ANALYSIS

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Comparison of Blood Cardioplegia and Del Nido Cardioplegia Use in Isolated VSD Patients

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Objective: **Ventricular septal defect (VSD) is the most common pathology among congenital heart diseases. Surgical closure, transcatheter closure or medical follow-up are among the treatment strategies. Surgical closure of VSD can now be safely performed with low morbidity and mortality. In this study, we aimed to compare the efficacy of blood cardioplegia and del Nido cardioplegia during VSD operation. *Material and Method:* In our Pediatric Cardiovascular Surgery Clinic, we retrospectively evaluated 186 patients, between 6 weeks and 18 years of age, who underwent operation due to isolated VSD between September 2013 and December 2017. Patients were divided into two groups as Group 1 (n = 108 using blood cardioplegia) and Group 2 (n = 78 using del Nido cardioplegia). Pre-operative data, peri-operative data and post-operative data of patients were retrospectively recorded and reviewed in detail. *Findings:* 153 patients (82.2%) were under 5 years old, 24 (12.9%) were between 5 and 10 years old, and 9 (4.8%) were between 10 and 20 years of age. 112 (60.2%) of the patients were male and 74 (39.8%) were female. The mean age of the patients was 3.8 ± 2.08 in Group 1 and 4.2 ± 2.13 in Group 2. There was no statistically significant difference in preoperative demographic data between Group 1 and Group 2 patients (p> 0.05). The duration of cardiopulmonary bypass (CPB), duration of intubation, intensive care unit stay and discharge time were found to be statistically significant when compared with Group 1 (p <0.05). *Result:* Congenital heart disease cases can have a long operation time. In the light of our findings, we recommend the use of del Nido cardioplegia, which is administered a single-time and reduces inotropic need and duration of operation as well as significantly reduce extubation and discharge times, instead of blood cardioplegia which is given every twenty minutes. It can be said that del Nido cardioplegia can be safely used in the cases of congenital heart surgery, although it is difficult to give a definitive judgment due to the inadequacy of our case count.**

INTRODUCTION

Isolated VSD is the most common congenital heart defect (1). Approximately 2 in every 1000 live births. Isolated VSDs and VSDs accompanying other major defects are considered to be the most common congenital heart malformations. Soto et al., classify ventricular septal defects into perimembranous, muscular, and double-committed subarterial (DCSA) classes (2). This classification gives practicality to VSD's classic surgical repair strategies. Perimembranous VSDs, the most common type with a frequency close to 80%, may show partial or complete closure with tricuspid septal leaflet pouch or aneurysm formation (3). Muscular VSDs that are seen in 5-10% of cases tend to close spontaneously more than perimembranous ones (4). DCSA VSDs, which are more commonly seen in Asia, especially in the Far East, account for 5-10% of isolated ventricular septal defects (5). In addition to surgical repair, medical follow-up and transcatheter closure attempts are also being performed in current treatment strategies of VSDs. In transcatheter closure applications, the incidence of failures in DCSA-VSD, variable complication rates in perimembranous types, revising surgical repair strategies and the need to approximate surgical mortality and morbidity to zero, are on the agenda. Although the technical equipment and surgical experience increases every day, VSD-related mortality rates can still be observed today. These mortalities are generally due to sepsis, pulmonary hypertensive crises, ventricular rhythm disorders or left-right cardiac failure.

Myocardial protection methods have a great importance in the safe application of cardiac surgeries including VSD closure operations. Due to the variety of the application methods and case groups of cardioplegia solution constituting the basis of myocardial protection, it is not easy to determine the best cardioplegia method in preventing myocardial damage. In this study, we aimed to study the applicability of del Nido cardioplegia which is used more commonly recently and classical blood cardioplegia in our cases.

FINDINGS

153 patients (82.2%) were under 5 years old, 24 (12.9%) were between 5 and 10 years old, and 9 (4.8%) were between 10 and 20 years of age. 112 of the patients were male (60.2%) and 74 were female (39.8%). There were 45 female and 63 male patients in Group 1 and 29 female and 49 male patients in Group 2. The

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Table 1 Pre-operative Patient Data

Variable	Total (n=186)	Group 1(n=108)	Group 2 (n=78)	p value
Mean Age (Years)	5.1 ± 3.12	3.8 ± 2.08	4.2 ± 2.13	>0.05
Sex (Female / Male)	74 F / 112 M	45 F / 63 M	29 F / 49 M	>0.05
Average BMI (kg / m2)	0.62 ± 0.26	0.63 ± 0.27	0.64 ± 0.28	>0.05
Severe Pulmonary Artery Pressure (n%)	22 (%11.8)	12 (%6.4)	10 (%5.3)	>0.05
Mildly High Pulmonary Artery Pressure (n%)	109 (%58.6)	63 (%33.8)	46 (%25.1)	>0.05
Pre-operative INR	1.2 ± 0,4	1.2 ± 0.05	1.3 ± 0.85	>0.05
Pre-operative Platelet Level (K / mm3)	235.000 ± 40.500	245.000 ± 44.000	305.000 ± 26.000	>0.05
Perimembranous VSD	145	84 (%77.7)	61 (%78.2)	>0.05
Double commited subarterial type VSD	15	10 (%9.2)	5 (%6.6)	>0.05
Muscle type VSD	14	8 (%7.4)	6 (%7.6)	>0.05
Mixed type VSD	12	6 (%5.7)	6 (%7.6)	>0.05

Values are n (%) for categorical variables and mean ± SD for continuous variables

INR: International Normalized Ratio,

BMI: *Body Mass Index*

Table 2 Operation Data

Variable	Total (n=186)	Group 1 (n=108)	Group 2 (n=78)	p value
VSD closed with pericard patch	133	75 (%69.4)	58 (%74.3)	>0.05
VSD closed with Dacron patch	34	22 (%20.3)	12 (%15.3)	>0.05
Primary VSD closure	19	11 (%10.3)	8 (%10.4)	>0.05
Aortic Cross Clamp Time (Minutes)	55.1 ± 15.35	63.6 ± 14.51	51.2 ± 10.21	**<0.05**
Hypothermia duration	37.8 ± 14.09	42.6 ± 15.31	33.4 ± 13.38	**<0.05**
Total cardioplegia volume given (ml)		594 ± 210	340 ± 50	**<0.05**
Erythrocyte Suspension Amount Used During Operation (ml)	185 ± 50	175 ± 50	195 ± 45	>0.05

Values are n (%) for categorical variables and mean ± SD for continuous variables

Table 3 Post-operative Patient Data

Variable	Total (n=186)	Group 1 (n=108)	Group 2 (n=78)	p Value
Inotropic Agent Usage Past CPB	130 (%69.8)	85 (%78.7)	45 (%57.6)	**<0.05**
Total Drainage (ml)	135 ± 65	125± 75	145± 55	>0.05
Hemoglobin levels (g / L)	9.8 ± 2.1	10.6 ± 2.0	9.5 ± 2.1	>0.05
Number of Platelets (K / mm3)	214.000 ± 30.000	225.000 ± 32.000	195.000 ± 28.000	>0.05
Duration of Entubation (hour)	6.7 ± 2.5	8.7 ± 2.6	5.3 ± 1.4	**<0.05**
Intensive Care Stay (days)	2.4 ± 0.3	3.1 ± 1.5	2.2 ± 1.3	**<0.05**
Total Hospital Stay (days)	8.05 ± 1.4	9.4 ± 1.2	6.6 ± 1.3	**<0.05**
Creatinine levels (mg / 100 ml)	0.8 ± 0.22	0.7 ± 0.28	0.9 ± 0.36	>0.05
Mortality (%)	4 (%2.1)	2 (%1.07)	2 (% 1.07)	>0.05

Values are n (%) for categorical variables and mean ± SD for continuous variables

mean age of the patients was 3.8 ± 2.08 in Group 1 and 4.2 ± 2.13 in Group 2. There was no statistically significant difference in preoperative demographic data between Group 1 and Group 2 patients ($p > 0.05$). Preoperative demographical data of the patients is available in Table 1.

The accordance of VSD types observed during the operation to Soto classification was observed. VSD was the most common perimembraneous type detected (79%). All VSDs were closed with pericardium patch, dacron patch or primarily. There was no statistically significant difference among the groups in these closure operations. 75 of the patients with pericardium patch were in Group 1 and 58 were in Group 2. 22 of the patients with Dacron patch were in Group 1 and 12 were in Group 2. 11 of primary closure VSDs were in Group 1 and 8 were in Group 2. Operation data of the patients is available in Table 2.

Blood cardioplegia was given to the patients in Group 1 every 20 minutes during the operation. 594 ± 210 was the total amount of blood cardioplegia used. del Nido cardioplegia was given at one time to the patients in Group 2. 340 ± 50 was the total amount of del Nido cardioplegia used. There was a statistically significant difference among the carioplegia amounts used ($p<0.05$). Although 175 ± 50 ml erythrocyte suspension (ES) was used in average in Group 1 patients, 86 (79.6%) were given 155 ± 45 ml ES and 15 were given (13.8%) 205 ± 55 ml ES.

Although an average of 195 ± 45 ml ES was used for Group 2 patients, 61 (78.2%) were given 165 ± 55 ml ES and 10 (12.8%) were given 250 ± 40 ml ES and the blood amounts used were not statistically significant ($p>0.05$).

Aortic cross clamp duration was 51.2 ± 10.21 minutes in Group 2, 63.6 ± 14.51 minutes in Group 1, total hypothermia duration was 33.4 ± 13.38 minutes in Group 1 and 42.6 ± 15.31 minutes in Group 2 and was statistically significant ($p<0.05$). When post-operation supportive treatments of the patients were compared, it was observed that Group 2 patients needed less inotrope treatment and this was statistically significant ($p<0.05$). Average intensive care unit intubation duration of the patients was 8.7 ± 2.6 hours in Group 1 and 5.3 ± 1.4 hours in Group 2. Average intensive care unit hospitalization time of the patients was 3.1 ± 1.5 in Group 1 and 2.2 ± 1.3 days in Group 2. Discharge time was 9.4 ± 1.2 days in Group 1 and 6.6 ± 1.3 days in Group 2 and these were statistically significantly different ($p<0.05$). Post-operation data of the patients is available in Table 3.

Morbidities observed in the patients were permanent pace maker requirement in 12 patients (6.4%), residual VSD in 6 patients (3.2%) (over 3 mm and clinically significant) and pneumothorax in 14 patients (7.5%). Mortality was observed in four patients after the operation. Morality occurred due to early sepsis in one patient (0.53%), pulmonary hypertensive crisis in two patients (1.07%) and right cardiac failure in one patient (0.53%). Cardiac index measurements couldn't be measured at the time data was obtained.

DISCUSSION

Self closure is not common in VSDs observed at a ratio of nearly 2 out of 1000 live births (1). But a higher closure is observed in muscular VSDs compared to perimembranous ones. A higher rate of self closure was also reported in females compared to males and small defects were self-closed more commonly compared to big defects (6). Self closure probability was reported higher for VSDs under 3 mm in a study by Erol et al while it was reported higher for VSDs under 4 mm in the study by Tomita et al (8). In this study, we compared the use of del Nido cardioplegia stated to provide safe myocardial protection with classical blood cardioplegia in 186 patients who had surgical intervention on VSDs without self-closure potential.

Cardioplegia solutions are used to keep myocardial tissue stable during the operation through electromechanic cardiac arrest provision (9). The aim here is to form a blood-free area with cardiac arrest, provide surgical comfort and keep oxygen consumption minimum during arrest. Although there is no standard cardioplegia application in heart surgery clinics, every clinic may have different applications. Special plegisol solution kept ready (Plegisol; Abbott Laboratories, Chicago, IL), blood cardioplegia prepared by anesthesia clinic during operation and Custodiol solution recently used especially for heart transplantation (Custodiol HTK; Kohler Chemie GmbH, Germany) can be named among these differences (11). In operations especially made with blood cardioplegia, there may be short cardiac pulse remissions due to high potassium after removing aortic cross clamp especially in operations made with blood cardioplegia and thus the operation duration is lengthened.

High dose of potassium in classical blood cardioplegia may cause intracellular sodium and calcium accumulation during cardiac arrest (12). Increased intracellular sodium and calcium may cause cellular edema and necrosis (13). Especially sodium and potassium imbalance in intensive care unit after the operation has the potential to cause atrial fibrilation, ventricular tachycardia and even ventricular fibrillation (14). To avoid such rhythm disorders after the operations, it is important to follow-up the patients closely and to adjust the electrolyte balance considering blood gas data (15). In studies on del Nido cardioplegia which is recently used more in the world and our country, it was observed that the compounds in this solution decreased calcium accumulation and energy consumption in ischemic period. Especially the lidocaine present in this solution has a significant effect on membrane stabilization and lengthening cardiac arrest. It was also shown that lidocaine had a direct effect on tissue vasoactivity and increased nitric oxide release in cellular level (17). Data stating that it decreases the harmful effects of calcium by preventing the magnesium and calcium accumulation it contains is also available (18). Mannitol present in del Nido cardioplegia also has an important role in decreasing intra and extra cellular edema and cleaning free radicals.

In a study by O'Blenes et al (19), de Nido cardioplegia and blood cardioplegia were used in elder mouse myocytes and it was found that del Nido cardioplegia increased depolarization in the membrane rest potential and created less spontaneous and inducible activities during cardiac arrest.

In a study by Ramanathan et al (20), 142 adult patients were examined and it was detected that del Nido cardioplegia was effective in returning to the normal sinus rhythm after removing aortic cross clamp and defibrilation operation was applied less in the patients. They also stated the cause for applying less defibrilation was the decreasing intracellular calcium accumulation.

Cardioplegies such as standard blood cardioplegia and plegisol should be applied at a certain pressure and time. It is recommended to apply them at an average pressure of 70mmHg (antegrade) and a time interval of 3-5 minutes (21). As a result, an average extension of 15-20 minutes was observed in aortic cross clamp duration of the operation by applying blood cardioplegia every 20 minutes in the cases in our study. As del Nido cardioplegia is given at once and the confidence interval is over 60 minutes (22), there is a gain of 15-20 minutes in cross clamp time. In a study by Pourmoghadam et al (22), 225 congenital heart surgery cases were examined, del Nido cardioplegia was used in 107 patients and a decrease was reported in cardiac cross duration. A significant difference was reported in cardioplegia volume and cardioplegia application number.

The application potential of del Nido cardioplegia is also widened with increasing application frequency. Safe usage area is not limited to congenital heart surgery. In a study by Ota et al (23), 108 random patients among 240 patients were examined and the patients were separated into two groups. One of the groups was given blood cardioplegia and the other was given del Nido cardioplegia. It was observed that cardiopulmonary bypass durations, aortic cross clamp durations and postoperative supportive treatment ratios of the patients given del Nido cardioplegia were lower.

It was shown that del Nido cardioplegia use in elder patients prevented spontaneous contractions during arrest, decreased troponin level, increased urine output of the patients after operation and provided a good cardiac protection. It was also reported that the use of del Nido cardioplegia in coronary artery bypass surgery provided safe myocardial protection (25).

In line with the literature, we detected that del Nido cardioplegia provided efficient myocardial protection in our study. Compared to Group 1 in which blood cardioplegia is used, we observed that the cardioplegia amount used in Group 2 in which we applied del Nido cardioplegia was statistically significantly lower. We also detected that aortic cross clamp duration, the requirement of inotrope supportive treatment, postoperative extubation and discharge durations were statistically significantly lower in Group 2 compared to Group 1.

CONCLUSION

In our study, we compared the most common VSDs among congenital heart diseases with cardioplegias we use in isolated surgical operations. We observed that both of these provided myocardial protection. But we recommend the use of del Nido cardioplegia, which is administered a single-time and reduces inotropic need and duration of operation as well as significantly reduce extubation and discharge times, instead of blood cardioplegia which is given every twenty minutes. We detected that del Nido cardioplegia can be safely used although it is difficult to give a definitive judgment due to the inadequacy of our case count.

MATERIAL AND METHOD

A total of 1190 congenital heart operations were made in our Pediatric Cardiovascular Surgery Clinic between September 2013 and December 2017. Considering the homogenicity of the study, 186 patients who were operated with the same diagnosis and had isolated VSD operation were evaluated retrospectively. Written consent form was taken from all patients before the operation. Types of VSD stated during operation were noted by examining the surgery notes in patient epicrisis reports in detail. When there is inconformity among the preoperative diagnosis and perioperative VSD types, the type primarily observed and stated by the surgeon in surgery notes was taken as basis. According to Soto classification, 145 patients (79%) had perimembranous, 15 patients (8%) DCSA, 14 patients (7%) muscular and 12 patients (6%) had mixed type VSD. In 22 (11.8%) patients who had high pulmonary artery pressure, pressures were measured with pulmonary catheterization. Checking the pulmonary vascular resistance (PVR) of the patients through these pressure measurements, it was decided whether the patient could have operation or not. Surgical strategy in isolated VSDs was separated into three main groups as VSD closure with patch, primary closure or palliation with pulmonary artery band before VSD closure. We excluded pulmonary banding patients from our study.

Patients were divided into two groups as Group 1 (n = 108 using blood cardioplegia) and Group 2 (n = 78 using del Nido cardioplegia). Blood cardioplegia and del Nido cardiopagia solution was prepared in sterile conditions by anesthesia clinic during operation. del Nido cardioplegia solution (Boston Children's Hospital): was prepared by adding mannitol 20% 16.3 ml, magnesium suplhate 50%, 4 ml, potassium chloride (2 mEq/ml) 13 ml, lidocaine 1% 13 ml and sodium bicarbonate 8.4% 13 ml in1 litre plasma-lyte (140 mEq/L Sodium, 5 mEq/L Potassium, 3 mEq/L Magnesium, 98 mEq/L Chloride, 27 mEq/L Acetate, 23 mEq/L Gluconate) and was given with totally oxygenized blood with a ratio of 20%. During the operation, standardization was provided by giving blood cardioplegia once in every 20 minutes and del Nido cardioplegia once in every 60 minutes. Pre-operative data, peri-operative data and post-operative data of patients were retrospectively recorded and reviewed in detail.

Surgical approach

Esophageal heat prob was located before heparinisation for post-intubation heat control of the patients. Catheterization was applied primarily through right jugular vein for the central catheter in all patients. If this was not possible, left jugular vein was used. Invasive arterial pressure measurement was generally made through the left radial artery. Median sternotomy was made in all patients. Pericardium was carefully dissected and kept in glutaraldehyde containing fluid in patients in whom pericardium patch was going to be used and it was kept in a fluid containing glutaraldehyde. Then using blue branule needle on pulmonary artery before entering CPB, pulmonary artery pressure was measured invasively over the Y connection between radial artery line. This operation was made especially in patients with high pulmonary artery pressure before the surgery. After the required pericardium removal and pressure measurements, complete dose was heparinized according to the weights of the patients and suitable ACT (Activated Clotting Time) value was acquired and CPB was entered with aortic and bicaval cannulation. Cardiac arrest was provided with standard blood cardioplegia in Group 1 patients and with del Nido cardioplegia solution in Group 2 patients. All patients were operated with moderate hypothermia (30-32 ^{0}C). After vena cavae were covered with snare technique, VSD was reached through tricuspid valve anterior leaflet removal from right atriotomy. The repair was made through pulmonary arteriotomy (14 patients 7.5%) in DCSA VSDs which are difficult to reach and through right ventriculotomy in further muscular VSDs (2 patients, 1.07%). Transthoracic ecocardiography was made for residual VSD in postoperative period in all patients. Postoperative intubation, mechanic ventilation, intensive unit hospitalization and hospitalization duration were recorded for the patients.

Statistics

Statistical studies were made on registered data with IBM Statiscal Package for the Social Sciences 24.0 (SPSS 24.0, SPSS Inc, Chicago, IL) software. Mean± standard deviation (mean±SD) and percentages were used for descriptive statistics. For the comparison of Group 1 and Group 2, t test and Wilcoxon tests were used. p<0.05 was regarded as statistically significant in the comparisons.

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