Blood-Based Versus Crystalloid-Based Cardioplegia for Congenital Cardiac Surgery; A Prospective Observational Study

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ABSTRACT

Aim: To compare crystalloid-based cardioplegia (CBC) and blood-based cardioplegia (BBC) in terms of clinical, pharmacokinetic, and pharmacodynamic characteristics in the context of pediatric cardiac surgery.

Methods: This observational prospective study was conducted at the Queen Alia Heart Institute in the period between January 2020 and October 2020. 109 patients who presented for congenital cardiac surgery utilizing cardiopulmonary bypass with a period of myocardial ischemia were enrolled in this study. Patients had received either BBC (58 patients) or CBC (51 patients). Both groups of patients were compared according to their preoperative (sociodemographic, aetiology, and risk score) and intraoperative (heart rhythm after the removal of the aortic cross-clamp, the dose of cardioplegia received, the onset of action of the cardioplegic solution, the intraoperative blood potassium, need of intraoperative haemofiltration, blood lactate levels and other) variables. P-value <0.05 is used for statistical significance.

Results: One hundred and nine pediatric congenital cardiac surgical patients (60 males and 49 females) received either BBC or CBC solution after placement of aortic cross-clamp for the repair of a variety of cardiac malformations. The age range was from 3 days to 18 years (Median=2 years). Patients' body weights ranged from 2.7 to 93 kg (Median=15.7 kg). The time of onset of the arrest from commencing the cardioplegia averaged 36.41 seconds (SD ± 23.28 seconds) and did not differ significantly between the two methods ($p = 0.145$). Patients treated with the CBC method were significantly older U (109) =2002.5, $p = 0.001$, and had more bodyweight U (109) =2072.5 and length U (109) =2035.4 as well than those who had had the BBC method performed on them ($p \leq 0.001$) according to the Mann–Whitney U test. They were also found to be 5.88 times more predicted for V-Fib as compared to children operated under BBC ($p = 0.04$). BBC was associated with lower blood lactate levels ($p < 0.001$) and the significant spontaneous conversion to normal sinus rhythm after the end of the surgical repair ($p = 0.004$). More patients from the CBC group required haemofiltration intraoperatively than those from the BBC group $\chi 2$ (1) =6.68, p=0.011. Hyperkalaemia as a complication of cardioplegia was more common in the BBC group (p=0.04). Predictors of hyperkalaemia after cardioplegia were younger age (p=0.019), low body weight (p=0.031) and short stature/height (p=0.32).

Conclusion: BBC was found to be superior to CBC as demonstrated by the significantly lower lactate levels at the end of the surgery, higher rates of spontaneous normal sinus rhythm after removal of the aortic clamp and the lower need for hemofiltration.

Keywords: blood, cardioplegia, crystalloid, lactate, rhythm

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Introduction

In the last few decades, there have been important advances in understanding the causes of myocardial injury during heart surgery (1, 2). Myocardial protection during cardiac surgery is defined as the set of strategies aiming at decreasing myocardial oxygen consumption, adapting it to the momentary tissue supply and/or making

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cardiac cells more resistant to ischemic episodes (3). The basic principles of adequate myocardial protection include rapid induction of cardiac arrest after aortic cross-clamping, mild to moderate hypothermia, appropriate buffering of the cardioplegic solutions, and avoidance of substrate depletion and attenuation of cellular oedema. To achieve the goals of myocardial protection, different techniques of cardioplegic solutions were developed (4).

Cardioplegia (CP) is the most important method of myocardial protection during cardiac surgery (5). Different types of CP are available; however, they can simply be classified as crystalloid-based and blood-based. Both crystalloid-based cardioplegia (CBC) and blood-based cardioplegia (BBC) are widely used in pediatric cardiac surgery (6). The choice of cardioplegic solution depends on the surgeon's preference or the local institutional policy (7). The advantages of CBC are the relatively low price, the simplicity of use, and myocardial protection for up to 2 h after a single dose (8). BBC's potential advantages include oxygen transfer by the red blood cells to the myocardium, free radical scavenging properties and physiologic osmotic, and oncotic pressures that protect against myocardial oedema (9).

It has been suggested by many authors that BBC is superior to CBC in different aspects of myocardial protection during pediatric cardiac surgery (10, 11). However, the benefits of BBC compared to CBC are still debatable (12, 13). In this study, we sought to compare these two types of CP solutions in congenital cardiac surgery. The primary aim of this study is to compare the effect of both types of cardioplegia on intra-operative serum potassium and lactate. The secondary aim is to compare the incidence of restoration of spontaneous normal sinus rhythm upon aortic-cross clamp removal. The study also compares the onset of action, doses needed per body weight, cardiopulmonary bypass time associated with the use of each method of cardioplegia.

Methods

This observational prospective study took place at the Queen Alia Heart Institute in Amman, Jordan in the time between January 2020 and October 2020. One hundred and nine pediatric patients who were presenting for surgery for congenital heart disease were enrolled in this study. Patients' demographic, clinical, preoperative, intraoperative, and laboratory variables were recorded on a special form designed for this study. Out of the 109 patients, 46.8% of the patients received crystalloid-based cardioplegia (CBC group; n = 51), while the other 53.2% received blood-based cardioplegia (BBC group; n = 58). The two groups had their times of onset, doses needed to achieve electrical silence, blood potassium and lactate levels at the end of the procedure, and rates of ventricular fibrillation post the aortic clamp removal compared. Inclusion criteria included: surgery for congenital cardiac defect, utilization of cardiopulmonary bypass and aortic cross-clamping mandating the use of the cardioplegic solution. Exclusion criteria included surgery for acquired cardiac disease, off-pump cardiac surgery, surgeries that do not need aortic cross-clamping and cardioplegia, preoperative renal impairment, preoperative mechanical ventilation, and sepsis. The potassium and lactate levels were measured simultaneously with each arterial blood gas (ABG) sampling. ABGs lactate and electrolytes are routinely performed every 30 minutes during cardiopulmonary bypass (CPB). Additional sampling is usually done before aortic-clamp removal, before separation from CPB, before leaving the operative theatre and shortly after arrival to the ICU. The samples are taken from the sampling port of the CPB reservoir or the patient's arterial catheter and are analyzed without delay to allow monitoring and optimization.

Anesthetic technique was standardized for all patients and included Midazolam (0.1-0.2 mg/kg, Fentanyl 2-5 micrograms/kg and Rocuronium (0.6 mg/kg) for induction of anesthesia. Maintenance was achieved with Sevoflurane 2% +/- Propofol infusion (4-12 mg/kg/hour). Doses were calculated as per body weight and age.

St. Thomas cardioplegia was used in all patients. One litre of St. Thomas cardioplegia contains potassium chloride 16 mmol, magnesium chloride hexahydrate 16 mmol, procaine hydrochloride 1

mmol. The initial dose of cardioplegia was 10 ml/kg. Re-dosing was given in a dose of 10 ml/kg every 15 minutes in crystalloid-based and 10 ml/kg every 40 minutes in blood-based cardioplegia.

The blood cardioplegia system consists of a 1/4 inch tube that connects with the oxygenator and another 1/16 inch tube that connects with the crystalloid cardioplegic solution bag. Both connections are passed via a Y connector into the roller pump where the crystalloid cardioplegic solution is mixed with the patient's oxygenated blood in a ratio of 4:1, and then it is passed through a Y connector that will deliver into a single 1/4 inch tube that goes to the inlet of the cardioplegia heat exchanger. The outflow line from the heat exchanger connects with sterile connector 1/4 inch tubing that connects with cardioplegia needle. The needle is inserted in the aortic root to deliver blood cardioplegia antegrade to coronary Ostia.

The hemofilter is placed in parallel to the CPB circuit as a passive shunt from higher to lower pressure. The inflow to the hemofilter originates from a connection of the high-pressure arterial line and the outflow returns to a lower pressure connection located on the venous reservoir.

Ethical committee approval for this study was obtained from the institutional review board of the Royal Medical Services (number 10/6/2021) on the 2nd of May 2021.

Statistical Data Analysis: The mean and standard deviation were used to describe the continuously measured variables as well as the frequency and percentages for the categorically measured variables. The Kolmogorov–Smirnov statistical test and the histograms were used to test the statistical normality assumption for the continuously measured variables. The Mann–Whitney U non-parametric test was used to assess the statistical significance of the mean differences between the cardioplegias on the continuously measured outcomes. The mean and SD were quoted for these comparisons due to the lack of distributional differences between the compared groups and the intentions to report the actual mean and SD values of the measured parameters. The chi-squared test of independence was used to assess the association between the categorically measured variables; however, Fisher's exact chi-squared was used for the contingency tables with violations of the statistical assumptions. As a secondary analysis, the multivariate binary logistic regression analysis was used to understand what may explain why surgical CHD patients undergoing various CP methods develop more or less ventricular fibrillation (V-Fib) after the release of the aortic clamp, intra-operatively. The association between the tested predictor factors and risk factors with the patients' probability of developing V-Fib was expressed as an odds ratio (OR) with an associated 95% confidence interval.

Results

Table 1 displays the yielded findings from the descriptive analysis of the patients' sociodemographic characteristics at hospital admission time. Table 2 displays the resultant descriptive analysis of the congenital cardiac surgical procedures and the intraoperative characteristics. The mean time required for the onset of the cardiac arrest from starting the cardioplegia (onset of action) was 36.88 seconds (SD = 23.52 seconds). The total administered dose of the cardioplegic agent per kilogram body weight at onset of cardiac arrest was equal to 11 mL (SD ± 6.69 mL); however, the mean total dose administered to the children per each kilogram of their weight per minute during the actual aortic cross-clamp time (ACCT) was measured 0.50 ml/Kg/minute. Almost half of the patients (45%) had required adjustment (re-dosing) of their cardioplegic agents, and 12.8% of them had required hemofiltration during the surgery. In addition, the mean serum potassium level at the end of the surgery was measured with 4.77 mmol/L (SD = 0.89 mmol/L) and 20.2% of patients had hyperkalaemia (k+>=5.5 mmol/L) after receiving the cardioplegia solution. The total ACCT was measured with a mean time equal to 49.97 minutes (SD=23.21 minutes) and the total cardiopulmonary bypass time (CPBT) for the patients was measured with 85.98 minutes on average (SD = 39. 1 minute). The children's immediate post-operative serum lactate level was measured with 1.53 mmol/L on average (SD=0.81 mmol/L).

The cardiac rhythm after aortic clamp release was distributed as follows: the majority of the children (82.6%) had normal sinus rhythm (NSR); however, 6.4% of them had required temporary pacemaker as an adjunct therapy and 11% had ventricular fibrillation that required immediate cardioversion.

Patients who operated for CHD treated with the two CP methods were compared with bivariate analysis methods. The resulted findings in Table 3 demonstrated that there was no statistically significant association/correlation between the patients' sex and the used CP method ($p = 0.116$) according to the chi-squared test of independence ($\chi 2=2.47$). However, the children's age had converged significantly on the used CP method, as children treated with the CBC method were significantly older according to the non-parametric Mann–Whitney U test ($p < 0.001$). A chi-squared test comparing the children's age groups also showed that patients aged 4–9 years and those aged above 10 years were significantly more predicted for receiving CBC compared to those younger than four years old ($p < 0.001$). The time until the onset of the arrest from commencing the CP did not differ significantly between the two cohorts, but the administered dose of CP agent at the onset of arrest differed significantly between children who received the two CP methods. Patients who received CBC required significantly more CP agent amount compared to those children who had received BBC ($p < 0.001$); however, the weight standardized dose of cardioplegia agent during the ACCT did not differ significantly between the two used CP methods ($p = 0.521$). Nonetheless, the children who had received CBC were found to be significantly more predicted for requiring dose re-adjustments (i.e., re-dosing) compared to those children who had received BBC ($p < 0.001$). Further, children who had received CBC were found to be significantly more inclined to require hemofiltration intraoperatively than those operated under BBC ($p = 0.011$) according to the chi-squared test of association ($\chi 2(1)=6.68$).

Serum potassium post-clamp release was slight, though not significantly, lower for the children treated with CBC compared to those treated with the BBC ($p = 0.139$). However, the occurrence of hyperkalaemia (k+>=5.5 mmol/L) was more common among patients of the BBC group ($p=0.040$). Interestingly, the post-operative serum lactate levels were significantly higher for the children who had received the CBC compared to those treated with the BBC method ($p < 0.001$).

Another non-parametric Mann–Whitney U test showed that the children who were operated under CBC required significantly lower mean ACCT and total CPBT compared to those treated under the BBC method on average ($p < 0.001$).

Patients' immediate post-aortic clamp release cardiac rhythm had converged significantly on the type of CP; it was found that the children operated under the CBC method were found to be significantly less inclined to NSR compared to those treated under the BBC method ($p = 0.01$). Moreover, the CHD patients who had received treatment with the CBC method were found to be significantly more predicted for V-Fib right after the release of the ACC compared to children operated with the BBC method ($p = 0.038$) according to the chi-squared test ($\chi 2(1)=4.31$).

As a secondary analysis, the odds of developing V-Fib immediately after the release of the ACC after the cardiac surgical repair were analyzed further with the multivariate logistic binary regression analysis (Table 4). Age had correlated non-significantly with their odds of having had V-Fib ($p = 0.082$). When age rose by one year, the odds of V-Fib immediately post aortic clamp release tended to rise by a factor equal to 1.189 times (or 118.9% times more) on average, accounting for the other predictors in the analysis model. Moreover, intra-operative serum potassium level had correlated significantly and positively (OR = 6.405) with the odds of developing V-Fib upon aortic clamp removal ($p = 0.026$). Furthermore, the children who had received the CCB method were found to be 7.327 times more predicted for V-Fib compared to children operated under BBC on average ($p = 0.026$) according to the multivariate binary logistic regression model.

Patients' sociodemographic characteristics, as well as their clinical parameters, were compared between children who developed hyperkalemia and those who did not. The resulting bivariate analysis, table-5, showed that patients' sex did not converge significantly on hyperkalemia, but patients who had hyperkalemia were found to be significantly younger, p=0.019. Patients aged<= 1 year were

indeed significantly more predicted for hyperkalemia compared to children older than one year in general, p=0.031. Patients who developed hyperkalemia were significantly less weighty than those who did not have hyperkalemia, p=0.031. Also, the hyperkalemic patients were indeed significantly shorter than those who had no hyperkalemia, p=0.032. But, the onset of action and the total cardioplegic dose at the onset of cardiac arrest as well as the weight standardized dose of cardioplegic agents did not differ significantly between those who developed and those who did not develop hyperkalaemia after receiving cardioplegia. Postoperatively, the CBC group had a shorter average intensive care unit length of stay (3.3 days) than the BBC group (4.5 days). The 30-day mortality was also less in the CBC group (2.5%) than in the BBC group (5.8%).

Table i: Descriptive analysis of the patients' sociodemographic characteristics. N=109

	Frequency	Percentage
Sex		
Female	49	45
Male	60	55
Age (years), mean (SD)		3.75 (4.4)
Age group		
<1 year	24	22
<=3 years	46	42.2
4-6 years	18	16.5
7-9 years	8	7.3
>=10 years	13	11.9
Weight (Kg) , mean(SD)		15.12 (13.86)
Height (centimetres), mean(SD)		88.03 (31.78)

Table II: Descriptive analysis of the congenital heart disease patients' cardiac operative and surgical outcomes

	Frequency	Percentage
Type of cardiac surgery		
Complete atrioventricular canal (CAVC) repair	3	2.8
Arterial switch repair	6	5.5
Other *	14	12.8
Ventricular septal defect (VSD) repair	37	33.9
Sub-aortic membrane (SAM) excision	9	8.3
Tetralogy of Fallot (TOF) repair	12	11
Atrial septal defect (ASD) repair	19	17.4
Aortic valvotomy/Aortic valve repair (AVR)	6	5.5
Pulmonary valvotomy/Pulmonary valve repair (PVR)	5	4.6
Total anomalous pulmonary venous circulation (TAPVC)	3	2.8
Mitral Valve repair MVR	5	4.6
Type of cardioplegic method used		
Blood	58	53.2
Crystalloid	51	46.8
The onset of arrest (in seconds) (onset of action)		36.41 (23.28)
Administered dose of a cardioplegic agent at the onset of arrest per kilogram bodyweight		11.02 (6.69)
Total dose (Kg/min) during the aortic cross-clamp time (ACCT)		0.50 (0.22)

Discussion

Myocardial protection plays a key role in achieving successful outcomes in cardiac surgery (14). The choice of the optimal cardioplegic technique to protect the pediatric heart during pediatric cardiac surgery remains a significant clinical debate (15). Solutions for myocardial protection can be divided by their chemical composition (and additives), according to the temperature at which they are administered (cold, tepid, or warm), or according to the component that is used to transmit the cardioplegic component (crystalloid vs blood) (16). There is controversy regarding which cardioplegic solution provides superior myocardial protection. The largest randomized clinical trials (RCT) that compare BBC and CBC were performed by Ovrum and Martin (17, 18). The trial by Ovrum and colleagues from the University of Oslo randomized 1440 adult cardiac surgical patients to antegrade cold blood or crystalloid and found no significant clinical differences between the two methods (17). Additionally, Martin and colleagues from the Emory University School of Medicine, Atlanta, randomized 1001 adult cardiac surgical patients and found no difference in mortality, use of inotropes or intra-aortic balloon pump, intensive care unit length of stay or hospitalization time between the two cohorts (18). Similarly, Young examined the superiority of BBC in a prospective randomized trial in pediatric CHD surgical patients and concluded that there was no clear superiority of BBC over CBC (19). On the other hand, a meta-analysis that included 5044 patients from 34 studies by Guru demonstrated the superiority of BBC over CBC (20) while Shahzad emphasized the advantages of BBC in pediatric CHD for cyanotic cardiac anomalies only (21). Pediatric myocardial protection protocols are generally based on practical experience, and institutions have developed their myocardial protection protocols that have proven to be effective and safe (22).

In our study, we found a positive and significant correlation between the use of the BBC method and smaller age ($p < 0.001$), low body weight ($p < 0.001$), longer cardiopulmonary bypass, and aortic cross-clamp duration ($p < 0.001$). Besides, we found a positive correlation between the use of BBC and two types of surgical procedures; the ventricular septal defect repair ($p=0.003$) and the arterial switch surgery for the transposition of great vessels ($p = 0.05$), which can be explained by the smaller age and bodyweight of this group of patients and the complexity of this procedure. However, there was no significant correlation between the use of BBC and surgery for other cyanotic cardiac defects such as tetralogy of Fallot ($p = 0.109$). This can be explained by the relatively older age and higher body weight at the time of presentation for definitive surgery, which is usually at the end of the first year of age. On the other hand, our results showed more extensive use of CBC for simple or STAT category 1 procedures, such as the repair of atrial septal defects or ventricular septal defects ($p = 0.001$ and $p = 0.002$, respectively). For such procedures, a single administration of CBC is usually sufficient for myocardial protection for the relatively short cross-clamp time.

We compared some of the pharmacokinetic characteristics of both BBC and CBC. There was no significant difference in the onset of action or in the total dose per kilogram body weight per minute of the actual aortic cross-clamp time. However, the use of CBC needed re-administration more frequently ($p < 0.001$), which may cause repeated interruptions of the flow of surgery due to the shorter duration of action of CBC. Both types of CP investigated in this study are of the depolarizing hyperkalemic type. Blood potassium levels at the end of surgery did not differ significantly ($p = 0.063$). Nevertheless, we found a positive correlation between the use of CBC and the use of intraoperative hemofiltration ($p = 0.015$). This is explained by hemodilution, a well-known complication of CBC in the pediatric subpopulation of cardiac surgery. This association was also observed by Gunday, who considered CBC as a strong predictor of hemodilution in pediatric cardiac surgical patients (23).

The two major findings of our study are the clinically significant lower blood lactate levels measured at the end of surgery in the BBC group ($p < 0.001$) and the clinically significant spontaneous conversion to NSR after the release of the aortic cross-clamp at the end of the surgical repair ($p = 0.004$). This is explained by the fact that BBC provides a closer approximation to normal physiology, which may translate into measurable clinical benefits.

We further investigated the odds of developing ventricular fibrillation after the release of aortic cross-clamp with a secondary multivariate logistic regression analysis, which showed that the CBC method was a significant predictor for the development of ventricular fibrillation. Another side effect of the cardioplegic solution is hyperkalaemia (Figure 1). Kant et al. reported hyperkalaemia complicating CPB during pediatric cardiac surgery (24). We further investigated this complication in our study. Patients who received BBC were more prone to this complication (p=0.04). Predictors of developing hyperkalaemia were younger age (p=0.019), lower body weight (p=0.031), and shorter length/height patients (p=0.032).

Limitations

There are a few limitations to this study. Firstly, the relatively small sample size (109) arises from the fact that a large proportion of pediatric cardiac surgeries is done without the need for aortic clamping and cardioplegia. Furthermore, congenital heart diseases are very heterogeneous regarding the severity of the lesions and complexity of the surgical procedures performed. Hence, it was impossible to eliminate all factors affecting the postoperative outcome or attribute the outcome solely to the type of cardioplegia.

Figure 1: Correlation between plasma potassium level and the mean predicted probability of ventricular fibrillation after removal of aortic clamp.

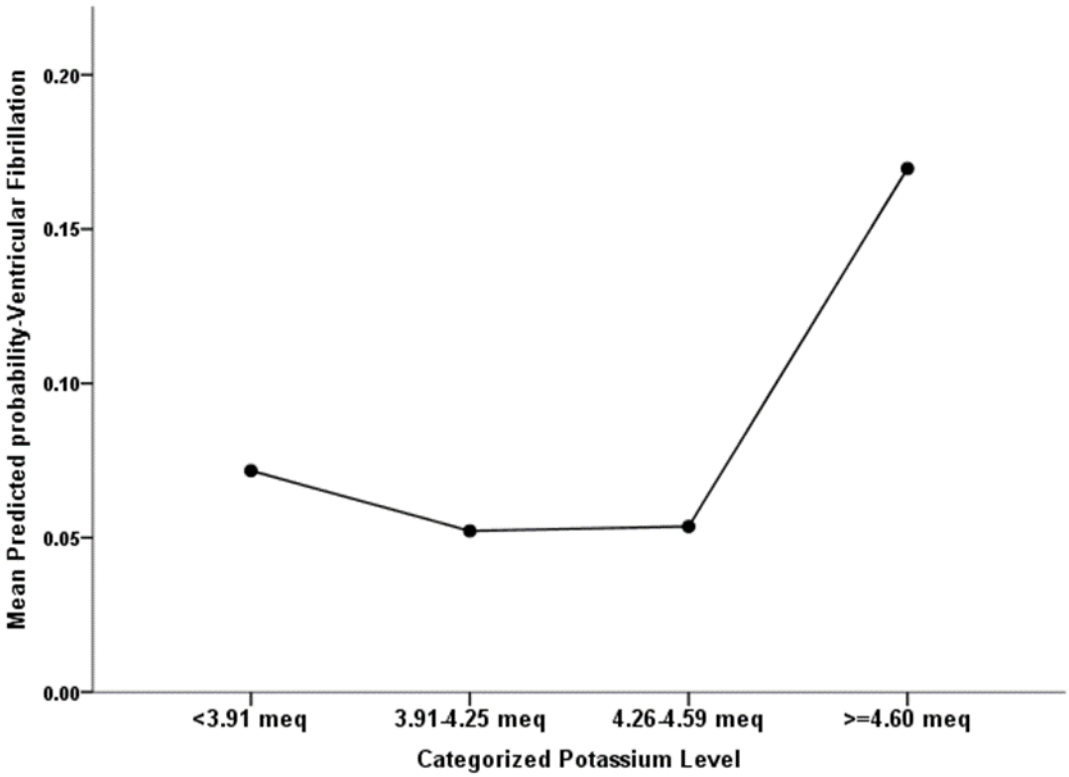

Figure 1: Correlation between plasma potassium level and the mean predicted probability of ventricular fibrillation after removal of aortic-clamp.

Conclusion

Blood is a more physiological vehicle of cardioplegia than crystalloid solutions. Blood-based cardioplegia was associated with lower lactate levels at the end of pediatric cardiac surgery and higher rates of spontaneous normal sinus rhythm after the removal of the aortic cross-clamp.

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