was comparable (5.7 ± 1.6 days vs. 6.2 ± 2.1 days, P = 0.08). Regression analysis revealed that CPB time, cardioplegia volume, and cross-clamp duration are significant predictors of LVEF at discharge (P < 0.001), highlighting the importance of intraoperative treatment, especially the reduction of CPB time, in enhancing postoperative outcomes.

Conclusion

This study underscores notable disparities in intraoperative and postoperative outcomes between adult and juvenile cardiac surgery patients, with CPB duration, cross-clamp duration, and cardioplegia volume affecting LVEF at discharge. Enhancing intraoperative treatment is essential for augmenting heart function and recovery in both cohorts.

Keyword: Modified del nido cardioplegia, Adult, pediatric, cardiac surgery, bypass

Chapter 1

INTRODUCTION

Modern cardiac surgery emphasizes a premium on myocardial protection in order to preserve heart function. The following are all part of the procedure: getting ready for surgery, administering anesthetic, treating the central nervous system (CNS), cooling the skin, operating, and stabilizing hemodynamics. Although they mean different things, cardioplegia and myocardial protection are used interchangeably (1). Electromechanical cardiac arrest, or cardioplegia, protects the myocardium during surgery. To minimize myocardial injury and achieve best outcomes, it is vital for the surgeon, anesthesiologist, and perfusionist to work together. The unique ingredients and impressive effectiveness of Del Nido cardioplegia are driving its meteoric rise in popularity(2,3).

A one-dose formulation with a 4:1 crystalloid-to-blood ratio, the Del Nido cardioplegia is intended for use in pediatric cardiac procedures. Benefits for pediatric patients include less time spent cross-clamping and fewer disruptions to surgical operations. Using this intervention improves postoperative outcomes, such as less need for mechanical breathing and shorter stays in the intensive care unit, while simultaneously lowering markers of cardiac damage like Troponin T and Troponin I. In children, O'Brien et al. found that modified Buckberg cardioplegia provides better protection for the heart than Del Nido cardioplegia. While St. Thomas cardioplegia has its benefits, randomized studies show that traditional methods, with their frequent dose intervals, may lessen metabolic stress and heart rewarming, leading to an anti-inflammatory effect.

As an alternative to blood, del Nido cardioplegia is used in adult cardiac procedures such as coronary bypassgrafting and valve replacement. While keeping the heart intact, Del Nido has been demonstrated in adult trials to shorten the duration of cardiopulmonary bypass, reduce the incidence of postoperative atrial fibrillation, and shorten the time spent on cross-clamp. In a study of adult reoperative aortic valve procedures, Sorabella et al. discovered that, similar to Del Nido (4), there were comparable rates of cross-clamp, bypass, and problems related to blood cardioplegia. Del Nido cardioplegia may be helpful for people undergoing complicated minimally invasive procedures, according to research by Loberman and Ziazadeh. It is also

possible that reducing insulin and glucose consumption after surgery is an indicator of a speedy recovery.

In specialized settings, current research is comparing Del Nido cardioplegia to other treatments. Del Nido was shown by Guajardo Salinas et al. to be just as effective as blood cardioplegia in CABG operations. Minimally invasive aortic valve treatments were found to shorten aortic cross-clamp durations and accomplish myocardial protection (Zizadeh et al., 2018). Del Nido required fewer dosages and defibrillations than Buckberg cardioplegia, according to Ramanathan et al., even if the two postoperative outcomes were similar. The need for prospective randomized studies to establish technical standards and optimize the application of Del Nido cardioplegia in adults persists, despite these encouraging outcomes (Valooran et al., (6) and others). Cardioplegia de Nido is a flexible and effective method for protecting the heart during cardiac procedures in both adults and children. Its better postoperative outcomes, shorter cross-clamp durations, and one-dose formulation make it a great substitute for blood cardioplegia. Though it has been shown to be helpful in many studies, more study is needed to improve its use and address concerns about its usefulness in specific surgical settings. Supported by considerable evidence and well-defined methods, Del Nido cardioplegia will improve patient care and outcomes as cardiac surgery advances.Assess the clinical effectiveness of modified Del Nido cardioplegia in cardiac surgery for both adults and children using a multi-center cross-sectional study. All contemporary cardiac surgery procedures prioritize the protection of the myocardium. "Myocardial protection" and "cardioplegia" are used interchangeably, however they do not mean the same thing. Preoperative planning, anesthetic selection, topical cooling, distension avoidance, surgical repair, hemodynamic parameter management, and appropriate cardiopulmonary bypass procedures are all part of myocardial protection (1). When it comes to protecting the heart, the anesthesiologist, surgeon, and perfusionist play crucial roles. Cardioplegia is an essential pharmaceutical intervention for cardioprotection during electromechanical cardiac arrest, which occurs during cardiac surgery (3,4).

Quickly stopping the heart during diastole, creating a steady working environment, and protecting it from ischemia-reperfusion harm are the goals of the myocardial protection strategy. Both medically and financially, del Nido cardioplegia is the best option. Therefore, this strategy for protecting the heart is more important (6). Various

age groups are included in this study, which includes current research on del Nido cardioplegia solution.

1.1 Myocardial Protection and Cardioplegia

Over the past hundred years, there has been tremendous progress in the surgical correction of congenital defects. Improved cardiac surgery safety was a result of research done in the 1950s by Kirklin, Lillehei, Bigelow, and Gibbon (3,7). Since its start in the 1950s, myocardial protection research has progressed. Some of the ideas that have developed in the methodology of cardioplegia over the past several decades include crystalloid or blood, heat, cold, continuous or intermittent, antegrade or retrograde (8). A dramatic decline in death rates has been observed in recent years due to the use of innovative cardioprotective strategies, tools, and core behaviors (9).

Bigelow first proposed the idea of myocardial preservation in the perioperative period in a review he wrote in 1950. Hypothermia can protect canine cardiac tissue, as Bigelow shown. Melrose did not reveal a pharmacological way to induce reversible cardiac arrest until 1955. Bretschneider developed a sodium-and calcium-free cardioplegia solution and published it in 1964. Another option for cardioplegia, St. Thomas, was established in 1975. St. Thomas Medical Center used this procedure (11). Follette et al. reported that in the late 1970s, he used blood cardioplegia to cause cardiac arrest. The del Nido cardioplegia solution, which was introduced in the early 1990s, greatly enhanced myocardial protection.

Whenever the technique requires cross-clamping the aorta, diastolic arrest must be performed. In the event of an ischemic arrest, cardioplegia prevents reperfusion injury and maintains heart function. The main parameters that impact myocardial protection are the temperature of the cardioplegia, its chemical components, and the distribution mechanism (antegrade or retrograde). Two ways to optimize myocardial energy production during warming and reperfusion are to mitigate free oxygen radicals and enhance substrates. These strategies alter acid buffering, myocardial edema, and intracellular calcium buildup (13-16). When the aorta is blocked, blood cannot flow to the coronary arteries. Reducing the severity of myocardial ischemia is the primary goal of cardioplegia. The ideal cardioplegia solution should be in order to stop electromechanical activity, minimize myocardial energy consumption, maintain intracellular electrolytes during ischemia, and quickly arrest the myocardium (3). In terms of form, function, anatomy, and physiology, the myocardium of adults and

neonates is very different. Consequently, protecting the myocardium requires a fresh approach one (1). Two main types of cardioplegia solutions are currently available: crystalloid and blood (Table 1). You can tell if a crystalloid formulation is intracellular or extracellular by looking at its ionic components (8).

1.2 del Nido Cardioplegia Solution

Protecting the myocardium during cardiac arrest-inducing surgical procedures requires cardioplegia solution, and this is true regardless of the patient's age. At Pittsburgh, Pennsylvania's University of Pittsburgh in the early 1990s, Pedro del Nido, Hung Cao-Dan, K. Eric Sommers, and Akihiko Ohkado developed a novel method to protect the heart. Adjustments to the initial solution led to its recognition as del Nido cardioplegia in both the medical and scholarly sectors. Oddly enough, Del Nido cardioplegia solution contains four crystalloid units for every whole blood unit in a single dose. Adult cardiac surgery is seeing an uptick in the usage of the formulation, despite its original use in juvenile patients (13).

The electrolyte content of extracellular fluid is mimicked by Plasma-Lyte A, the base solution of del Nido Cardioplegia. Sodium has an electrolyte concentration of 140 mEq/L, potassium of 5 mEq/L, chloride of 98 mEq/L, magnesium of 3 mEq/L, and acetate of 23 mEq/L in this solution at pH 7.4. Table 2 details the components of this fundamental cardioplegia solution. The patient's oxygen-rich whole blood is divided into two parts and then combined with three parts of a base solution. It is common practice to use the bypass circuit to obtain this blood. This cardioplegia has trace amounts of calcium because to the 20% blood in the muscle. There are a number of benefits to using trace calcium levels as opposed to acalcemic or normal values (17-21).

The standard dosage for del Nido cardioplegia solution is 20 mL/kg. When treating individuals over 50 kg, it is standard practice to limit cardioplegia dosages to one liter. A greater cardioplegia may be helpful for patients with aortic regurgitation, hypertrophied hearts, or previous coronary artery disease. For treatments that do not require a lengthy cross-clamp (less than 30 minutes), a cardioplegia dose of 10 mL/kg can be administered. We provide delivery service for temperatures between 8 and 12 °C. The usual dosage for cardioplegia is 20 mL/kg, administered slowly over one to two minutes at a pressure of 100 to 200 mm Hg. Applying this method to pediatric patients results in a cardioplegia conduction flow rate of 10–20 mL/kg/min (13).

1.2.1 Use of del Nido Cardioplegia in Pediatric Patients

Thanks to the del Nido cardioplegia solution, numerous pediatric cardiac operations have been performed. Initially, cardioplegia impacts both young children and newborns in the same manner; the sole distinction is that the volume alters in reaction to variations in pressure and flow (13). Reducing the time of the cross-clamp and minimizing disruptions to the surgical procedure are the primary benefits of the single-dose cardioplegia approach. The del Nido solution, an extracellular cardioplegic solution, is an effective tool for juvenile cardiac surgery in achieving these aims (22). The release of troponin T was shown to be lower in adolescents compared to adults when administered cardioplegia solution (23). Their assessment of the short-term outcomes in patients following pediatric heart surgery was based on rat cardiomyocytes, the del Nido technique for pediatric cardioplegia administration, and the modified Buckberg strategy for standard adult cardioplegia.

Pediatric cardiothoracic surgeons in North America report that, regardless of the duration of cross-clamp, 38% of kids receive cardiac protection in the form of a single dose of del Nido cardioplegia solution.

The study conducted by Charette et al. (25) evaluated 34 pediatric patients with aortic cross-clamp durations exceeding 90 minutes using a combination of del Nido's single-dose solution and a modified multi-dose adult solution. Cardioplegia dose quantities and perioperative glucose levels varied significantly across the groups. In order to find out how often St. Thomas and del Nido cardioplegia solutions defibrillated pediatric patients undergoing cross-clamping, Buel et al. (26) conducted a study. After the cross-clamp was removed, the defibrillation rates decreased in the del Nido group, regardless of the patient's weight (4).

One hundred school-aged children with ventricular septal defects or tetralogy of Fallot who willingly had surgery were included in the study. The group who took del Nido had shorter hospital stays, used mechanical breathing less frequently, and spent less time in the intensive care unit overall. The del Nido group also has lower Troponin-I release rates per 24 hours, according to the research (27).

In order to detect inflammatory reactions, a randomized clinical experiment compared del Nido solution with numerous doses of St. Thomas cardioplegia solution in patients undergoing cardiopulmonary bypass surgery for tetralogy of Fallot (Gorjipour et al., 28). Their findings showed that the St. Thomas group's anti-inflammatory cytokine response was significantly stronger than Del Nido's. Shorter delivery intervals of St.

Thomas cardioplegia solution may have contributed to a decreased risk of cardiac rewarming and hypoxia, as well as an increase in metabolic demand (5-7).

1.2.2 Use of del Nido Cardioplegia in Adult Patients

Pediatric cardiac surgery has made extensive use of the Del Nido cardioplegia solution for about twenty years (29). Incorporating the del Nido cardioplegia solution into adult cardiac surgery is a pioneering development, despite its extensive use in juvenile cardiac surgery.

Due to its potential cost-effectiveness, ease of administration, and capacity to minimize surgical disruptions, the del Nido solution is gaining popularity for adult cardiac surgery (31). There has been some time of successful usage of cardioplegia del nido in adult cardiac surgery clinics (13). The del Nido cardioplegia is gaining popularity for adult cardiac operations due to its long recovery period and ease of administration (30). It has been suggested by O'blenes et al. (21) that adult patients may benefit from using the same cardioplegic solution (del Nido cardioplegia) as is used for young hearts. There are similarities between the features of young cardiomyocytes and those of mature hearts. Cardiomyocyte membrane potential was compared to that of a standard cardioplegic solution in rats whose hearts had deteriorated with age. Using freshly harvested cells, they replicated cardiac arrest and reperfusion. To prevent hypercontraction due to Ca2+ during early reperfusion, del Nido cardioplegia may be a better way to safeguard adult hearts.

Isolated cardiomyocytes from rats that had been cardioplegically halted for 60 minutes using del Nido cardioplegia were investigated for rates of recovery by Govindapillai et al. (32) after approximately 24 months of age. According to study, del Nido cardioplegia can benefit isolated aged hearts by lowering troponin release and inhibiting spontaneous spasms after cardiac arrest. Studies in isolated hearts of elderly rats showed that del Nido cardioplegia results in less myocardial injury during arrest and less spontaneous activity during functional recovery compared to the typical multiple-dose 4:1 blood cardioplegia technique.

In adult studies, researchers contrasted the del Nido and St. Thomas methods. Bypass and cross-clamp times were shown to be shorter in the del Nido group of 100 patients who had valve replacement or coronary artery bypass grafting. Moreover, following surgery, the del Nido group demonstrated an enhanced ejection fraction (33). Prolonged cardiopulmonary bypass and cross-clamp periods are usual outcomes of redo surgeries. Sorabella et al. (34) evaluated the effectiveness of del Nido

cardioplegia and blood cardioplegia in 113 adult patients who underwent reoperative aortic valve surgery. There was no difference between the two groups in terms of patient outcomes, surgical complications, bypass duration, or cross-clamp time (34). The lengths of clamping and cardiopulmonary bypass were similar in the del Nido and whole blood cardioplegia groups, according to Loberman et al. (35) when they compared patients undergoing coronary artery bypass grafting and valve implantation. The del Nido group exhibited higher CK-MB levels at 24 hours, despite the fact that their postoperative atrial fibrillation was less (4).

The del Nido cardioplegia solution is often safe for use during surgery on an adult's isolated mitral or aortic valve. Compared to other surgical procedures, this one does not carry the same risks, requires less insulin, has less variability in intraoperative blood glucose levels, and is less expensive (31).

Clinical results for patients undergoing aortic valve replacement surgery while hospitalized were examined by Ota et al. (29) as they reflected on the use of del Nido cardioplegia solution. The results of patients who underwent traditional blood cardioplegia were evaluated with those of other groups. The del Nido cardioplegia technique may have enhanced the procedure in a number of ways, including shorter cross-clamp periods, the removal of retrograde cannulation, and the use of numerous dosages of cardioplegia (29).

Valooran et al. published a study describing the outcomes of del Nido cardioplegia in adult cardiac surgery (22). Del Nido cardioplegia has the potential to enhance prognosis by reducing insulin requirements and intraoperative peak glucose levels, according to research. This approach can reduce the occurrence of atrial fibrillation and the rates of defibrillation. They mentioned the lack of prospective randomized studies and the need for a protocol-based approach when using it with adults.

Ziazadeh et al. (36) evaluated the efficacy and results of del Nido cardioplegia versus conventional blood cardioplegia in minimally invasive aortic valve surgery. The study was conducted with 178 participants from a single center and did not use random assignment. In minimally invasive aortic valve procedures, Del Nido has simplified the process of adhering to the cardioprotective protocol and reduced the duration of aortic cross-clamp use. Del Nido associated it with reduced glucose levels and shorter cardiopulmonary bypass periods; it also preserved the myocardium and produced clinical outcomes comparable to blood cardioplegia (6,7).

They compared 40 patients undergoing coronary artery bypass surgery to those who received either a single dose of 1:4 del Nido cardioplegia or 4:1 blood cardioplegia in their 37th and final study. When administered as prescribed, a single dose of Del Nido cardioplegia has been shown to improve outcomes following cardiac surgery (8).

The effectiveness of blood cardioplegia with del Nido in protecting adult hearts following coronary artery bypass grafting was the subject of an additional investigation. In terms of clinical results and myocardial protection, the two forms of cardioplegia are indistinguishable. There is evidence that del Nido can reduce glucose levels and the amount of time spent on cardiac bypass (38).

Ramanathan et al. (39) performed a retrospective review after 142 adult patients underwent valvular, aortic, and bypass operations with del Nido and Buckberg cardioplegia assistance. In the del Nido group, cardioplegia dosage was reduced and defibrillation was less common. The frequency of events after surgery did not vary significantly, but (39).

Before del Nido cardioplegia is widely used in adult cardiac surgery, many unresolved problems must be addressed. New research shows that despite del Nido cardioplegia's useful properties, there is currently no recognized approach for its systematic administration. This is a big downside. Despite limited research on its efficacy in adults, Del Nido cardioplegia is affordable (22). There is a lack of published research on the subject's effects on animals or humans, despite multiple unofficial assertions of adult consumption at specified sites (31).

Few randomized trials have been conducted in juvenile populations, and no studies have been conducted with adult populations using del Nido cardioplegia therapies, according to Sanetra et al. (6). The authors state that in order to determine the viability and efficacy of the del Nido cardioplegia solution in protecting the myocardium compared to alternative options, randomized, prospective trials are required (6). Our clinic has adopted the del Nido solution, which has many advantages for patients. These include probable savings in healthcare expenditures, preservation of surgical procedures, and convenience of administration. We need additional similar randomized trials to obtain more definitive numerical data, although at first we noticed promising outcomes.

OBJECTIVE

To examine the clinical efficacy of modified Del Nido cardioplegia in adult and pediatric cardiac surgery.

Chapter 2

LITERATURE REVIEW

In order for cardiac surgery to be effective, the myocardium needs to be sufficiently protected. Protecting cardiac tissue and preventing further damage from ischemia has been a relentless goal of academics and doctors since the 1950s. Numerous institutions that teach cardiac surgery now rank hypothermic and hyperkalemic cardioplegia treatments among the world's finest. Despite the abundance of cardioplegia systems, there is still no agreed-upon formulation, route, or method (4).

In 1995, a new formula was used in congenital heart surgery to treat cardioplegia. In a modified depolarizing solution, this substance was patented in a single dose. A safer and more prolonged myocardial ischemic arrest has been linked to the del Nido solution, which is a mixture of crystalloid and blood. There has been an uptick in the use of this solution in pediatric congenital heart surgery programs due to claims that it protects intracellular high-energy phosphates and intracellular pH, reduces calcium ion influx before and after ischemia arrest, and so on (5-7).

Numerous observational studies have linked the del Nido solution to the effectiveness and security of surgical procedures for adults. Despite these promising results, prospective randomized trials have not addressed protocol modification in the treatment of adult ischemic myocardium. Using del Nido cardioplegia regimens as compared to an existing approach that uses whole blood during routine CABG, valve, and CABG/valve surgeries was the goal of this randomized controlled experiment (8, 9).

In order to protect the myocardial muscle from harm, cardioplegia solution is an essential safety measure to follow during cardiac surgery. The myocardium may be protected from low flow or perfusion pressure periods with the use of cold crystalloid cardioplegia, which is often given in mild to severe hypothermia and may reduce oxygen consumption (10).

Following this, studies conducted at room temperature and mild hypothermia confirmed the critical role of blood in transporting potassium to the cardioplegic solution. If you want better cardiac outcomes after surgery, try utilizing blood instead of a crystalloid solution. The myocardium may receive oxygen with less danger of hemodilution when blood flows more properly. Therefore, warm blood cardioplegia (11) has been suggested as a risk-free way to protect the myocardium.

Crystalloid and blood types, cold, tepid, or warm solution temperatures, and antegrade vs retrograde delivery did not differ significantly from one another in preserving the myocardium during cardiac arrest, according to multiple investigations carried out in the 1980s and 1990s. However, it is still not apparent which cardioplegia kind is better. The del Nido cardioplegic solution was recently introduced to reduce intracellular damage caused by the influx of calcium ions during ischemia arrest while preserving intracellular phosphates concentration and intracellular pH value. The treatment of congenital heart disease and other long surgical procedures benefit greatly from this (12,13). Utilizing a 20% volume of completely oxygenated patient blood, the del Nido cardioplegia promotes buffering-effect anaerobic glycolysis and maintains aerobic metabolism for a brief period. Children were the original target audience for Del Nido cardioplegia because, after heart surgery, young myocardium cannot withstand high amounts of intracellular calcium. The magnesium sulfate, mannitol, and lidocaine concentrations in the del Nido solution are significantly higher than those in competing cardioplegias. An intriguing multi-center randomized trial was published by Ad and colleagues. Involvement from six American cardiovascular and thoracic hospitals allowed them to compare del Nido cardioplegia to blood-based cardioplegia in terms of safety and efficacy, even in adult cardiac surgery (14,15).

The study comprised 89 patients who met the criteria for medical stability to undergo coronary artery bypass grafting (CABG), single valve surgery, or a combination of the two. Whole blood cardioplegia was administered to the control group, whereas del Nido cardioplegia was administered to the del Nido group. Defibrillation need, troponin release, cardiomyocardial preservation by return to spontaneous rhythm, need for inotropes use, and baseline during anaesthesia induction were the four main end-points at baseline, 2 hours after cardiopulmonary bypass weaning, 12 hours after admission to the intensive care unit, and 24 hours after admission. Both sets of participants were otherwise comparable before and throughout the operation. Patients in the del Nido group were administered one liter of the cardioplegic solution during an aortic cross-clamp procedure; in the event that left ventricular hypertrophy was detected, an additional 500 milliliters were administered. Administration temperatures ranged from eight to eleven degrees Celsius, and the dosage for whole blood cardioplegia was one to two liters, with further doses given every twenty minutes (16,17).

Del Nido patients were less likely to require inotropic support (65.1% vs. 84.2% in the control group), had fewer defibrillations (4.7% vs. 13.2% in the del Nido group), and were more likely to retun spontaneously (97.7% vs. 81.6% in the control group), but the significance level was not reached (P value greater than 0.001). The del Nido group had a substantially lower aortic cross-clamp time at 70 minutes compared to the control group at 83 minutes (P=0.018). At 12 and 24 hours post-op, the del Nido group had significantly reduced troponin I release rates (P=0.040) (18), whereas the two groups were comparable overall.

For all studies, the control group had a larger average total volume of cardioplegia (1,746±852 vs. 5,077±2,457 mL) and, surprisingly, gave more doses per patient. Major complications that occurred during the operation did not include death, renal failure, perioperative myocardial infarction, or stroke. Researchers Ad et al. found that del Nido cardioplegia is a safe and effective alternative to the current gold standard for protecting the heart during adult cardiac surgery. Both Li and Mishra and colleagues presented studies that came to similar conclusions. Original studies compared del Nido cardioplegia to conventional cardioplegia in people having cardiac surgery. Li found that del Nido cardioplegia significantly reduced the amount of time spent on CPB and cross-clamp. There was no difference between the two groups in terms of myocardial enzyme release, inotropic support following surgery, atrial fibrillation, or death while hospitalized. Using shorter cardiopulmonary and aortic cross-clamps and lower doses of cardioplegia, the second investigation found that del Nido solution was equally safe as St. Thomas' cardioplegic solution (19,20).

Much debate has raged over the years concerning cardioplegia and the optimal solution, temperature, and administration method for protecting the myocardial during cardiac surgery. Experimental studies have demonstrated that blood cardioplegia outperforms cold crystalloid cardioplegia. Cardioplegic medicines have been the subject of numerous randomized and non-randomized clinical trials, with the goal of determining which one provides the best protection for the heart. While warm blood cardioplegia failed to provide any results in certain experiments, cold blood cardioplegia showed promise in others. According to another study, a worse prognosis was linked to cold blood cardioplegia. Lastly, blood troponin levels were not significantly different in two trials that used the del Nido solution (21-23).

Unlike other sporadically given cardioplegia procedures, the del Nido method requires shorter periods for aortic cross-clamp and cardiopulmonary bypass (23,24), which this review expertly incorporates. We looked at 141 individuals who were stable after having an aortic valve replaced (with or without coronary artery bypass grafting) in a retrospective, non-randomized research. The patients were assessed based on how often cold crystalloid cardioplegia antegrade or warm blood cardioplegia was administered. For example, when comparing patients with warm blood cardioplegia to those with crystalloid cardioplegia, the levels of total CK, CK-MB, and cardiac troponin I in the serum were lower in the former group at the time of ICU admission. The percentage of patients with CK-MB/CK ratios $\leq$ 10% was 5.9% in the cold crystalloid cardioplegia group, compared to 7.8% in the control group ($P<0.0001$). Clinical outcomes were not different between the two types of cardioplegia, even though cold crystalloid cardioplegia significantly reduced myocardial enzyme release. This is why we hypothesised that cold cardioplegia, as opposed to warm cardioplegia, would provide superior myocardial protection in cases of left ventricular hypertrophy, i.e. aortic valve dysfunction (25,26).

Ad and colleagues noted that lidocaine can alleviate intracellular calcium ion entry, increase nitric oxide release, and maintain intracellular pH. Because of these characteristics, it may be useful in preventing ventricular arrhythmias during coronary reperfusion following aortic clamp removal. The experimental group actually had a lower rate of defibrillation (4.7% vs. 13.2%) after aortic clamp release compared to the control group. One possible explanation for why this polymorphism had no impact on the clinical outcome of the trial is because subjects with impaired left ventricular systolic function were removed. Patients with systolic left ventricular dysfunction or considerable cardiac dilatation may benefit from aortic de-clamping if it speeds up their cardiac rhythm recovery, which in turn reduces the risk of myocardial damage and postoperative low cardiac output syndrome (27,28).

2.1 Origin of del Nido cardioplegia

Cardiac surgeries, such as CABG and valve replacement, use a cardioplegic solution known as Del Nido cardioplegia to cause a cardiac arrest. Dr. Pedro J. del Nido, a pediatric heart surgeon, created it in the early 1990s.Dr. del Nido, a researcher at Boston Children's Hospital and Harvard Medical School, saw a need for a cardioplegic solution that may prolong the preservation of heart muscle without requiring repeated treatments.The necessity to re-administer the medication intermittently during surgery

to sustain cardiac arrest is a known danger and process disturbance associated with traditional cardioplegic therapies (29,30). Unique to the Del Nido cardioplegia solution is the fact that a single dosage can preserve the myocardium. It has a lower potassium concentration but higher magnesium and lidocaine contents compared to standard cardioplegic solutions. Elevated magnesium levels boost cellular defenses, whereas decreased potassium cardioplegia content lowers the risk of myocardial edema. Del Nido cardioplegia is becoming more common in congenital cardiac procedures, and it is no longer reserved for children. Its development was a leap forward for cardiac surgery because of its stated goals of better patient outcomes and more efficient operations (31).

2.2 Del Nido: A User's Guide on Using It Safely

Can you explain Del Nido cardioplegia? The extracellular crystalloid solution known as Del Nido cardioplegia includes almost no calcium and is administered at specific times and in specific amounts. Simply said, the solution is the solution. The ingredients of the crystalloid solution include plasmalyte-A, lidocaine, potassium, sodium bicarbonate, mannitol, and magnesium sulfate. Fluids used in Del Nido cardioplegia that have a neutral pH, including This solution is isotonic. An example of a balanced crystalloid is Plasmalyte-A, which has a pH of 7.4 and contains electrolyte ions that are comparable to those in human plasma. The metabolic process of ATP in the heart is dependent on intracellular cations such as magnesium and the bicarbonate building blocks acetate and gluconate, which are both present in Plasmalyte-Asolution (32,33). Because of its hyperosmotic characteristics, mannitol can scavenge free radicals and reduce inflammation. As a calcium channel blocker, magnesium aids in the healing of damaged myocardium. As a hydrogen ion scavenger, sodium bicarbonate aids in maintaining a constant pH inside cells. Research indicates that the buildup of intracellular sodium and calcium may hinder myocardial recovery, despite the fact that potassium chloride induces a fast depolarization stop. The del Nidocardioplegia solution contains 24 mEq/l of potassium. Lidocaine belongs to the class Ib of antiarrhythmic medications and is a sodium channel blocker. It lessens the impacts of hyperkalemic depolarized arrest and prolongs the myocyte refractory time by polarizing the cell and decreasing intracellular sodium and calcium influx (34,35). One part of oxygenated pump blood and four parts of the Del Nido cardioplegia solution is used to provide the dosage. It is possible to deliver del Nido cardioplegia analogously via an aortic root catheter, however this depends on the severity of the aortic valve

insufficiency and the details of the operation. Via means of the angled coronary sinus or coronary ostia. Injecting 5-10 mL of del Nido cardioplegia into the saphenous vein or radial artery graft can evaluate the distal anastomosis in cases where cardiac bypass grafting is required. For a full 90 minutes, the myocardium is best protected by a single dose of 20 mL/kg. Flow rates of 200 to 300 mL/min and pressures of 100 to 120 mm Hg are used during administration. While the mother is in labor, her blood aids with aerobic metabolism, provides buffering capacity, and increases cardiac perfusion. The Del Nido cardioplegia solution contains no calcium ions other than what is added to the blood. This way you know you're only giving a tiny dose of calcium. A temperature of 4 degrees Celsius is the delivery temperature. The symptoms of hypothermia include a drop in oxygen intake and metabolic rate (36,37).

2.3 Various cardioplegia options for pediatric patients compared to del Nido cardioplegia

Del Nido cardioplegia is the go-to procedure for pediatric cardiology clinics when it comes to protecting the heart during cardiac surgery. This recommendation is backed by multiple clinical trials. It successfully regulates calcium levels and reduces troponin T levels, according to a 2009 seminal study by O'Brien [4]. Results regarding intraoperative parameters and surgical risk factors were consistent across trials, lending credence to Charette's experiment, even if there were notable variations in cardioplegia dosage and perioperative glucose levels [5].Regardless of the length of cross-clamp, surgeons in North America usually administer Del Nidocardioplegia with a single dose [6].On a consistent basis, Del Nido has outperformed other options. Improved cardiac index, decreased troponin release and myofibrillardis array, and shorter intensive care unit, hospital, and ventilator stays were the outcomes of a randomized trial comparing Del Nido and St. Thomas cardioplegia. In terms of inflammatory response, Del Nido was comparable to modified St. Thomas solution. The longer intervals between dosages may have contributed to the higher lactate levels observed postoperatively (38,39). Compared to histidine-tryptophan-ketoglutarate (HTK) cardioplegia, Del Nido offers a number of benefits, including as reduced troponin generation, decreased need for inotropic support, shorter hospital and intensive care unit stays, and better maintenance of cardiac index. Electron microscopy confirmed these findings, demonstrating that Del Nido outperforms other options for pediatric heart surgery by preserving glycogen stores and myocardial architecture. Inflammatory reactions and lactate levels can differ, but Del Nido is still

a good option for protecting the myocardium in kids. In juvenile cardiac surgery, Del Nido has established itself as the gold standard because to Talwar's study showing that it is clearly superior to HTK for cardioplegia (40).

Adults' perceptions of del Nido cardioplegia in relation to other forms of cardioplegia

Comparative studies have shed light on the results and effectiveness of Del Nido cardioplegia for adult patients having cardiac operations. The DelNido group outperformed the St. Thomas No. 2 group in terms of left ventricular function preservation (41-43) and aortic cross-clamp and bypass durations. Both the Del Nido cardioplegia reveal study and the aortic cross-clamping study failed to detect any ventricular electrical activity or changes in ejection percentage in adults having congenital heart surgery. Patients receiving mitral or aortic valve surgery in adults had quicker procedural durations and decreased glucose levels in the Del Nido group, but those in the Buckberg group had similar troponin levels and postoperative ejection percentages. While Del Nido offered some benefits over Buckberg cardioplegia in terms of requiring fewer doses and less defibrillation, there was no statistically significant difference in postoperative sequelae, according to retrospective investigations. In specialist procedures such as aortic valve surgery, the Del Nido method of cardioplegia reduced the time needed for bypass and cross-clamp while maintaining equivalent postoperative outcomes compared to traditional whole-blood cardioplegia. It has shown promise and shortened procedure times in minimally invasive aortic valve surgery, all while keeping cardiac parameters constant. Results from redo surgeries using del Nido cardioplegia were comparable to those from studies using blood cardioplegia (44,45).

Compared to blood cardioplegia, Del Nido cardioplegia had troponin levels that were equivalent and fewer instances of ventricular fibrillation; it was also effective across a variety of ventricular masses and ischemia durations.Overall, Del Nido provides benefits over whole blood cardioplegia, such as a reduced incidence of postoperative atrial fibrillation, but certain studies have found increased CK-MB levels using it at times. Del Nido cardioplegia is just as safe as, and often more effective than, conventional methods of adult heart surgery. According to research, Del Nido (DN) cardioplegia solutions can be utilized in place of histidine-tryptophan-ketoglutarate (HTK) solutions in complicated valve procedures that involve prolonged ischemia. Results showing no change in post-operative cardiac biomarker levels and beneficial effects on cardiac arrest indicate that DN offers no different kind of protection to the

heart. There are a lot of benefits to using DN instead than HTK. These advantages include a decrease in the incidence of serious arrhythmias, better hemodynamics after surgery, lower ICU stays, and a quicker recovery to spontaneous rhythm with fewer transfusions. Due to its numerous advantages, DN may be considered by cardiac surgeons performing complicated valve operations, especially in cases where prolonged ischemia is anticipated (46-48).

2.3 Adjustment to the basic method in Del Nidocardioplegia

2.3.1Analyzing Del Nido Cardioplegia Base Fluids

When dealing with Del Nido cardioplegia, it is imperative to always employ a neutral-pH base fluid. Balanced crystalloids mimic the electrolyte composition of human plasma to preserve their isotonicity. Plasma lyte solutions, for instance, can have a pH as high as 7.4.Developing nations still have a ways to go before Plasma-Lyte A becomes widely available and affordable. There are some situations where Ringer's Lactate can be substituted.A bicarbonate source, lactate is used to make Ringer's Lactate, which has a pH of 6.6. Due to its in vivo glucose conversion potential via the gluconeogenic pathway, diabetics should proceed with caution when administered large volumes of fluids containing lactate. Analyzing the pH, electrolyte composition, and practical concerns of the available base fluid options for Del Nido cardioplegia, this article gives a thorough analysis of the topic. In a randomized controlled experiment, researchers from AIIMS Delhi looked at the possibility of switching from the more expensive and rare Plasmalyte-A solution to the more widely available and cheaper Ringer Plain solution for children with Del Nidocardioplegia.

This study shows that Modified Del Nido cardioplegia, which is based on Ringer Plain, may keep the heart working and protect the myocardium just as well as the expensive or unavailable Plasmalyte-A cardioplegia. Pathan et al. studied the efficacy and safety of modified del Nido cardioplegia during open-heart procedures done on children with congenital cardiac abnormalities at the Department of Cardiac Surgery, PAQSJIMS. During the procedure, ringer lactate was utilized.With less intrusive surgery and inotropic support, their study showed that this strategy successfully restored spontaneous sinus rhythm compared to standard approaches. There were no statistically significant changes in intubation length, critical care unit stay, or the use of vasoactive medications post-operation when comparing modified del Nido with cold blood cardioplegia. The modified solution's efficacy and safety are further demonstrated by this. The focus of this investigation was expanded to encompass adult

cardiac surgery in a 2019 study by Kantathut et al. Scientists contrasted blood cardioplegia with a variant of DelNido cardioplegia that makes use of Ringer lactate. Modified Del Nidocardioplegia resulted in reduced troponin-T release, shorter myocardial protection, and lower aortic cross-clamp removal rates of ventricular fibrillation (48-50).

Chapter 3

MATERIALS AND METHODS

3.1 Study Design

This multicentered descriptive cross-sectional study was conducted to evaluate the clinical outcomes of modified Del Nido cardioplegia in adult and pediatric cardiac surgeries.

3.2 Study setting

The study was carried out over a period of four months at the Departments of Cardiac Surgery at Lady Reading Hospital (LRH) and Pak Medical Center and Hospital in Peshawar.

3.3 Study Duration

The duration of the study was 06 months

3.4 Sample size

A total of 200 patients were included in the study, with the sample size determined based on a 20.4% proportion of postoperative inotropic support as a clinical outcome, a 95% confidence level, and a power of 1.5%.

3.5 Sampling technique

Consecutive (non-probability) sampling was employed to select participants who met the specified inclusion criteria

3.6 Selection Criteria

3.6.1 Inclusion criteria

which included pediatric patients with congenital heart diseases, stable adults undergoing isolated or combined CABG or valve surgeries, and individuals capable of providing informed consent.

3.6.2Exclusion criteria

Patients with previous cardiac surgeries, preoperative inotropic or mechanical circulatory support, implanted pacemakers, or specific pulmonary conditions were excluded to minimize confounders and bias.

3.7 Data collection Procedure

One example of the steadfast adherence to ethical standards was the practice of seeking informed consent from all individuals, including children's legal guardians.

The patient's anesthetic requirements, clinical history, and medical records were all thoroughly reviewed during the preoperative evaluation to guarantee they were a good fit for the treatment. Following open-heart cardiac surgery and a median sternotomy, antegrade Del Nido cardioplegia was given through the aortic root at temperatures between 8 and 12 degrees Celsius. If heart activity returned within 90 minutes, cardioplegia was re-administered.

The main outcomes that were evaluated were life expectancy, death, and the utilization of intra-aortic balloon pumps (IABP). Secondarily, we looked at things like postoperative LVEF, inotrope index, eGFR, CK-MB levels, lactate monitoring, and ICU admission. They were taken at the beginning of the study as well as one, two, and four hours following admission. Long stays in the hospital or intensive care unit, time on the ventilator, blood transfusions, dialysis needs, stroke rates, need for reoperation, and infections at the surgical site were among the other indicators we looked at. In order to aid in clinical decision-making and monitor metabolic condition, arterial blood gas analysis was used every three hours to assess lactate levels.

Data collected for the study included patients' identities, surgical procedures, and immediate postoperative findings, among other things. Each patient's sex, age, underlying condition, previous cardiac surgery history, and EuroSCORE II (European System for Cardiac Operative Risk Evaluation II) scores were meticulously documented. The patient's ischemic heart disease diagnosis, the type of pre-operative echocardiographic abnormalities, and the use of intra-aortic balloon pumps or extracorporeal membrane oxygenation were all meticulously documented.

Intraoperative data set included: total operation time, cardioplegic solution type and quantity, duration of cardiopulmonary bypass (CPB) and aortic cross-clamping (ACC) use, need for defibrillation or pacing during CPB weaning, and the amount of time CPB and ACC were used. Another part of the data set included the overall amount of transfusions administered during the exercise. The graft details described for CABG included the number of distal anastomoses and the adoption of Y-composite grafts.

Measured early postoperative outcomes included readmission rates, 30-day mortality, 30-day duration of ventilator-dependent, 30-day surgical complications, 1-year major adverse cardiac and cerebrovascular events, and the need for postoperative extracorporeal membrane oxygenation or intraaortic balloon pump support. Analysis of peak cardiac enzyme levels (CK-MB and troponin I) and echocardiographic anomalies following surgery allowed for further evaluation of myocardial protection.

Selection criteria for patients undergoing coronary artery bypass grafting (CABG) and traditional myocardial protection procedures If a patient's distal coronary bed status is poor or their left ventricular ejection fraction (LVEF) is low, our clinic will advise them to have standard CABG. Therefore, conventional CABG is ultimately performed on more than 20% of patients requiring surgery for ischemic heart disease.

Under general anesthesia, all patients had the common procedure of coronary artery bypass grafting. After the graft was harvested, the following procedure was a conventional median sternotomy, which involved a central cannulation. The starting dosage for the blood cardioplegia group was 1,000 mL of a 4:1 blood dilution, administered as an antegrade injection at 4 °C. Every fifteen to twenty minutes, or as needed, doses of 200 mL were given retrogradely. The last anastomosis was immediately followed by the retrograde administration of 500 mL of warm blood. In comparison, the del Nido cardioplegia group received a single antegrade administration of 1,000 mL of the drug at 4 °C in a 1:4 blood dilution (1). If the estimated duration of the ACC was more than 90 minutes, a second dosage of 500 mL was administered retrogradely 60 minutes after the first dose. Both groups experienced mild hypothermia (32–34 °C) throughout the procedure and were given topical cooling treatments.

Compared to Del Nido cardioplegia, which is caused by blood

The patients were divided into two groups in this study based on the cardioplegic solution that was used during surgery. People who had this operation done between August 2019 and November 2021 were a part of the blood cardioplegia study. Patients who had the operation done between 2021 and 2023 made up the del Nido cardioplegia group. The substitution of one cardioplegic technique for another was the determining element. Each data set was carefully compared with the other. Key objectives of this study were to examine patient characteristics before surgery, intraoperative variables, and early postoperative outcomes.

3.8 Data Analysis

A version of SPSS 26.0 was used for data analysis. Mean ± SD was used to represent quantitative factors like age and BMI, whereas frequencies and percentages were used to summarize categorical variables. A p-value less than 0.05 was deemed significant when evaluating the connection between categorical variables using the chi-square test. The correlations between the quantitative variables were assessed using linear

regression analysis. Tables and graphs illustrating the results gave a thorough look at the clinical results of modified Del Nido cardioplegia after heart surgery. The results of this study have important implications for the development of better cardioplegia techniques and the enhancement of patient outcomes in both adult and juvenile populations.

CHAPTER 4

RESULTS

In terms of demographics, there are clear differences between the study's younger patients and its older adult participants. The adult population, which made up 60.8% of the total, had a significantly older average age of 43.19 ± 17.65 years compared to the pediatric population, which had an average age of 6.51 ± 3.49 years (p=0.001). The gender distribution was not significantly different (p=0.06), however both the adult and pediatric patient populations were skewed toward males. Compared to children, adults had a substantially larger mean weight (62.9 ± 15.9 kg) and body surface area (1.63 ± 0.4 m^2), with p-values of 0.001. No statistically significant difference in residency was found (p=0.24), despite the fact that most patients lived in rural areas. A considerably higher number of adults (26.3%) were classified as NYHA Class II/III compared to children (7.9%; p=0.005). When comparing the frequency of Stage 1-2 chronic renal illness, there was no statistically significant difference between the two groups (p=0.11). There was a statistically significant difference (p=0.001) since only adults (18.4%) reported smoking. With a p-value of 0.001, the ejection fraction was considerably lower in adults (53.3 ± 7.6%) compared to children (58.3 ± 8.6%). Extra factors, such as inotropes, prior cardiac surgery, and ventilator support prior to surgery, were uncommon and comparable among groups (p>0.05).

Table 4.1 Baseline Characteristics and Preoperative Clinical Factors of Adults and Pediatric Patients Undergoing Cardiac Surgery with Modified Del Nido Cardioplegia

Demographics/Characteristic	**Adults (N=120)**	**Paediatrics (N=80)**	**P-value**
Age in years (Mean ± SD)	43.19 (17.65)	6.51 (3.49)	0.001
Gender			
Male	82 (41%)	44 (22%)	0.06
Female	38 (19%)	36 (18%)	
Height in cm (Mean ± SD)	163.7 (7.7)	112.8 (14.4)	0.59
Weight in kg (Mean ± SD)	62.9 (15.9)	16.6 (8.3)	0.001

Body Surface Area in m² (Mean ± SD)	1.63 (0.4)	0.67 (0.2)	0.001
Residence			0.24
Urban	58 (29%)	34 (17%)	
Rural	62 (31%)	46 (23%)	
New York Heart Association (NYHA) Classification			0.005
Class I	88 (73.3%)	74 (92.5%)	
Class II and III	32 (26.7%)	06 (7.5%)	
Chronic Kidney Disease			0.11
Stage 1-2	113 (94.2%)	79 (98.8%)	
Stage 3-4	07 (5.8%)	01 (1.2%)	
Ejection Fraction (%) (Mean ± SD)	53.3 (7.6%)	58.3 (8.6%)	0.001
Smoking History			0.001
Yes	15 (18.8%)	0 (0%)	
No	105 (81.2%)	80 (100%)	

Surgical and postoperative variables reveal significant differences between pediatric and adult patients. In comparison to children, adults had significantly longer CPB timings (103.2 ± 44.4 min vs. 73.53 ± 41.1 min, p=0.001), aortic cross-clamp periods (67.5 ± 32.6 min vs. 52.2 ± 32.6 min, p=0.002), and volumes of infused MDN cardioplegia (972.4 ± 427.5 ml vs. 393.7 ± 250.9 ml, p=0.001, respectively). The duration of cardioplegia was significantly longer for adults (62.9 ± 30.1 min vs. 48.5 ± 31.2 min, p=0.001), even though their body temperature was slightly lower during CPB (28.4 ± 1.4°C vs. 28.9 ± 2.1°C, p=0.03). The LVEF at discharge was significantly higher in adolescent patients (62.5 ± 4.7% vs. 55.9 ± 9.1%, p=0.001) when contrasted with adults. The rates of death and complications, such as acute kidney injury (AKI), dialysis, reintubation, stroke, reoperation, surgical site infection, and new-onset atrial fibrillation, were not substantially different between the two groups (p>0.05). A child's postoperative hospital stay was 5.7 ± 1.6 days, while an adult's was 6.2 ± 2.1 days (p=0.08), however the difference was not statistically significant. There was a small but non-significant increase in the incidence of adverse events in adults (6.8% vs.1.3%, p=0.07), including the necessity for intra-aortic balloon pumps.

Table 4.2 Intraoperative and Postoperative Outcomes of Adults and Pediatric Patients Undergoing Cardiac Surgery with Modified Del Nido Cardioplegia

Variable	Adults (N=120)	Paediatrics (N=80)	P-value
Intraoperative Variables			
CPB Time in min (Mean ± SD)	103.2 (44.4)	73.53 (41.1)	0.001
Aortic Cross-Clamp Time in min (Mean ± SD)	67.5 (32.6)	52.2 (32.6)	0.002
Infused MDN Cardioplegia Volume in ml (Mean ± SD)	972.4 (427.5)	393.7 (250.9)	0.001
MDN Cardioplegia Time in min (Mean ± SD)	62.9 (30.1)	48.5 (31.2)	0.001
Body Temperature in °C (Mean ± SD)	28.4 (1.4)	28.9 (2.1)	0.03
Minimum Hematocrit during CPB in % (Mean ± SD)	26.1 (1.9)	26.5 (2.0)	0.17
Postoperative Outcomes			

Postoperative Hospital Stay in days (Mean ± SD)	6.2 (2.1)	5.7 (1.6)	0.08
LVEF at Discharge in % (Mean ± SD)	55.9 (9.1)	62.5 (4.7)	0.001
Death			0.25
Yes	2 (1.7%)	0 (0%)	
No	118 (98.3%)	80 (100%)	
IABP			0.07
Yes	8 (6.8%)	1 (1.3%)	
No	112 (93.2%)	79 (98.7%)	
AKI			0.14
Yes	9 (7.6%)	2 (2.6%)	
No	111 (92.4%)	78 (97.4%)	
Dialysis			0.55
Yes	3 (2.5%)	1 (1.3%)	
No	117 (97.5%)	79 (98.7%)	
Reintubation			0.16
Yes	3 (2.5%)	0 (0%)	
No	117 (97.5%)	80 (100%)	
Stroke after Bypass			0.25
Yes	2 (1.7%)	0 (0%)	
No	118 (98.3%)	80 (100%)	
Reoperation			0.16
Yes	3 (2.5%)	0 (0%)	
No	117 (97.5%)	80 (100%)	
Surgical Site Infection			0.16
Yes	3 (2.5%)	0 (0%)	

No	117 (97.5%)	80 (100%)	
New Onset of Atrial Fibrillation			0.55
Yes	3 (2.5%)	1 (1.3%)	
No	117 (97.5%)	79 (98.7%)	

The pie chart displays the distribution of cardiac surgery surgeries. After VSD Repair (27% of all procedures), AVSD Repair (40% of all surgeries) is the most common type of surgery. Restoring televisions (16% of instances) and coronary artery bypass grafting (12%) are two more notable treatments. Very little (1-3%) of the total corrected errors go toward the following procedures: MVR, AVR, DVR, VSD+PDA, and TOF. Septal defect repairs (VSD and AVSD) make up the majority of cardiac surgeries, accounting for 67% of all procedures in the dataset, according to this distribution. In Figure 1,

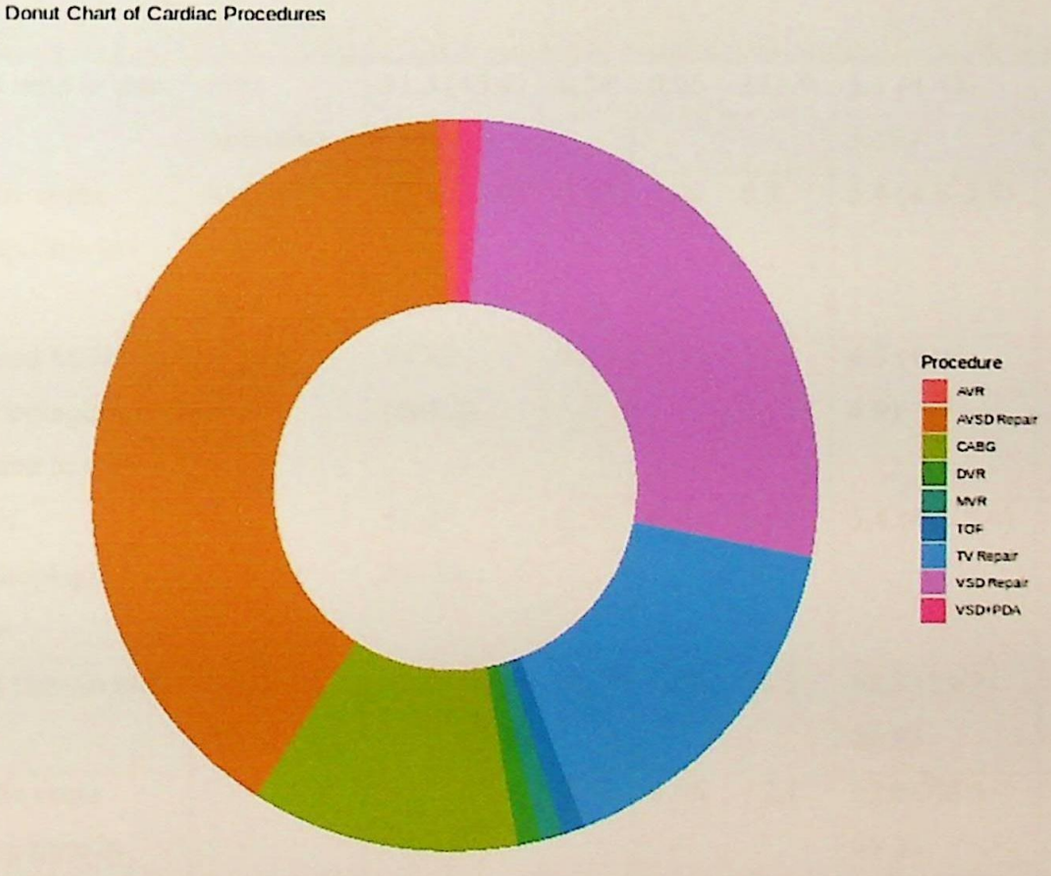

Figure 4.1 Distribution of surgical procedures among patients

Both the length of time a patient spends in the hospital after surgery and their LVEF (left ventricular ejection fraction) at discharge are significantly correlated with intraoperative factors, according to the study. There is a positive correlation between postoperative hospital stay and cardioplegia time, infused MDN cardioplegia volume, aortic cross-clamp time, and CPB time; the largest effects of these variables are CPB time (R=0.24, p=0.001) and infused MDN cardioplegia volume (R=0.48, p=0.001). In a similar vein, there is a strong association between injected MDN cardioplegia volume and LVEF at discharge (R=0.48, p=0.001). The clinical importance of these factors is indicated by the fact that they explain up to 23% of the variance (R^2=0.23), as shown by the regression models. The findings are confirmed to be robust because all connections have significant p-values ($p \leq 0.01$).

Table 4.3 Correlation and Regression Analysis with Post operative hospital stay and Score as LVEF at Discharge

Independent Variable (Intraoperative Variables)	Dependent Variable	Mean (±SD)	R	R^2	F	B (95% CI)	*p*-value
CPB time in min	Post operative hospital stay in days	91.5 (45.4)	0.24	0.05	111.9	5.1 (4.48-5.56)	0.001
Aortic cross clamp time in min		61.5 (33.4)	0.18	0.03	6.4	5.4 (4.8-5.9)	0.01
Infused MDN cardioplegia volume in ml		745.7 (464.2)	0.48	0.23	59.9	4.5 (4.06-4.9)	0.001
MDN Cardioplegia Time		57.24 (31.2)	0.17	0.03	5.59	5.4 (4.8-5.9)	0.01
CPB time in min	LVEF at Discharge	91.5 (45.4)	0.23	0.05	10.5	62.3 (59.7-64.9)	0.001
Aortic cross clamp time in min		61.5 (33.4)	0.28	0.08	17.1	62.9 (60.5-65.3)	0.001

Infused MDN cardioplegia volume in ml		745.7 (464.2)	0.48	0.23	58.1	64.9 (63.1-66.9)	0.001
MDN Cardioplegia Time		57.24 (31.2)	0.26	0.07	14.2	62.5 (60.1-64.9)	0.001

CPB: Cardiopulmonary bypass, MDN: Modified Del Nido Cardioplegia

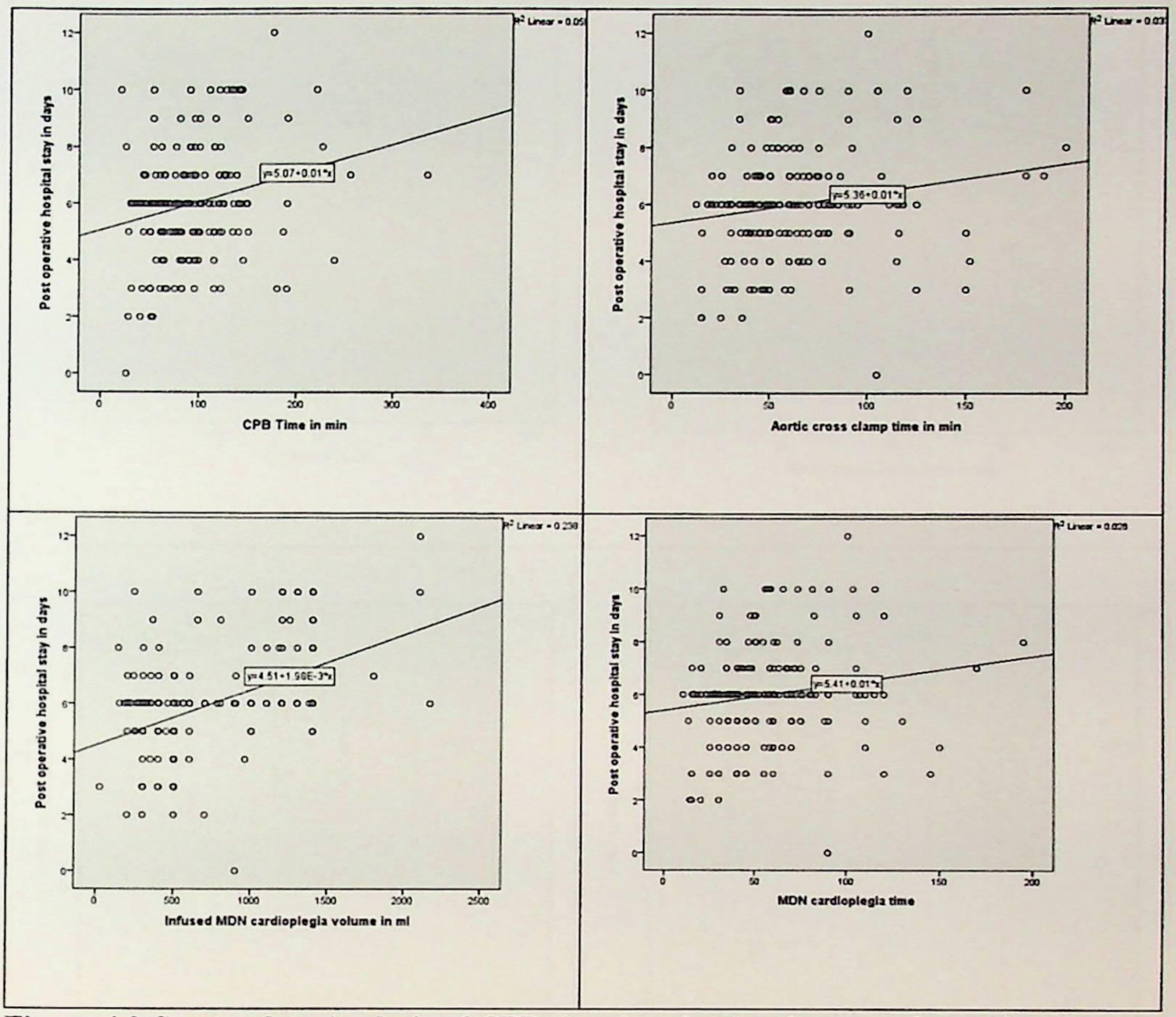

Figure 4.2 Scatterplots Analysis of CPB time in min, Aortic cross clamp time in min, Infused MDN cardioplegia volume in ml and MDN Cardioplegia Time with Post operative hospital stay in days

are positively correlated with one another, suggesting that CPB Time (Min) and Post Operative Hospital stays (days) are statistically significant (p-value 0.001 and Pearson correlation coefficient 0.242, respectively). It appears that longer durations of CPB time are associated with longer durations of postoperative hospital admissions. Aortic cross clamp time in minutes is positively correlated with postoperative hospital stays in days (p=0.012) according to the Pearson correlation coefficient (r=0.181). This suggests that the length of time spent in the hospital following surgery is directly proportional to the duration of the aortic cross clamp. Statistical analysis failed to reveal a relationship between the volume of infused MDN cardioplegia (in milliliters) and the number of days spent in the hospital following surgery (Figure) 4.2).

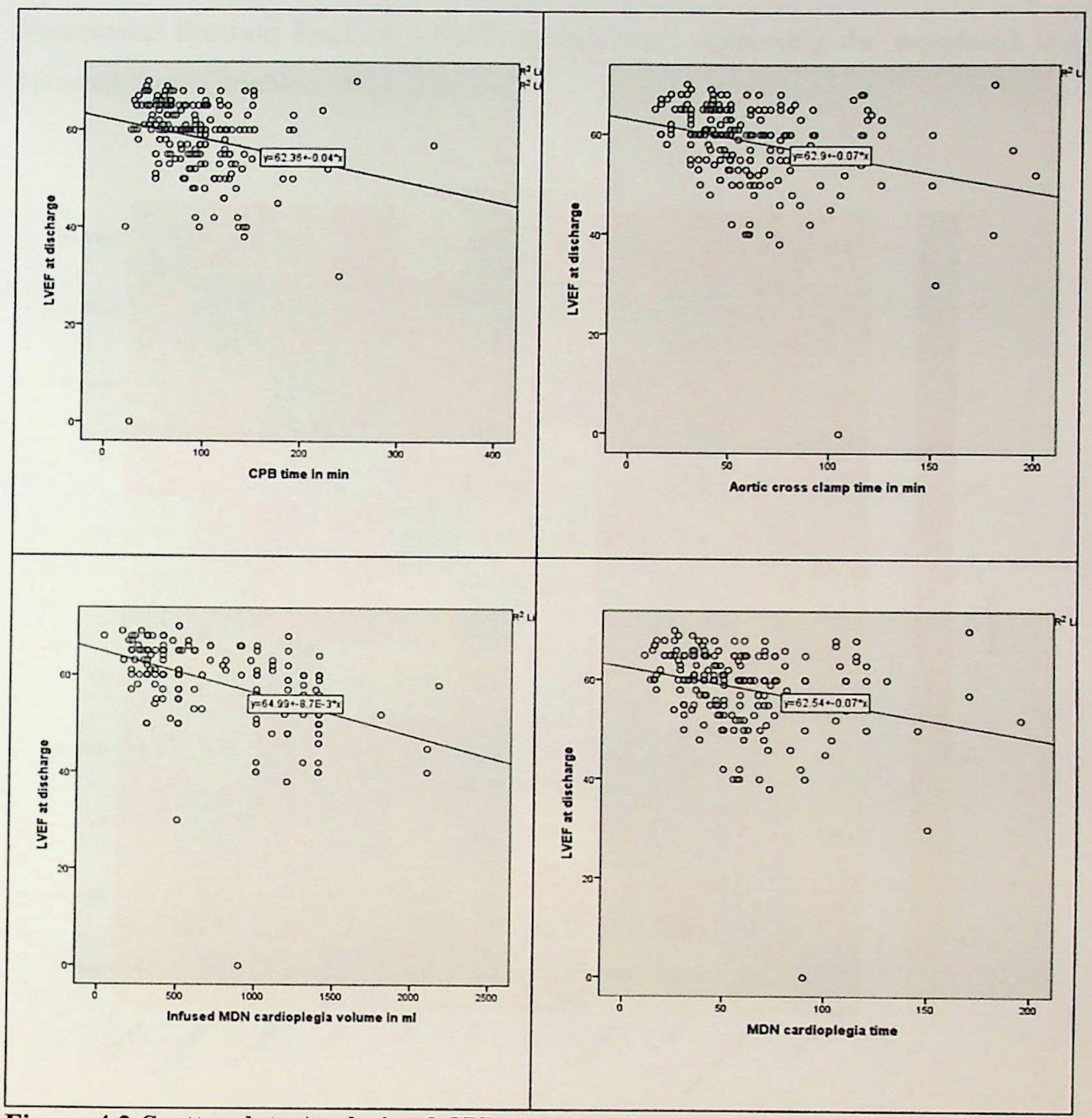

Figure 4.3 Scatterplots Analysis of CPB time in min, Aortic cross clamp time in min, Infused MDN cardioplegia volume in ml and MDN Cardioplegia Time with LVEF at Discharge

Using CPB Time (Min) as the predictor variable, the regression analysis shows a statistically significant model ($F(1, 192) = 10.559$, $p = 0.001$). This model accounts for 5.2% of the variance in LVEF at discharge ($R^2 = 0.052$, Adjusted $R^2 = 0.047$). At discharge, LVEF decreases by an average of 0.042 units with every minute increase in CPB Time, according to the standardized regression coefficient (Beta) of -0.228 and the unstandardized coefficient of -0.042 (95% CI: -0.068 to -0.017, $p = 0.001$). Reducing CPB time may improve post-operative cardiac function, as this inverse correlation shows that longer CPB durations are associated with lower Left

Ventricular Ejection Fraction (LVEF) at discharge, supporting the suggested link between these variables. (**Figure 4**)

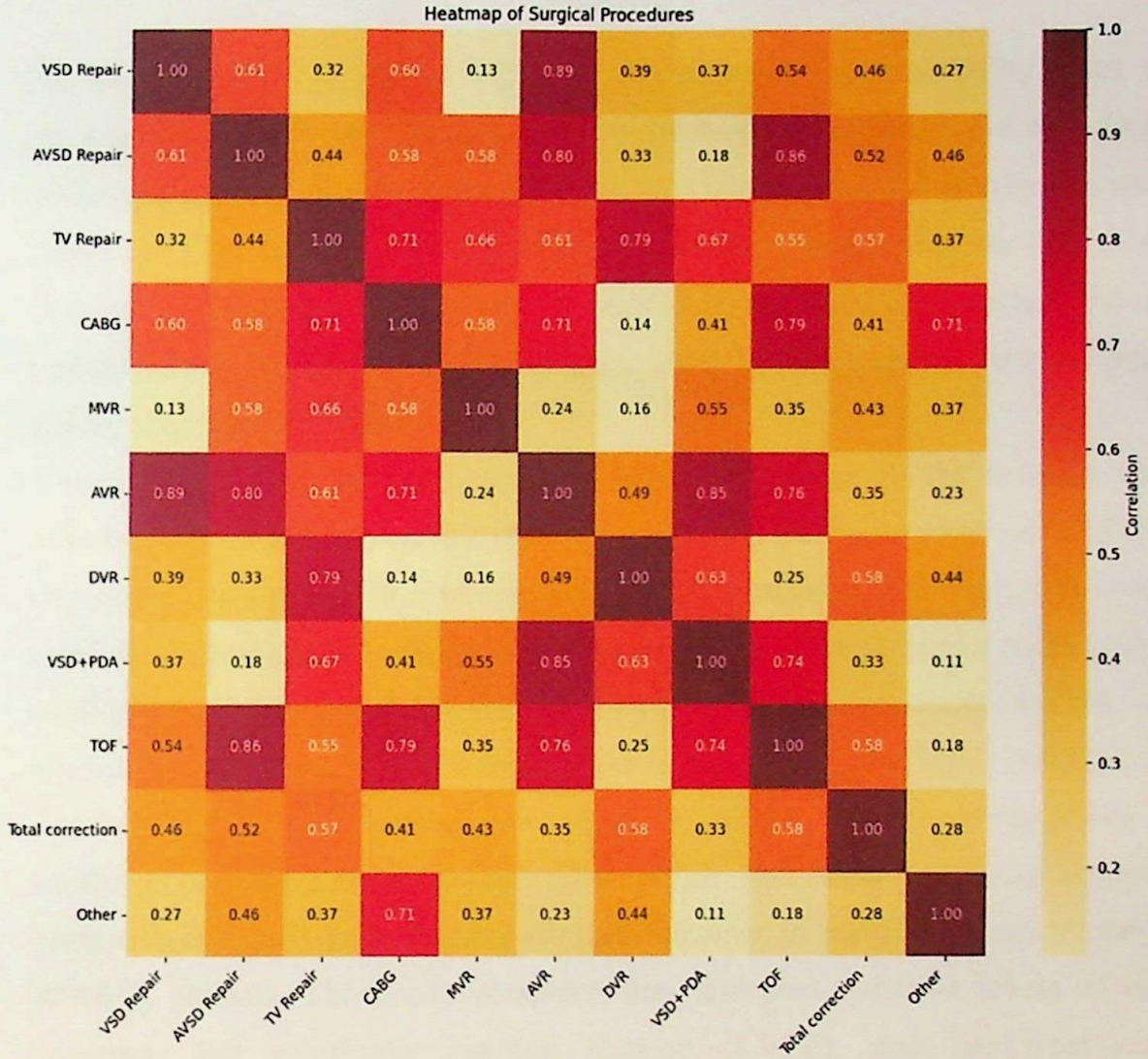

Figure 4.4 A correlation heatmap showing the relationships between all surgical procedures. The darker the color, the stronger the correlation between procedures. The diagonal is always 1.0 as it represents the correlation of a procedure with itself.

CHAPTER 5

DISCUSSION

Our findings showed that at 30 days, the mortality and morbidity rates were comparable between the two groups. The duration of hospital stays and invasive cardiac procedures, as well as the prevalence of new-onset atrial fibrillation, did not change in a statistically meaningful way. Consistent with earlier studies, this one examined the impact of del Nido cardioplegia vs blood cardioplegia on early postoperative outcomes, ICU and hospital stays, and propensity-matched patients undergoing isolated CABG(14, 15).

Protecting the myocardium from early ischemia damage in the anterior cardiac chamber (ACC) and myocardial reperfusion injury after clamp removal is of utmost importance during cardiopulmonary bypass (CPB) surgeries. Therefore, it is crucial to carefully formulate and choose blood cardioplegia since it is the most prevalent cardioplegic choice worldwide. Del Nido cardioplegia has been used for adult cardiac procedures as well as those involving children because to its efficacy and safety. The optimal cardioplegia treatment for adults is still up for debate (16). Del Nido cardioplegia with standard blood cardioplegia was used to assess myocardial protection and early postoperative clinical outcomes in coronary artery bypass graft (CABG) patients. This study compared pre- and post-operative levels of cardiac enzymes, left ventricular ejection fraction (LVEF), and the frequency of cardiopulmonary bypass resynchronization (CPBR) weaning defibrillation (17).

Researchers observed that magnesium plus lidocaine cardioplegia, also known as del Nido cardioplegia, prevented reperfusion damage and hypercontraction caused by calcium in rats. Lidocaine safeguards the heart by boosting cell survival, lowering inflammation, promoting oxygen transport, decreasing intracellular calcium binding, and upregulating anti-apoptotic genes. A thorough functional and biochemical study suggests that Del Nido cardioplegia may offer better protection for the heart(18, 19). Although there were no differences in LVEF changes between the del Nido and control groups after surgery, the former demonstrated superior troponin I variations (2.8[-0.4; 4.2] vs. 4.5[2.9; 7.4] ng/mL, $p = 0.004$). those with Del Nido cardioplegia showed superior cardiac protection upon reperfusion compared to those with blood cardioplegia, and they required defibrillation less frequently after CPB weaning. If

myocardial protection is insufficient, defibrillation may be necessary to wean off cardiopulmonary bypass (20, 21). Compared to blood cardioplegia, del Nido cardioplegia is superior for CABG surgeries, according to our findings.

The del Nido cardioplegia group saw a marked decrease in the amount of time spent administering the cardioplegic solution both anterogradely and retrogradely. The surgery takes longer because to the longer intervals that are required during coronary anastomosis due to higher cardioplegia. Using lower maintenance dosages in Del Nido cardioplegia reduces surgical interruptions. Because patients with Del Nido cardioplegia needed fewer defibrillations, surgical procedures may have been interrupted less frequently. The ACC time was cut by 13.5 minutes and the surgical time by 28 minutes due to the decrease in interruptions. Del Nido cardioplegia may hold the key to improved surgery at a reduced cost to patients, especially considering the increasing expense of healthcare and the lengthening operating hours (22, 23).

When treating multivessel coronary artery disease, conventional wisdom dictates the use of antegrade and retrograde cardioplegic administration. However, postoperative outcomes were identical when antegrade infusion was used alone to treat cardioplegia as when it was used to cause cardiac arrest and sustain it with retrograde infusion, in line with earlier research. Unfortunately, previous studies that looked at how cardioplegic delivery procedures correlated with postoperative outcomes came to contradictory conclusions (24, 25). One study found that after CABG, patients with three-vessel disease had a better left ventricular stroke work index when administered retrogradely rather than antegradely. Research on early clinical outcomes in individuals with three-vessel disease found that a combination of antegrade and retrograde cardioplegia had a higher protective effect on the myocardium than antegrade-only delivery. Blood and St. Thomas' Hospital solutions (51,52) were used in the experiments instead of the lidocaine-inclusive del Nido solution (26), which possesses cardiac protective qualities.

The responsibility for safeguarding the myocardium after CABG does not lie with the delivery method, but with the cardioplegic treatment for multivessel disease. This dispute may be resolved based on the outcomes of the Del Nido cardioplegia experiments. For individuals undergoing high-risk operations, further research has validated the findings. In the initial few days after surgery, del Nido and blood cardioplegia had similar rates of mortality and morbidity in all subgroups. Troponin I

levels were decreased in patients with del Nido cardioplegia, especially those with left main disease. Following surgery, this subgroup of del Nido experienced a substantial improvement in LVEF (27–29). Patients with Del Nido cardioplegia who were 70 years old or older required less defibrillation than those with blood cardioplegia (53-55). As stated in the Methods, our stringent conventional CABG selection criteria for patients with ischemic heart disease led to the study's retrospective design and low participant count. For the first time, this single-surgeon study investigates del Nido cardioplegia in conventional CABG, reducing variability and bias. Using large-scale prospective investigations in future study will be necessary for a fuller and more generalized knowledge. The subgroup study's small sample size raises doubts about the relative efficacy of del Nido cardioplegia in high-risk patients.

CHAPTER 6

CONCLUSION

In conclusion, this study highlights significant differences in demographic, intraoperative, and postoperative variables between adult and pediatric patients undergoing cardiac surgery. Adults experienced longer CPB and aortic cross-clamp times, as well as higher cardioplegia volumes, which were identified as key predictors of postoperative LVEF. Despite these differences, pediatric patients demonstrated better postoperative cardiac function, as reflected by higher LVEF at discharge. These findings emphasize the importance of meticulous intraoperative management, particularly minimizing CPB and cross-clamp times, to optimize cardiac outcomes and improve recovery in both adult and pediatric patients.

Recommendation

Both adult and paediatric cardiac surgery patients have the potential to benefit from modified Del Nido cardioplegia, according to the study. The results support the use of modified Del Nido cardioplegia as a standard cardioprotective measure in cardiac procedures involving a wide range of patient populations. To further establish its efficacy, future study should focus on long-term outcomes, such as myocardial healing and survival rates. Further research into this technique's usefulness in particular high-risk populations and its potential expansion into less invasive cardiac operations could yield useful information for enhancing surgical methods.

Limitation

It is important to note that this study has a few limitations. Because it is a cross-sectional study, we can't draw any firm conclusions about whether or not the clinical outcomes were caused by the use of modified Del Nido cardioplegia. Additionally, the outcomes might have been affected by variations in surgical procedures and perioperative care among the participating centres. The results may not be applied to a broader population due to the limited sample size in some subgroups, such as paediatric patients. Finally, there is a dearth of long-term follow-up data, which limits our ability to comprehend the study's long-term advantages because the primary focus was on short-term results. To overcome these constraints, future prospective research must include bigger and more varied populations and adhere to standardised techniques.

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APPENDICES

APPENDIX 1

CONSENT FORM

Study Title:
Clinical Outcomes of Modified Del Nido Cardioplegia in Adult and Pediatric Cardiac Surgery: A Multicentered Cross-Sectional Study

Introduction:
You are being invited to participate in a research study. Before deciding, it is crucial to understand the purpose, procedures, potential risks, and benefits involved. This form provides detailed information to help you make an informed decision.

Purpose of the Study:
The purpose of this study is to assess the clinical outcomes of modified Del Nido cardioplegia in patients undergoing cardiac surgery, including both adults and pediatric patients, across multiple centers.

Procedures:
If you agree to participate:

- Information regarding your cardiac surgery and post-operative recovery will be collected and analyzed.
- Data collection will include your medical history, intra-operative findings, and outcomes after surgery.
- Your routine medical care will not be altered by participation in this study.

Duration:
Data will be collected during your hospital stay, including the surgery and post-operative period.

Potential Risks:
There are no additional risks associated with participating in this study beyond those inherent to your cardiac surgery.

Benefits:

- Your participation will contribute to improving the understanding and efficacy of modified Del Nido cardioplegia in cardiac surgery.
- While you may not experience direct benefits, the findings could enhance care for future patients undergoing similar procedures.

Voluntary Participation:
Your participation is completely voluntary. You have the right to decline or withdraw from the study at any time without affecting the quality of care you receive.

Confidentiality:
All information gathered during the study will remain confidential and will only be used for research purposes. Your identity will not be disclosed in any publication or presentation of the study results.

Compensation:
There will be no financial compensation for your participation in this study.

Consent Statement:

I have read and understood the information provided above, and all my questions have been answered. I voluntarily agree to participate in this study.

Participant's Name: _____
Signature: _____
Date: _____

Investigator's Name: _____
Signature: _____
Date: _____

Appendix-2
Informed Consent in Urdu Format

رضامندی فارم

:مطالعے کا عنوان

بالغوں اور بچوں کے کارڈیک سرجری میں ترمیم شدہ ڈیل نیڈو کارڈیوپلیجیا کے کلینیکل نتائج: ایک کثیر المرکزی کراس سیکشنل مطالعہ

:تعارف

آپ کو اس تحقیقی مطالعے میں شرکت کی دعوت دی جا رہی ہے۔ فیصلہ کرنے سے پہلے، مطالعے کے مقصد، طریقہ کار، ممکنہ خطرات، اور فوائد کو سمجھنا ضروری ہے۔ یہ فارم آپ کو ایک باخبر فیصلہ کرنے میں مدد کے لیے تفصیلی معلومات فراہم کرتا ہے۔

:مطالعے کا مقصد

اس مطالعے کا مقصد یہ جانچنا ہے کہ ترمیم شدہ ڈیل نیڈو کارڈیوپلیجیا کا کارڈیک سرجری سے گزرنے والے مریضوں، بشمول بالغ اور بچوں، پر کیا کلینیکل نتائج مرتب ہوتے ہیں، اور یہ مطالعہ مختلف مراکز میں کیا جا رہا ہے۔

:طریقہ کار

:اگر آپ شرکت پر رضامند ہیں

- آپ کی کارڈیک سرجری اور بعد از آپریشن بحالی سے متعلق معلومات جمع کی جائیں گی اور ان کا تجزیہ کیا جائے گا۔
- ڈیٹا میں آپ کی طبی تاریخ، آپریشن کے دوران کے مشاہدات، اور سرجری کے بعد کے نتائج شامل ہوں گے۔
- اس مطالعے میں شرکت سے آپ کے معمول کے طبی علاج پر کوئی اثر نہیں پڑے گا۔

:دورانیہ

ڈیٹا آپ کے ہسپتال میں قیام کے دوران، جس میں سرجری اور بعد از آپریشن کا وقت شامل ہے، جمع کیا جائے گا۔

:ممکنہ خطرات

اس مطالعے میں شرکت سے آپ کو کسی اضافی خطرے کا سامنا نہیں ہوگا، سوائے ان خطرات کے جو آپ کی کارڈیک سرجری سے وابستہ ہیں۔

:فوائد

- آپ کی شرکت سے ترمیم شدہ ڈیل نیڈو کارڈیوپلیجیا کی کارڈیک سرجری میں افادیت اور تفہیم کو بہتر بنانے میں مدد ملے گی۔
- اگرچہ آپ کو براہ راست فوائد حاصل نہیں ہو سکتے، لیکن اس مطالعے کے نتائج مستقبل میں اسی قسم کی سرجری سے گزرنے والے مریضوں کی دیکھ بھال کو بہتر بنا سکتے ہیں۔

:رضاکارانہ شرکت

آپ کی شرکت مکمل طور پر رضاکارانہ ہے۔ آپ کو حق حاصل ہے کہ آپ اس مطالعے میں شرکت سے انکار کر دیں یا کسی بھی وقت اپنی رضامندی واپس لے لیں، اور یہ فیصلہ آپ کو ملنے والے علاج کے معیار پر اثر انداز نہیں ہوگا۔

:رازداری

مطالعے کے دوران جمع کی گئی تمام معلومات کو خفیہ رکھا جائے گا اور صرف تحقیقی مقاصد کے لیے

استعمال کیا جائے گا۔ آپ کی شناخت مطالعے کے نتائج کی اشاعت یا پیشکش میں ظاہر نہیں کی جائے گی۔

:معاوضہ
اس مطالعے میں شرکت کے لیے آپ کو مالی معاوضہ نہیں دیا جائے گا۔

:رضامندی کا بیان
میں نے اوپر فراہم کردہ معلومات کو پڑھا اور سمجھ لیا ہے، اور میرے تمام سوالات کے جوابات دے دیے گئے ہیں۔ میں اس مطالعے میں رضاکارانہ طور پر شرکت کے لیے رضامند ہوں۔

_____ :شرکت کرنے والے کا نام
_____ :دستخط
_____ :تاریخ

_____ :تحقیق کار کا نام
_____ :دستخط
_____ :تاریخ

APPENDIX-3

Ethical Approval

SUPERIOR UNIVERSITY

OFFICE OF THE DEAN-FAHS

Ref.: IRB /FAHS/Allied-HS/10/24/MS/RS-3516

Date: 29th October 2024

Name: Naseeb-ur-Rahman (MS Allied Health Sciences)

Registration: SU91-MSAHW-S23-181

Subject: Ethical Approval Letter

The Research Ethical Committee convened on Dated: **17th October, 2024** to discuss your protocol titled **"Clinical outcomes of modified del nido cardioplegia in adult and pediatric cardiac surgery;A multicentered cross sectional study"**

No further corrections and recommendations were suggested. The above-mentioned protocol has been approved after considering various research issues including ethical concerns with condition that the researcher will submit completion report at the end of his/her research.

Prof. Dr. Muhammad Naveed Babur
Dean/Convener REC
Faculty of Allied Health Sciences
Superior University, Lahore

APPENDIX-4
QUESTIONNAIRE
Questionnaire

Baseline characteristics

Age_____years
Gender
- o Male
- o Female

Height
Weight
BMI
Type of Surgery _____
Residence
- o Urban
- o Rural

NYHA Classification
- o Class I
- o Class II
- o Class III
- o Class IV

Comorbidities
- o AF
- o Diabetes
- o Hypertension
- o Diabetes mellitus
- o Stroke
- o CAD
- o PCI history
- o COPD
- o Active IE
- o PAD

CKD
- o stage 1–2
- o stage 3–4
- o stage 5

Previous cardiac surgery
- o Yes
- o No

Preoperative ventilator
- o Yes
- o No

Preoperative inotropes
- o Yes
- o No

EF_____%
Smoking History
- o Yes

- o No

Perioperative characteristics

CPB time (min)	
Aortic cross clamp time (min)	
Infused cardioplegia volume (ml)	
Cardioplegia infusion times	
1	
2	
3	
≥4	
Nadir bladder temperature (°C)	
Nadir hematocrit during CPB (%)	
Nadir DO_2i during CPB	
Concomitant cardiac surgeries	
Mitral valve repair	
Mitral valve replacement	
Aortic valve replacement	
Tricuspid valve repair	
CABG	
Maze procedure	
VATS surgeries	
Postoperative hospital stay (days)	
ICU stay (hours)	
Ventilation duration (hours)	
Inotrope index	
0 h post-op.	
24 h post-op.	
48 h post-op.	
LVEF at discharge (%)	

Post-operative outcomes

Primary Endpoint/outcomes	
Death	o Yes o No
IABP	o Yes o No
ECMO	o Yes o No
Secondary Endpoint/Outcomes	
Infusion	o Yes o No
AKI	o Yes o No
Dialysis	o Yes o No
New Onset of AF	o Yes o No
Reintubation	o Yes o No
Stroke	o Yes

	o No
Reoperation	o Yes o No
Surgical Site Infection	o Yes o No

February 19, 2025

PLAGIARISM CERTIFICATE

For MPhil and PhD

This is certified that the thesis entitled:**Clinical Outcomes Of Modified Del Nido Cardioplegia In Adult And Pediatric Cardiac Surgery; A Multicentered Cross Sectional Study.**

Student Name:Naseeb Ur Rehman

Reg /Roll No:SU91-MSAHW-S23-181

Submitted on date:18.02.2025

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