Clinical Impact of del Nido versus Custodiol HTK Cardioplegia Solutions in the Postoperative Period in Pediatric Cardiac Surgery Patients

by

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Abstract

Del Nido and Custodiol Histidine-Tryptophan-Ketogluterate (HTK) are common solutions employed during pediatric heart surgery. They differ in their mechanism of cardiac arrest; del Nido causes a depolarizing arrest and HTK a hyperpolarizing arrest. While both of these solutions have been evaluated for their impact on patient outcomes independently, limited research exists comparing them directly. This study retrospectively compared patient outcomes between two groups of patients based on which cardioplegia solution was used. Patients were grouped by del Nido (n=30) or Custodiol HTK (n = 30) and stratified by STAT score. T-tests using MiniTab 18 statistical software were performed between del Nido and Custodiol Groups for each parameter at each STAT level. Compared variables included duration of mechanical ventilation, total length of hospital stay, and change in systemic ventricle ejection fraction. No statistical difference was observed between clinical outcomes on the parameters measured between the cardioplegia solutions used at any STAT level. Multiple studies have compared Custodiol and del Nido to conventional cold blood cardioplegia, but few compare them directly. Previous studies have found no significant difference between del Nido and Custodiol when studies compared to cold blood cardioplegia. It stands to reason when compared directly, no significant difference would be found between del Nido and Custodiol. The results of this study are consistent with previous findings. Both solutions are viable choices for myocardial protection in pediatric heart surgery.

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1. Introduction

Myocardial protection is of paramount importance during cardiac surgery involving cardiopulmonary bypass (CPB) and aortic cross-clamping, especially in cases of extended myocardial ischemia. Various approaches to myocardial protection have been developed over the history of cardiac surgery, but two common components are hypothermia and the manipulation of electrochemical gradients with a cardioplegic solution. Altering the electrochemical gradients results in the cardiac arrest necessary to produce a motionless surgical field as well as to reduce the energy utilization of cardiac myocytes. Even during arrest, myocytes must maintain proper metabolic processes, leading to the potential for ischemic damage to occur.

The goals of all cardioplegia solutions are to arrest the heart and mitigate ischemic damage, but currently there is no universal agreement on the superiority of one solution for all patient groups, which has led to the development of many different solutions and techniques. These solutions can be broadly categorized as either depolarizing or hyperpolarizing, depending on how each affects the membrane potentials of myocardial cells. Depolarizing agents tend to be used more frequently and achieve cardiac arrest via hyperkalemia. Hyperpolarizing agents are hyponatremic and hypocalcemic and induce cardiac arrest by depleting extracellular concentrations of sodium and calcium. Additives to solutions vary based on surgical team preference. Del Nido and Custodiol HTK (Histidine-Tryptophan-Ketoglutarate) are two commonly used cardioplegia solutions.

Del Nido cardioplegia is a modified depolarizing solution which was developed in for use in pediatric patients in the early 1990s, but has seen use in the adult population as

well [1]. Custodial HTK is a hyperpolarizing agent which is also used for organ preservation during transplant procedures [2]. While each of these solutions have been studied on their own, limited research is available when comparing the two directly. This study retrospectively compared the postoperative effects of del Nido and Custodiol HTK on systemic ventricle ejection fraction, length of ICU stays, and duration of mechanical ventilation in 60 patients to directly compare outcomes of these two solutions.

2. Background

2.1 The Need for Myocardial Protection During Heart Surgery

The only way to adequately perform most cardiac surgeries is to stop the mechanical activity of the heart. To accomplish this, cardioplegic solutions are delivered through the coronary vasculature to arrest the contractile cells and put the heart in a motionless state. Because cardioplegia is delivered intermittently during procedures, the myocardium is in an ischemic state for most of the aortic cross-clamp time. Without any protective intervention, ischemic myocardial cells will die quickly, negating any benefit provided by the surgery. A combination of hypothermia and cardioplegia solutions lessen the impact of ischemia and provide adequate myocardial protection in most patients. However, some patients still experience complications from ischemic damage, necessitating the need to continually reevaluate solutions and techniques.

2.2 Mechanisms Mediating Ischemic Myocardial Damage

Development of cardioplegia solutions is based on an understanding of how ischemia disrupts normal cellular processes and initiates damage-causing pathways. Fundamentally, proper heart function and aerobic metabolism depend upon maintaince of proper intracellular pH, high-energy phosphate stores (ATP), and cell membrane/ionic homeostasis [3]. Irreversible cardiac damage can occur if any of these components vary too much from physiologic levels. Cell injury is generally reversible if perfusion is reestablished within the first 5 to 20 minutes of ischemia [4], with tissue swelling and cell necrosis occuring after 20 minutes without intervention [4]. The progression from ischemia to cell necrosis is illustrated in Figure 1.

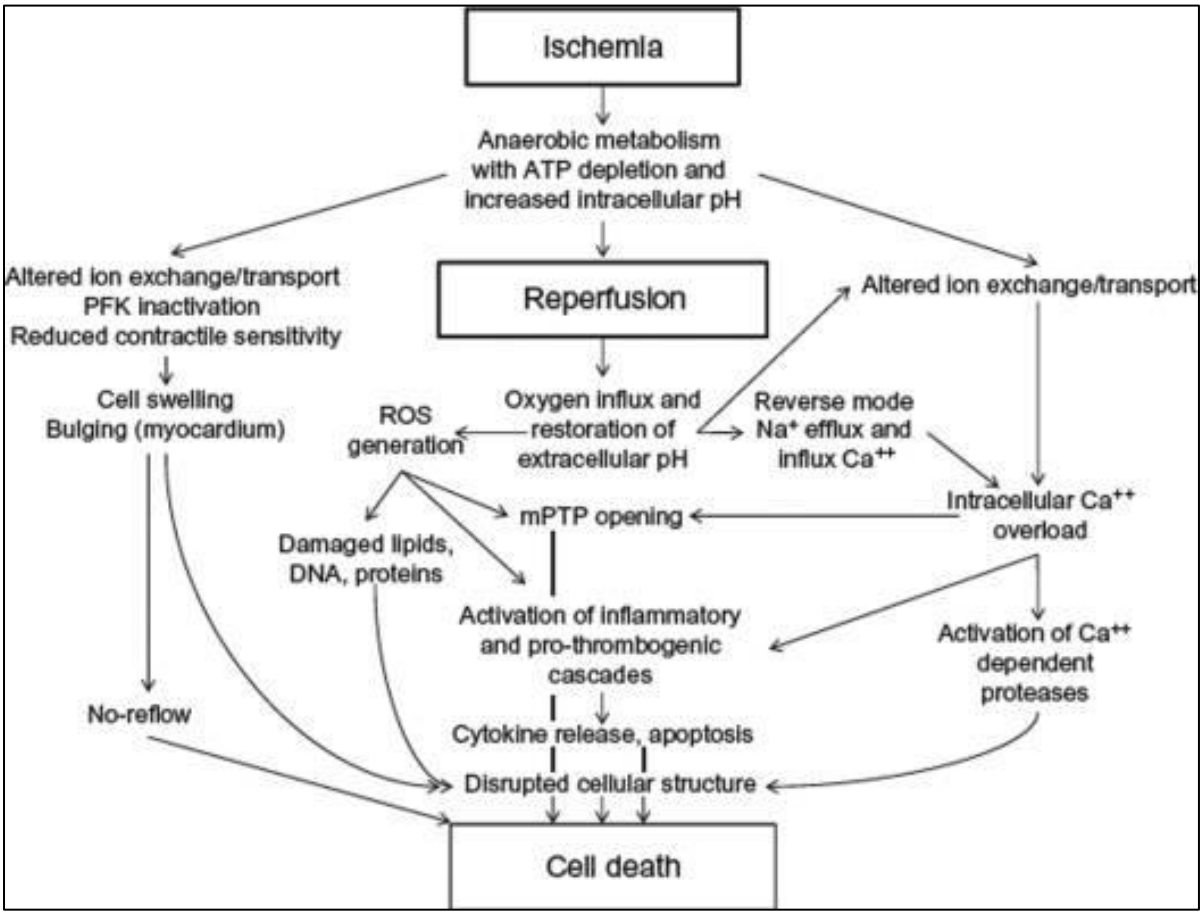

Figure 1: Progression of Cell Injury from the Onset of Ischemia to Cell Death and an Overview of Reperfusion Injury [4]. ROS = Reactive Oxygen Species, PFK = Phosphofructokinase.

It is clear the severity of injury induced by ischemia increases dramatically with time [5]. The key to preventing irreversible injury or cell death is to reestablish blood flow to the ischemic tissue when the cells are still in a state of reversible injury. Slowing down cellular metabolism through the use of hypothermia and chemical agents keeps cells in the reversible state of ischemic injury longer, which allows full function to return once blood flow has been reestablished [5]. Reducing cellular metabolism slows ATP usage and pH changes, both of which cause cellular injury when altered.

Myocardial acidosis has been shown by Khuri *et al*. to correlate with regional myocardial ischemia and to serve as a predictor of long-term patient survivability (Figure 2) [6]. This study examined 535 patients undergoing coronary artery bypass grafting or valve repair/replacements between 1982 and 1997. To collect data, the researchers inserted two pH sensitive glass electrodes into the anterior and posterior walls of the left ventricle [6]. Three pH values, corrected to 37° C, were recorded for each patient: right before cross-clamp, integrated mean during cross-clamp, and the last value before probes were removed, typically within minutes after CPB was terminated. Electrodes generated readings every 20 seconds and the lower pH value from either anterior or posterior wall was recorded and used to determine the magnitude of ischemia. Three pH_{37C} values were identified as thresholds affecting long term survivability: <6.63 before cross-clamp, mean <6.35 during cross-clamp, and <6.73 at CPB termination. Acidosis during the cross-clamp period was found to independently correlate with adverse long- and short-term clinical outcomes. Figure 2 emphasizes this point by showing patients who had their pH_{37C} raised from below threshold before cross-clamp to above threshold during cross-clamp had nearly double the survival rates of patients with pH_{37C} below threshold before and during cross-clamp. Based on these data, and others, cardioplegia solutions are formulated with an emphasis on pH buffering, although they do not all buffer, nor do they arrest the heart, in the same manner.

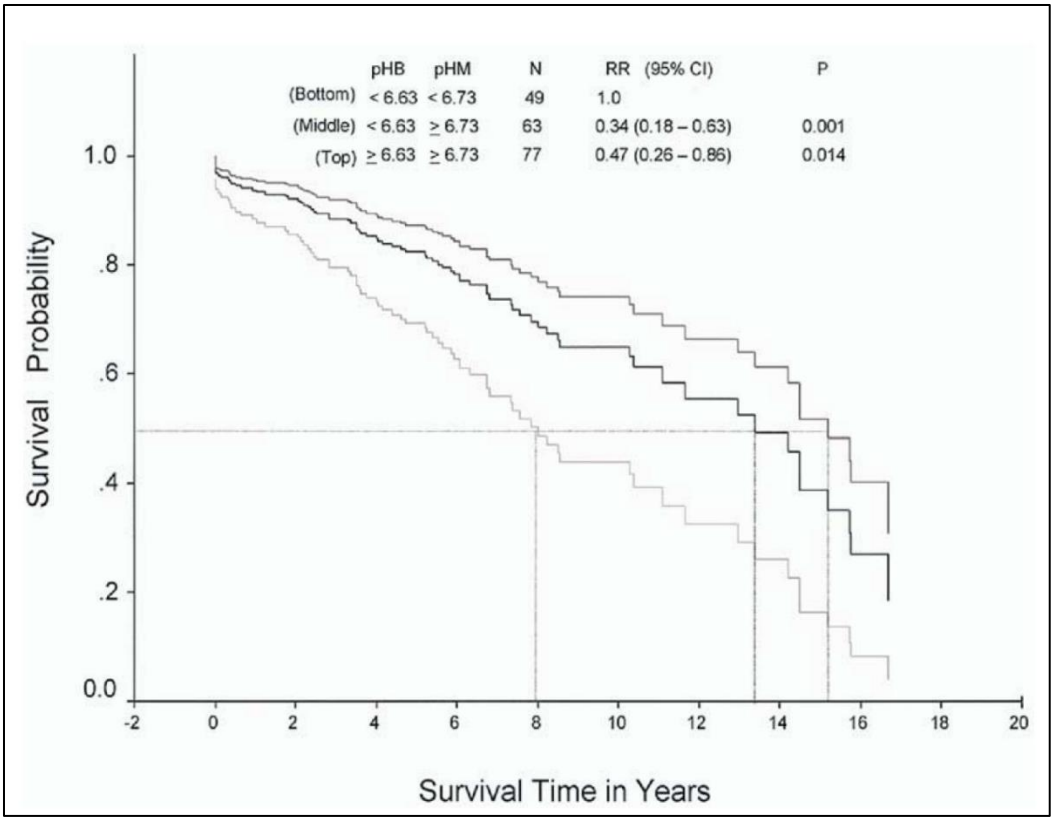

Figure 2: Risk-Adjusted Survival Curves of Three Groups of Patients with Differing Operative Myocardial pH Values [6]. Top tracing shows patients with pH_{37C} before and during cross-clamp above threshold values. Bottom tracing shows patients with pH_{37C} before and during cross-clamp below threshold values. Middle tracing shows patients with pH_{37C} before cross-clamp below threshold and pH_{37C} above threshold. pHB = pH_{37C} before cross clamp. pHM = pH_{37C} integrated mean pH during cross-clamp.

The exact mechanism of reperfusion injury is still debated, but the prevailing theory is that post-ischemic intracellular calcium concentrations are increased secondary to increased intracellular sodium, which accumulates during periods of ischemia [1]. The increased intracellular sodium forces the sodium-calcium exchanger to act in reverse, pumping sodium out of the cell while calcium is pumped intracellularly [1]. An additional pathway for calcium entry during depolarization is directly through slow calcium-channels.

2.3 Depolarizing Solutions

Most cardioplegia solutions can be classified as either depolarizing or hyperpolarizing solutions. The most common method of myocardial protection during cardiac surgery is depolarized diastolic arrest with a hyperkalemic infusion [7]. During administration, myocardial cells depolarize, allowing sodium channels to open and sodium to flow into the cell like a normal action potential. But, because of the elevated extracellular potassium concentration, sodium channels are locked in an inactive state, preventing the cells from repolarizing and keeping them in an unexcitable state [7].

Depolarizing solutions have been used since the 1970s and are currently considered to be the gold standard of myocardial protection [5]. These solutions tend to contain between 10-25 mEq/L of potassium which, when administered via an aortic root injection, raises cell membrane potential to approximately -50 mV from a resting membrane potential of -90 mV [5]. Diastolic arrest occurs at – 50 mV because fast sodium channels, which have a threshold potential between -65 to -70 mV, are inactivated at this potential [5]. The Nernst potential for sodium-calcium exchangers is also -50 mV, meaning at a diastolic arrest of -50 mV, no net movement of calcium or sodium ions should occur across the cell membrane [5].

2.4 Hyperpolarizing Solutions

Hyperpolarizing solutions are used as an alternative to hyperkalemic solutions and work by making the membrane potential more negative than resting potential [5]. This is achieved by using solutions with no calcium and low sodium to induce an arrest. They also add procaine, a sodium-channel blocker, to prevent action potential propagation [5].

Transmembrane ion gradients are maintained closer to normal physiologic levels by utilizing a hyperpolarizing arrest as opposed to hyperkalemic depolarized arrest [5]. This approach has the theoretical benefit of reducing the severity of ionic imbalance during the ischemic period. Additionally, few ion channels and pumps are active and the metabolic demand of the myocardium is greatly reduced [8]. The potential for influxes and overload of sodium and calcium during hyperpolarized arrest is reduced because at hyperpolarized membrane potentials, sodium and calcium channels are closed [5].

These channels have threshold potentials near -40 mV, which is close to predicted membrane potentials of cells exposed to depolarizing cardioplegia solutions. Rising intracellular calcium is a concern because it is associated with irreversible muscle contracture and myocyte necrosis [1, 9]. Additionally, placing cells in a prolonged depolarized state increases the consumption of high-energy phosphate stores when compared to hyperpolarizing solutions [9]. Based on these concerns, some surgical teams prefer the use of hyperpolarizing solutions.

While cardioplegia solutions can be grouped into two general groups, additional differences exist in the additives used in each solution. Each additive used serves a specific purpose: ion channel blockers, buffer pH, and so on. A general understanding of some common cardioplegia additives is beneficial when choosing which solution to use. While formulations and techniques vary, the goals of each solution are the same: to lower cell metabolism, to achieve electrical and mechanical quiescence, and to reduce the impact of prolonged ischemia.

2.5 Components of Cardioplegia Solutions

Cardioplegia consists of three major components: an arresting agent, hypothermia, and additional protective agents in the form of additives. Formulations vary between solutions and surgical preference. Some common additive agents are outlined in Table 1.

Table 1: Some Common Cardioplegia Additives and Their Function [5].

Additive Agent	Purpose
Adenosine	Coronary vasodilator. Enhances cardioplegia delivery
Magnesium Sulfate	Calcium channel competitor. Prevents calcium influx.
Lidocaine/Procaine	Sodium channel blocker. Prevents sodium influx.
Histidine/Sodium Bicarbonate/THAM	Buffering agent. Counteracts acidosis from ischemia.

Hypothermia is an almost universal component of any cardioplegic solution. While the exact mechanisms by which hypothermia reduces ischemic injury are not fully understood, prevailing theories suggest it reduces cellular energy consumption [10]. Metabolic cell regulation is controlled by many temperature dependent enzyme reactions, which do not occur outside of normothermic conditions [10]. The greatest reductions in myocardial energy consumption result from hypothermic conditions and the Q_{10} effect, which is a 50% reduction in cell metabolism for every 10° C decrease in myocardial temperature [7]. Drescher *et al*. demonstrated that hypothermia helped to mitigate cell damage caused by reactive oxygen species. Hypothermic cells retained 81.2% of their function compared to 54.2% in normothermic cells [10]. When combined with

cardioplegia solutions, hypothermic conditions led to a nearly four-fold increase in cell survivability when compared to normothermic cardioplegia [10].

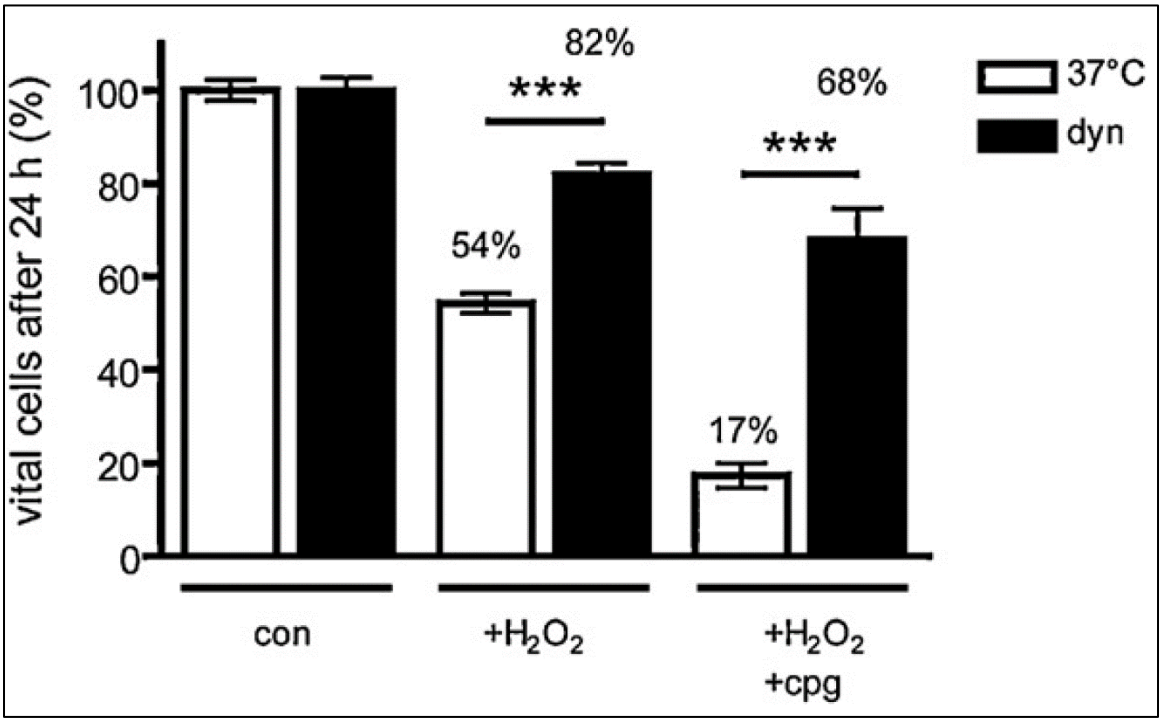

Figure 3: Vitality of Cells 24 Hours After H_2O_2 Damage and Application of Cardioplegia (cpg) During Dynamic Hypothermia (dyn) and Normothermia (37° C) [10].

Adenosine is used in depolarizing agents to enhance cardiac arrest. When compared to hyperkalemic solutions alone, a combination of adenosine and hyperkalemia reduces the time to induce cardiac arrest [5]. This is thought to be associated with transient hyperpolarization caused by adenosine prior to the hyperkalemic-induced depolarization. Electrical arrest of the SA node conduction prior to mechanical quiescence produces a more rapid global arrest [5].

The accumulation of intracellular calcium during ischemia has been associated with irreversible cell injury; therefore, the addition of calcium-channel blockers and calcium-channel competitors to normocalcemic cardioplegia solutions is common. Theories concerning the mechanism of calcium-related cell injury include ATP consumption through calcium-dependent ATPases, impaired ATP synthesis from calcium-related mitochondrial damage, and activation of several calcium-dependent degradative enzymes [11]. Magnesium sulfate in high concentrations is used as a calcium-channel competitor and displaces calcium ions from L-type calcium-channels in the cell membrane [11]. While the addition of magnesium to hypocalcemic cardioplegia has not been shown to affect ventricular recovery, its use in normocalcemic solutions drastically improves recovery compared to when it is absent [11].

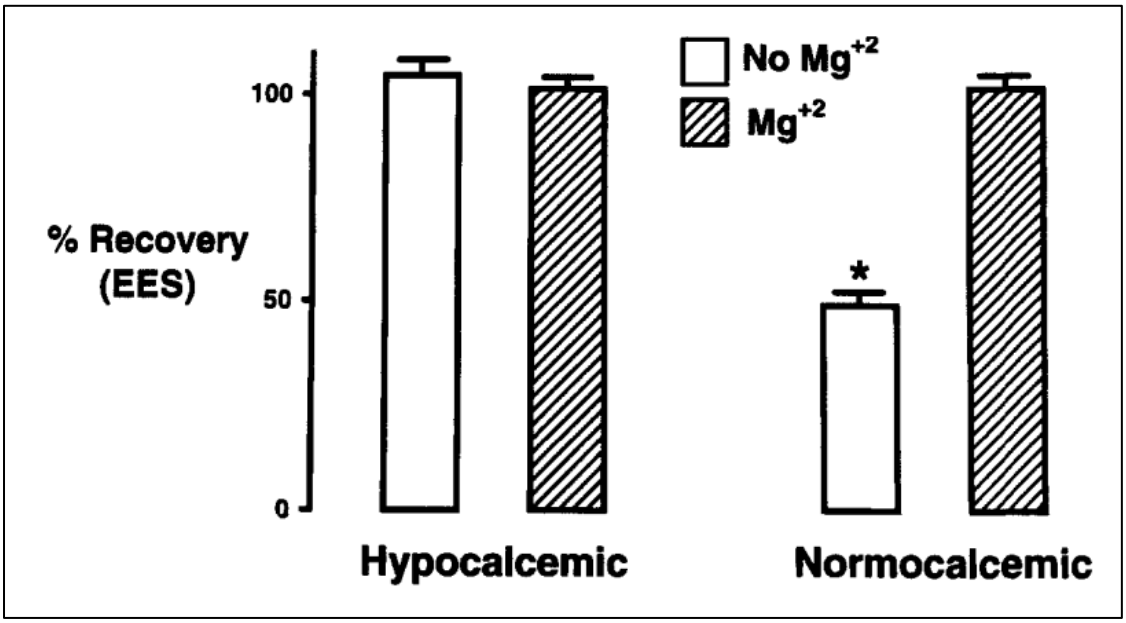

Figure 4: Left Ventricular Systolic Function Measured via End-Systolic Elastance (EES) as a Percentage Compared to Baseline After Infusion of Hypocalcemic and Normocalcemic Cardioplegia Solutions [11].

During hyperkalemic depolarized arrest, high extracellular potassium causes fast sodium-channels to be inactivated [12]. Over time a sodium window current can allow calcium to enter the cell, leading to intracellular calcium accumulation and eventual cellular damage [12]. Keeping sodium-channels in an inactivated state keeps the cell membrane depolarized, reducing sodium window currents, and preventing intracellular calcium buildup. Sodium-channel blockers, such as lidocaine or procaine, have been added to some cardioplegia solutions [12]. Sodium-channel blockers cause the cell membrane to become slightly polarized in comparison to depolarizing solutions without these agents. Hyperkalemic solutions containing sodium-channel blockers, such as del Nido cardioplegia, are classified as modified depolarizing solutions.

The buffering ability of any cardioplegia solution is of immense importance. Normal myocardial pH is approximately 7.2 and many intracellular metabolic processes, such as glycolysis, are pH regulated [6]. Ischemia causes acidotic conditions, which inhibit normal cell function; therefore, buffers are always added to cardioplegia solutions to limit pH changes. Common buffers include sodium bicarbonate, tromethamine (THAM), or the amino acid histidine [2, 3, 6]. As shown in Figure 2, maintaining proper myocardial pH during the cross-clamp period improves short- and long-term patient outcomes [6].

Additives in cardioplegia solutions are common, but their use varies. This is partially due to cardioplegia solutions being developed for specific patient populations. Differences in patient anatomy and physiology vary with different diseases, but developmental differences must also be considered. Pediatric and adult myocardium

have different anatomy and metabolic requirements which should be considered when selecting cardioplegic solutions.

2.6 Differences in Adult and Pediatric Cardiac Physiology

The pediatric heart has several physiologic differences when compared to an adult myocardium. These include increased dependence on glucose, increased sensitivity to calcium, and less contractile fiber (Table 2) [13]. A detailed understanding of these differences might impact the choice of cardioplegia and the details of its delivery during surgery.

Cardiac myocytes can derive ATP from fatty acid oxidative phosphorylation, anaerobic glycolysis, lactate, ketone, and amino acid metabolism, as well as endogenous stores of glycogen and triglycerides [13]. Ninety percent of ATP generation in the adult myocardium is derived from fatty acid metabolism, whereas in the neonatal/pediatric heart, glucose is the main source of energy production [13].

Table 2: Major Differences Between Pediatric and Adult Cardiac Physiology [7]. Starling response is an increased ejection with an increase in venous return.

	Adult Heart	**Pediatric Heart**
Main Energy Substrate	Fatty Acids	Glucose
Main Metabolic Pathway	Krebs Cycle/Oxidative Phosphorylation	Glycolysis
Average Contractile Proteins	60%	30%
Starling Response	High	Low

In pediatric/neonatal and adult hearts, calcium plays a key role in cardiac contraction, but how it enters the cell differs between immature and mature hearts. In adult hearts, when voltage gated L-type calcium-channels open, the influx of calcium triggers the opening of calcium channels located on the sarcoplasmic reticulum [14], from which 90% of cytosolic calcium arises [14]. In neonates, the density of L-type calcium channels is lower than it is in older children or adults. As a result, calcium influx into immature hearts occurs through the sodium-calcium exchanger instead of L-type calcium channels [14]. This is demonstrated by exposing both adult and neonatal rabbit hearts to the calcium-channel blocker nifedipine and observing the resulting contraction. Because neonatal hearts receive calcium through the sodium-calcium exchanger instead of calcium-channels, contraction is not as drastically affected as it is in adults [14] (Figure 5).

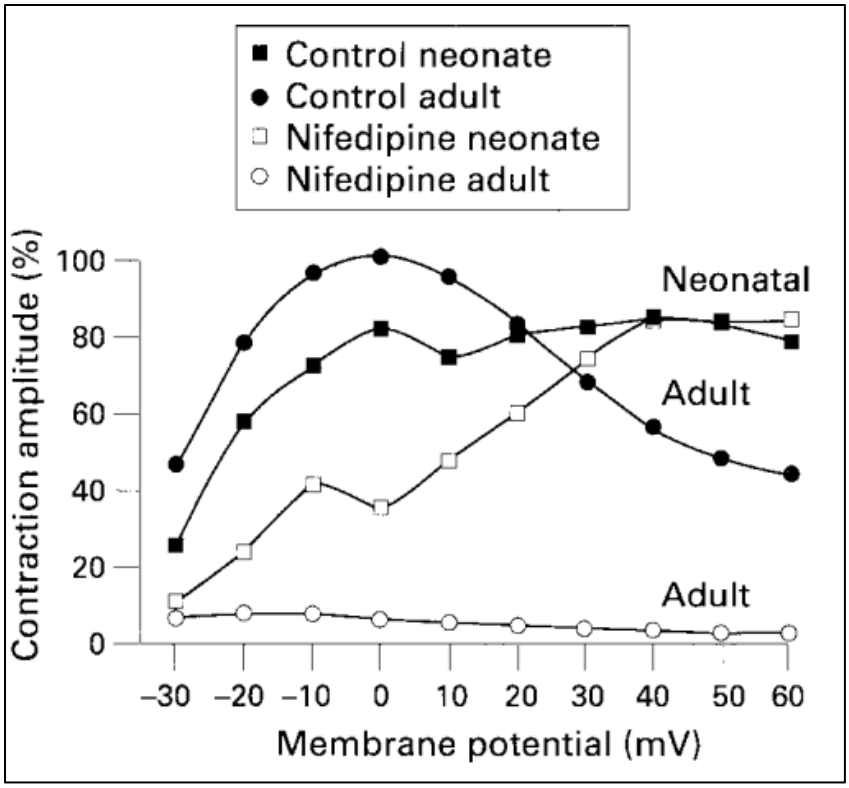

Figure 5: Effects of the Calcium-Channel Blocker Nifedipine on Contraction Amplitude in Neonate and Adult Rabbit Hearts [14].

Maintaining proper calcium metabolism and preventing calcium overload is important during cardiac surgery, but it is critical during pediatric cardiac surgery. Improper management of calcium can cause irreversible myocardial damage and even cell death [11]. Immature cardiac tissue has a decreased ability to regulate calcium, which can be explained by several structural differences. In pediatric hearts, the sarcoplasmic reticulum is still developing and has a smaller capacity to store calcium [13], and the enzyme responsible for the re-uptake of calcium into the sarcoplasmic reticulum, Calcium-ATPase (CaATPase), has decreased activity in developing hearts [13]. Finally, the main source of calcium required for contraction is supplied via entry through the sodium-calcium exchanger and calcium-channels from the extracellular

space, instead of from the sarcoplasmic reticulum [13]. The combination of these factors decreases the ability of pediatric hearts to release and re-uptake calcium from the sarcoplasmic reticulum during an action potential and is why the addition of calcium-channel blockers in cardioplegia is beneficial during pediatric heart surgery [13]. These differences also explain why calcium overload is possible during post-ischemic reperfusion and why pediatric cardioplegic solutions generally contain lower than normal calcium levels [13].

The increased ability of immature hearts to tolerate ischemia better than adult hearts may be explained, at least partially, by the increased use of glucose for ATP production. Several theories support this explanation. One is that in the pediatric heart, hydrogen ions generated during periods of stress can be used during the pyruvate dehydrogenase step of anaerobic glycolysis [15]. Not only does this reduce acidosis, but it is an efficient use of metabolic waste products. Additional data support the idea that glycogen metabolism may help to stabilize and to maintain proper function of the sarcoplasmic reticulum, ensuring proper calcium management during ischemia and preventing calcium overload during reperfusion [13]. When glycolysis was inhibited in rabbit hearts during 20 minutes of global ischemia, contractile recovery during reperfusion was markedly depressed when compared to hearts where anaerobic glycolysis was allowed to occur [16]. The same study showed calcium transport into the sarcoplasmic reticulum during ischemia was supported almost exclusively by ATP generated by endogenous glycolysis, suggesting that preserving anaerobic glycolysis during ischemia may be linked to enhanced calcium handling during reperfusion [16].

As researchers identified physiological differences between neonatal and adult hearts, it became apparent that approaches to myocardial protection should address these differences. Various groups formulated new or modified adult cardioplegia solutions to better address the pediatric population. Two of the most commonly used solutions in pediatric surgery are del Nido and Custodiol HTK.

2.7 Del Nido Cardioplegia

During the 1980s and 1990s, cardioplegia was universal between adult and pediatric heart surgery, with modifications made to delivery flow, volume, and pressure [3]. As it was discovered that the pediatric myocardium was more tolerant to ischemia and more susceptible to calcium overload, del Nido cardioplegia was developed and has been widely used in pediatric centers since its development in the 1990s [1, 3]. The crystalloid base portion of del Nido cardioplegia is 1-liter of Plasma-Lyte A, which is used because it mimics normal extracellular ion concentrations within the body [3]. A list of additives is found in Table 3. This base solution and additives are delivered as a 1:4 ratio of patient blood from the bypass circuit to crystalloid solution [3]. No calcium is added to the base solution and the only source of calcium is from the patient's whole blood. Del Nido cardioplegia achieves electromechanical arrest via depolarization caused by the final potassium concentration of 24 mEq/L, which is achieved by adding 13 mL (26 mEq) of potassium to the Plasma-Lyte A base.

Table 3: List of Additives in del Nido Cardioplegia [3].

Additive	Concentration
Potassium	26 mEq/L
Mannitol 20%	16.3 mL
Sodium Bicarbonate 8.4%	13 mL
Magnesium	4 mEq/L
Lidocaine 2%	6.5 mL

Mannitol functions as an osmotic diuretic and is conventionally used during cardiopulmonary bypass to increase urine production, reduce cerebral edema, and scavenge oxygen free-radicals [3]. Superoxide anion, hydrogen peroxide, and hydroxyl ions are all oxygen free-radicals which contribute to myocardial injury during both cardioplegic arrest and upon reperfusion [3]. Under normal physiologic conditions, these reactive oxygen species are metabolized by enzymes, but normal enzyme function is subdued during arrest, allowing free radicals to accumulate, and increasing ischemic damage. Myocardial edema is another common problem during cardiac surgery and has also been shown to play a large role in post-ischemic cardiac injury [3]. The hyperosmotic nature and free-radical scavenging abilities of mannitol help attenuate both reactive oxygen species accumulation and myocardial edema during ischemia and reperfusion [3].

The addition of magnesium and lidocaine make del Nido a modified depolarizing solution because these two additives reduce calcium and sodium influx during the arrest.

Magnesium has innate calcium-channel blocking abilities while lidocaine acts as a sodium channel blocker; both indirectly inhibit Na^{+}/Ca^{2+} exchange and inhibit action potential formation [3]. Because myocardial contraction is highly dependent upon intracellular calcium levels, reducing calcium entry helps prevent diastolic rigidity. The addition of magnesium has been shown to increase cardiac myocyte recovery after periods of ischemia [11]. As shown by O'Brien *et al*., this collection of additives delivered as del Nido cardioplegia demonstrates superior calcium handling capabilities when compared to an adult solution containing less magnesium, no sodium-channel blockers, and no mannitol [17]. Table 4 shows a comparison of del Nido components compared to a modified Buckberg solution.

Table 4: Comparison of del Nido and Modified Buckberg Cardioplegic Solutions [17].

Additive	del Nido	Modified Buckberg
Na, mmol/L	153	152
K, mmol/L	26	18
Cl, mmol/L	132	126
Ca, mmol/L	0.4	1.4
Mg, mmol/L	6.2	4.6
Lidocaine, mg/L	140	---
Mannitol, g/L	2.6	---

Other than calcium handling, cardioplegia solutions need to support ATP production, and limit acidosis while cells are in an anaerobic state. Del Nido does not contain any substrates because they are available within cardiac cells, but the addition of bicarbonate acts as a buffer to limit the scope of acidic conditions. The addition of sodium bicarbonate to del Nido cardioplegia increases buffering capacity and helps to maintain an intracellular pH close to 7.4, allowing glycolysis to be maintained throughout the ischemic period [3]. The addition of 20% patient whole blood further promotes anaerobic glycolysis because of its endogenous buffering capacity as well as allowing for aerobic metabolism to occur during the delivery period [3]. The addition of blood to the solution reduces ischemic stress and reperfusion injury when compared to completely crystalloid solutions (Table 5) [18].

Table 5: Clinical Outcomes of 40 Pediatric Patients After Undergoing VSD Repair with either Cold Crystalloid or Cold Blood Cardioplegia [18].

	CCC (n = 21)	CBC (n = 19)	*p* Value
Postoperative inotropic support			0.23
Nil	3	1	
Minimal	6	11	
Significant	12	7	
Inotropic support duration (hours)	25 (0 to 137)	21 (0 to 107)	0.5
Postoperative arrhythmias			
Atrioventricular block	4	1	0.35
Temporary pacemaker	5	2	0.41
Supraventricular tachicardia	3	0	0.23
Ventilation (hours)	9 (2 to 21)	8 (2 to 29)	0.72
ICU stay (days)	2 (2 to 4)	2 (2 to 2)	0.22
Hospital stay (days)	8 (7 to 10)	8 (6 to 11)	0.98

Medians and interquartile ranges are shown for continuous variables.

ICU = intensive care unit; CCC = cold crystalloid cardioplegia; CBC = cold blood cardioplegia.

Standard dosing for del Nido is a single dose of 20 mL/kg with a maximum dose of 1 liter for patients weighing more than 50 kg [3]. Procedures with an expected cross-clamp time less than 30 minutes can safely use a dose of 10 mL/kg [3]. Redosing is performed generally at the surgeon's preference, but del Nido was developed as a single dose model and redosing may not occur unless the cross-clamp time exceeds 3 hours or electrical activity is seen [3].

In summary, del Nido cardioplegia was developed to address specific requirements of the pediatric and infant heart, with the main purpose being to prevent calcium overload during ischemia and reperfusion. This is achieved with the addition of

lidocaine acting as a sodium channel blocker and magnesium sulfate, which acts as a calcium channel competitor. The addition of mannitol scavenges oxygen free-radicals during ischemia and lowers the risk of reperfusion injury. Sodium bicarbonate is used to maintain a pH of approximately 7.4, which counteracts any acidosis and allows anaerobic glycolysis to be maintained during ischemia. Patient whole blood is mixed into the solution during infusion in a 1:4 ratio, increasing the buffering capacity of the solution and aiding in coronary perfusion during induction and any subsequent doses.

2.8 Custodiol HTK Cardioplegia

In contrast to the ion channel blockers used in del Nido to limit calcium entry at depolarized potentials, Custodiol HTK hyperpolarizes the heart to induce cardiac arrest. Hyperpolarizing solutions prevents calcium overload because few channels or ion pumps are active at hyperpolarized membrane potentials [19]. Additionally, energy consumption is low and the metabolic demand of cardiac myocytes is minimal at these highly negative potentials [19].

One of the attractive qualities of HTK is its claim to offer adequate myocardial protection for a 3-hour period with a single dose, allowing the surgeon to complete complex repairs without the need to stop or slow down for additional doses [2]. HTK is classified as an intracellular solution because it contains low sodium and calcium concentrations. When administered, it causes extracellular sodium washout, hyperpolarizes the cell membrane, and induces diastolic arrest [2]. HTK components are listed in Table 6.

Table 6: List of Additives in Custodiol HTK [2].

Additive	Concentration
Sodium	15 mmol/L
Potassium	9 mmol/L
Magnesium	4 mmol/L
Calcium	0.015 mmol/L
Histidine	198 mmol/L
Tryptophan	2 mmol/L
Ketogluterate	1 mmol/L
Mannitol	30 mmol/L

The high concentration of histidine acts as a buffer against acidosis caused by the accumulation of anaerobic metabolism waste products, and alpha-ketoglutarate is an intermediary in the Krebs cycle, improving ATP production during reperfusion as well as preventing lactate production during glycolysis [2]. Tryptophan serves to stabilize and protect cell membranes during arrest. Mannitol is added to prevent reperfusion injury by scavenging free radicals and to counteract myocardial edema by maintaining a slightly hyperosmotic extracellular osmolarity [2].

The major advantage of HTK over conventional cardioplegia solutions is its immense buffering capacity because of the high content of histidine [20]. Histidine is an amino acid which acts as the body's main intracellular buffer and promotes conditions optimal for hypothermic glycolysis to occur [21]. Because pediatric hearts rely on

glycolysis for ATP generation, promoting optimal conditions for glycolysis to occur is expected to reduce the risks of ischemic injury.

2.8 Project Statement

Both del Nido and Custodiol HTK solutions have been designed to reduce calcium overload in myocardial tissue, but they differ in their mechanisms of arrest, ion concentrations, buffering systems, and additives. Both are commonly used in pediatric perfusion because there is not adequate evidence at this time to determine if either is superior. Although they have both been tested against standard depolarizing solutions, there are little data comparing patient outcomes of these solutions directly. The goal of this project was to compare pediatric patient outcomes between children arrested with del Nido compared to those arrested with Custodiol HTK. This was done by retrospectively comparing patient records from 60 children (30 per group) to test the following hypotheses:

1. There will be no significant difference in change systemic ventricle ejection fraction between del Nido and Custodiol groups.
2. There will be no significant difference in total length of hospital stay between del Nido and Custodiol groups.
3. There will be no significant difference in duration of mechanical ventilation between del Nido and Custodiol groups.

3. Methods

After obtaining Institutional Review Board (IRB) consent, 60 patient charts at the Children's Hospital of Wisconsin (CHW) from January 2017 to December 2017 were retrospectively analyzed for echocardiogram data, duration of mechanical ventilation, and total length of hospital stay. Patient names, dates, and medical record numbers (MRN) were deleted and all data were decrypted and stored on CHW secured drives within the hospital. Patients within the del Nido and Custodiol groups were compared by The Society of Thoracic Surgeons-Europeon Association for Cardio-Thoracic Surgery (STAT) score to ensure equal comparison.

3.1 STAT Score

STAT Score is a way to risk assess for congenital heart surgeries based on associated mortality rates [22]. Procedures categorized at Category 1 have the lowest associated mortality rates and Category 5 procedures have the highest associated mortality rates [22]. Common procedures and their STAT score are listed in Table 7.

Table 7: STAT Score Categories of Common Congenital Defect Surgical Procedures.

STAT Score Category	Procedures
1	Atrial Septal Defect, Vascular Ring, Ventricular Septal Defect, Pacemaker Generator Change
2	Bi-directional Glenn, Aorta Coarctation, Fontan, New Pacemaker Implant, Tetralogy of Fallot, Valve Replacement
3	Arterial Switch, AV-Septal Defect, AV-Canal, Conduit Placement, Rastelli Procedure
4	Double Outlet Right Ventricle, Interrupted Aortic Arch, Systemic to Pulmonary Artery Shunt, Total Anomalous Pulmonary Venous Return, Heart Transplant, Truncus Arteriosus
5	Norwood, Heart and Lung Transplant

3.2 Statistical Analysis

Patients were divided into groups by cardioplegia used and then stratified by STAT score. Accurate statistical comparison between these groups is not possible with low sample sizes. Patient groups are shown in Table 8.

Table 8: Patient Distribution Between del Nido and HTK Cardioplegia.

STAT Score	del Nido (n=30)	HTK (n=30)
1	20	12
2	4	4
3	5	6
4	1	7
5	0	1

After patients were organized into groups by cardioplegia and STAT score, a 2-sample t-test was performed on ventilator time, total duration of hospital stay, and change in systemic ejection fraction. An alpha value = 0.05 was used as rejection criteria.

Ventilator time was defined as the time from intubation in the operating room to extubation in the ICU. Hospital stay was measured from the day of the procedure until discharge from the hospital. Change in systemic ejection fraction was calculated by measuring the difference in ejection fraction from intraoperative transesophageal echocardiogram just prior to the procedure and ejection fraction at time of discharge. Comparisons were made between groups of the same STAT score on each parameter.

4. Results

A total of 60 charts were reviewed with nine patients with STAT scores of 4 and 5 eliminated from the study because the del Nido group contained one STAT category 4 patient and no STAT category 5 patients; the HTK group contained seven STAT category 4 patients and one STAT category 5 patients. As a result, comparisons were only made for STAT scores 1, 2, and 3. No significant differences were found between the HTK group and the del Nido group across all parameters and STAT scores (see Tables 9, 10, and 11).

Table 9: Mean Ventilator Time for del Nido and HTK Patients.

STAT Score	HTK Mean Ventilator Time (Days)	del Nido Ventilator Time (Days)	P-Value
1	0.167 ± 0.389	0.3 ± 1.13	0.634
2	1.50 ± 1.73	1.25 ± 2.50	0.876
3	1.33 ± 1.21	0.6 ± 0.894	0.282

Table 10: Mean Length of Total Hospital Stay for del Nido and HTK Patients.

STAT Score	HTK Length of Stay (Days)	del Nido Length of Stay (Days)	P=Value
1	6.58 ± 2.43	7.2 ± 5.30	0.658
2	11.25 ± 6.80	11 ± 10.7	0.97
3	15.7 ± 12.0	9.6 ± 4.22	0.292

Table 11: Mean Change in Systemic Ventricle Ejection Fraction in del Nido and HTK Patients.

STAT Score	HTK Systemic EF Change	del Nido Sysytemic EF Change	P-Value
1	-3.08 ± 3.96	-5.30 ± 7.95	0.303
2	7.8 ± 14.6	-5.75 ± 7.41	0.174
3	-3 ± 10.2	-3.6 ± 4.56	0.901

The 7.8% increase in systemic ventricle ejection fraction in the STAT score 2 HTK group is explained by an increase of 29.0% in one of the four subjects. Eliminating this patient results in a mean systemic ventricle ejection fraction change of 0.67 ± 4.16%. Running a separate t-test yielded a p-value = 0.220, indicating no significant difference.

5. Discussion

The prevention of intracellular calcium accumulation and maintaining a neutral intracellular pH during cardiac ischemia appear to be important for preventing irreversible myocardial damage [6, 9]. Pediatric cardiac myocytes are especially susceptible to influxes in calcium because of an immature sarcoplasmic reticulum, which has a decreased ability to store excess calcium ions and the decreased activity of the enzyme CaATPase, which is responsible for sequestering calcium into the sarcoplasmic reticulum [9, 17]. Maintaining an intracellular pH close to normal physiologic levels during ischemia allows for the continued production of ATP through anaerobic glycolysis [6]. During cardiac surgery requiring cardiopulmonary bypass and aortic cross-clamping, intracellular myocardial pH is achieved using buffering agents.

Del Nido and Custodiol HTK are two commonly used cardioplegia solutions in pediatric heart surgery. They differ in both composition and in the mechanism through which they induce cardiac arrest. While much literature exists analyzing each of these solutions, little research is available comparing del Nido and Custodiol HTK directly. This study attempted to provide direct comparisons of patient outcomes, and found no significant difference in ventilator duration, total length of hospital stay, or change in systemic ventricle ejection fraction. The data from this study, although limited in number, support the use of both solutions in pediatric heart surgery requiring cardiopulmonary bypass and aortic cross-clamping.

There are few studies directly comparing del Nido and HTK, but multiple large studies exist evaluating these solutions against others. A systematic review of nine studies comparing a total of 925 patient cases using Custodiol HTK and 911 patient cases using extracellular or blood cardioplegia found no significant difference in patient mortality, 2.70% versus 2.63%, respectively [2]. Additionally, a review of five studies comparing the incidence of perioperative myocardial infarction in 677 patient cases using Custidiol HTK with 677 patient cases using extracellular or blood cardioplegia found no significant difference between the two groups, 2.81% versus 1.62%, respectively [2]. Conflicting data exist comparing Custodiol HTK and conventional blood cardioplegia in the pediatric population. Bojan *et al.* reported a rise in troponin release in Custodiol patients compared to patients who received warm blood cardioplegia [23]. Conversely, Korun *et al.* found no significant difference between Custodiol and blood cardioplegia in patients undergoing arterial switch procedures [24]. The results of the current study appear to be consistent with those comparing Custodiol and conventional blood

cardioplegia. Although debate still exists about the effectiveness of myocardial protection of Custodiol in pediatrics, the present study, as well as others, seem to suggest Custodiol provides adequate protection when compared to other methods.

Initially, del Nido cardioplegia was developed to address the inability of immature myocardial cells to tolerate high levels of intracellular calcium during reperfusion, post cross-clamp [1]. While developed for use in pediatrics, del Nido has seen increased use in the adult population. Sorbella *et al.* evaluated the use of del Nido in 52 adult patients compared to 61 patients receiving whole blood cardioplegia undergoing redo aortic valve replacement surgery [1]. No significant difference in ventilator time, post-operative ejection fraction, or ICU stay was reported between del Nido and whole blood cardioplegia groups [1]. Additionally, del Nido has been shown to reduce intracellular calcium accumulation during arrest as well as during reperfusion when compared to conventional cold blood cardioplegia [25]. This is especially important in pediatrics because the immature myocardium is less capable of dealing with ischemic and post-ischemic calcium overload [25]. Patients treated with del Nido cardioplegia showed less spontaneous myocardial electrical activity and less evidence of myocardial damage when compared to blood cardioplegia [25].

When compared to conventional blood cardioplegia solutions, both del Nido and Custodiol provided similar myocardial protection, so it stands to reason when compared to each other directly there would be no significant difference between them. The findings of this study support this theory. There was no significant difference detected in duration of mechanical ventilation, total length of hospital stay, or change in post-operative ejection fraction. Both del Nido and Custodiol offer the advantage of being

given as a single dose for extended periods of time, 90 minutes for del Nido and 2 hours for Custodiol [1, 26]. The ability to safely arrest the heart for an extended length of time allows surgeons to work uninterrupted, which can be beneficial when correcting complex congenital heart defects.

6.0 Conclusions

Based on the totality of data from this study as well as others, current evidence would indicate that del Nido and Custodiol HTK have similar postoperative outcomes. Practitioners can be comfortable using either solution for myocardial protection in pediatric heart surgery. Ultimately, the choice of which cardioplegia solution to use comes down to surgeon preference. The decision should take into account the case and patient characteristics. If it is anticipated the procedure will be lengthy and require complex surgical technique, selecting a cardioplegia solution which can be safely given as a single dose for an extended period is recommended. The findings from this study and the existing literature indicate del Nido and Custodiol HTK perform in a similar fashion and offer similar levels of protection through different methods.

6.1 Limitations and Future Recommendations

Although this study provided direct comparison of pediatric patient outcomes from a single clinical site, it suffers from low numbers, especially after stratifying by STAT score. The largest group for both del Nido and HTK was STAT 1, with 20 and 12 patients, respectively. Comparisons in STAT 2 and STAT 3 had substantially smaller samples, resulting in low statistical power and a high chance of committing a type II statistical error. This could be addressed in future studies by increasing the sample size

and trying to match sample sizes for each STAT score category. The small sample sizes for each STAT level violated normality assumptions for t-tests; increasing sample sizes could fix this. With only one patient in the STAT 4 category, statistical analysis was not possible for this category. Future studies might also consider additional patient variables as either predictors or outcomes. Variables that might be considered as predictors could include duration of aortic cross-clamp, length of cardiopulmonary bypass, hematocrit at termination of bypass, and average mean arterial pressure while on bypass. Expanding the sample size and achieving a more even distribution of STAT scores are ways future studies could improve upon the design of this one.

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Appendix A: Del Nido Data

Table A-1: Del Nido Patient Data.

del Nido Code	STAT Score	Preoperative Ejection Fraction	Discharge Ejection Fraction	Ejection Fraction Difference	Time on Ventiliator Post-op (days)	Length of Stay Total (days)
1	1	69	69	0	0	4
2	1	66	63	-3	0	5
3	1	63	48	-15	0	12
4	1	71	64	-7	0	4
5	1	66	56	-10	0	15
6	1	73	72	-1	0	9
7	1	68	77	9	0	4
8	1	62	67	5	0	4
9	1	68	55	-13	1	7
10	1	68	65	-3	0	5
11	1	72	54	-18	0	7
12	1	69	67	-2	0	5
13	1	72	47	-25	0	5
14	1	64	60	-4	0	5
15	1	69	64	-5	0	8
16	1	64	65	1	0	6
17	1	62	61	-1	0	4
18	1	62	62	0	0	5
19	1	65	57	-8	0	4
20	1	69	63	-6	5	26
21	2	69	59	-10	0	4
22	2	65	65	0	0	6
23	2	48	62	-14	0	7
24	2	29	30	1	5	27
25	3	62	61	-1	0	5
26	3	72	61	-11	1	13
27	3	70	67	-3	0	8
28	3	66	67	1	2	15
29	3	69	65	-4	0	7
30	4	69	58	-11	6	40

Appendix B: HTK Data

Table B-1: HTK Patient Data.

HTK Code	STAT Score	Preoperative Ejection Fraction	Discharge Ejection Fraction	Ejection Fraction Difference	Time on Ventiliator Post-op (days)	Length of Stay Total (days)
1	1	70	66	-4	0	4
2	1	63	53	-10	1	12
3	1	68	62	-6	0	8
4	1	65	63	-2	0	7
5	1	72	67	-5	0	7
6	1	69	68	-1	0	4
7	1	69	63	-6	0	6
8	1	67	60	-7	0	4
9	1	68	67	-1	1	5
10	1	65	68	3	0	5
11	1	67	70	3	0	9
12	1	62	61	-1	0	8
13	2	68	72	4	0	4
14	2	53	55	2	3	16
15	2	68	64	-4	0	7
16	2	31	60	29	3	18
17	3	75	60	-15	2	29
18	3	65	67	2	2	14
19	3	53	67	14	0	5
20	3	73	69	-4	1	9
21	3	70	66	-4	0	5
22	3	67	56	-11	3	32
23	4	68	68	0	2	25
24	4	65	65	0	2	16
25	4	64	76	12	4	24
26	4	67	64	-3	1	6
27	4	74	64	-10	5	79
28	4	64	70	6	2	26
29	4	67	54	-13	1	8
30	5	61	63	2	1	12

Thesis Approval Form

Master of Science in Perfusion

Milwaukee School of Engineering

This thesis, entitled "Clinical Impact of del Nido versus Custodiol HTK Cardioplegia Solutions in the Postoperative Period in Pediatric Cardiac Surgery Patients," submitted by the student John Pawlak, has been approved by the following committee:

Faculty Advisor: _____ Date: _____

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