

Comparative Study between Three Solutions for Cardioplegia in Pediatric Cardiac Surgery: Histidine-Tryptophan-Ketoglutarate (HTK) Solution, Blood Cardioplegia and Crystalloid (St. Thomas) Cardioplegia

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Abstract

Background: Cardioplegia is the solution used to arrest and protect the heart during aortic cross-clamping. Crystalloid and blood cardioplegia are both widely used in clinical practice. Custodial-HTK solution is an intracellular cardioplegic solution containing histidine, tryptophan and ketoglutarate.

Aim: we compared the myocardial protective effects of 3 types of cardioplegia solution: The histidine-tryptophan-ketoglutarate (HTK) solution, blood and St.Thomas cardioplegia in pediatric cardiac surgery.

Settings and Design: This study design was a prospective randomized controlled double blinded clinical study.

Patients and Methods: 60 children aged 3-10 yrs of either sex who underwent elective cardiac surgery for acyanotic heart diseases using cardiopulmonary bypass were randomly allocated to three groups each one 20 patients: Group A received HTK cardioplegia. Group B received blood cardioplegia. Group C received St. Thomas cardioplegia. Hemodynamic parameters, duration of CPB, aortic cross clamping and the whole surgical duration, mechanical ventilation duration and the length of ICU stay were measured. Venous blood samples were collected for measurement of cardiac marker proteins (CK-MB) and troponin (t). Uses of inotropic support were also recorded.

Statistical Analysis Used: one-way ANOVA test and Chi-square test were used. Results: The main findings in our results were that troponin (t) levels were not statistically significant different among the study groups except that recorded 24 h, with the highest level was in the group (B) and the lowest one in the group (C). CK-MB levels also were not statistically significant different among the study groups except that recorded after 12 h the highest one in group (C) and the lowest one in group (B).

Conclusion: Single dose of cold HTK cardioplegia in pediatric cardiac surgery is as effective as multiple doses of cold blood and crystalloid (St.Thomas) cardioplegia in protecting the myocardium.

Keywords: Cardioplegia; Myocardial protection; Pediatric cardiac surgery

Introduction

Cardioplegic arrest is one of the most common myocardial protection strategies [1]. It is used for patients of all ages requiring cardiac surgery in which the heart must be stopped [2]. Pediatric patients are at high risk of cardiac ischemic injury, which is due to reduced free radical scavenging, increased sensitivity to calcium, and unknown factors related to the unique environment of the cyanotic heart. Meanwhile, the immature heart's unique physiology including, the preference for glucose as a substrate, large stores of glycogen and the low activity of 5'-nucleotidase, could provide some protection against ischemic damage. Together with therapeutic hypothermia, cardioplegia can supplement metabolic substrate and decrease cardiac oxygen consumption [3]. Cardioplegia for infant and pediatric patients was originally the same as that used for adults and was simply adjusted for volume, flow, and pressure [4]. A wide variety of cardioplegic solutions are routinely being used. There is an ongoing discussion

about the relative effectiveness of these solutions considering myocardial protection [1]. The cardioplegic solutions can be classified into two main groups. One is based on extracellular components with high potassium, magnesium and bicarbonate levels, while the other is based on intracellular electrolytes. Blood and crystalloid cardioplegia are the main myocardial protective solutions used in pediatric cardiac surgery [3]. The histidine-tryptophan-ketoglutarate (HTK) solution is used widely for multiorgan preservation for transplantation, but it is also recognized as a cardioplegic agent that allows single dose administration [5]. Cardioplegia with HTK-Custodiol or Bretschneider solution for cardiac arrest during cardiac operations has been widely used clinically. It is simple to use, administered as one single dose, and it is claimed to give sufficient myocardial protection for more than 2 h of cardiac arrest [6]. Each liter of HTK Custodiol cardioplegia contained: $\text{Na}^+ \rightarrow 15 \text{ mmol.l}^{-1}$, $\text{K}^+ \rightarrow 9 \text{ mmol.l}^{-1}$, $\text{Mg}^{++} \rightarrow 4 \text{ mmol.l}^{-1}$, $\text{Ca}^{++} \rightarrow 0.015 \text{ mmol.l}^{-1}$, Histidine $\rightarrow 198 \text{ mmol.l}^{-1}$, Tryptophan $\rightarrow 2 \text{ mmol.l}^{-1}$, ketoglutarate $\rightarrow \text{mmol.l}^{-1}$, Mannitol $\rightarrow 30 \text{ mmol.l}^{-1}$. Ph 7.02-7.20 [7]. Blood cardioplegia components are usually: $\text{Na}^+ \rightarrow 118 \text{ mEq.l}^{-1}$, $\text{K}^+ \rightarrow 18 \text{ mEq.l}^{-1}$, $\text{Mg}^{++} \rightarrow 1.6 \text{ mEq.l}^{-1}$, $\text{Ca}^{++} \rightarrow 0.3-0.5 \text{ mEq.l}^{-1}$ and

PH 7.6-7.8 [8]. St. Thomas' Hospital solution is the most popular crystalloid cardioplegia available and has been used worldwide [9]. Components of St.Thomas cardioplegia are $\text{Na}^+ \rightarrow 144 \text{ mEq.l}^{-1}$, $\text{K}^+ \rightarrow 20 \text{ mEq.l}^{-1}$, $\text{Mg}^{++} \rightarrow 32 \text{ mEq.l}^{-1}$, $\text{Ca}^{++} \rightarrow 4.8 \text{ mEq.l}^{-1}$ and PH 5.5 [8]. The aim of this study is to compare the myocardial protective effects of HTK, blood and St.Thomas cardioplegia in pediatric cardiac surgery.

Patients and Methods

The Ethical Committee of our institute approved this randomized prospective double-blinded controlled study to be done in Cairo National heart institute for two years (from June 2015 to October 2017) on 60 children Scheduled for elective cardiac surgery for acyanotic heart diseases using cardiopulmonary bypass after obtaining a written informed consent for anesthesia from each parent and assent from children after explaining to them the nature of study and complications.

Inclusion Criteria

Included 60 children aged 3-10 yrs of either sex who were admitted to Cairo National heart institute for elective cardiac surgery for acyanotic heart diseases under cardiopulmonary bypass.

Exclusion criteria

Patients with redo cardiac surgery endocarditis, heart failure, moderate to severe pulmonary hypertension, neurological, renal, hepatic and pulmonary diseases.

Patients were randomly allocated to three groups: Group A (20 patients) received HTK cardioplegia. Group B (20 patients) received blood cardioplegia. Group C (20 patients) received St.Thomas cardioplegia. All patients were subjected to a preoperative clinical examination and routine preoperative laboratory investigations including complete blood count, arterial blood gases, coagulation profile (including prothrombin time, partial thromboplastin time, bleeding time, INR and activated clotting time), liver and renal function tests were performed. Radiological examination in the form of chest x-ray and echocardiography was done.

All patients were premedicated in the preoperative area with intramuscular ketamine 7 mg.kg^{-1} , midazolam $0.1-0.15 \text{ mg.kg}^{-1}$ and atropine sulfate 0.01 mg.kg^{-1} min before induction of general anesthesia. ECG, peripheral oxygen saturation and noninvasive blood pressure were monitored. Supplemental oxygen was given through a face mask. A peripheral intravenous cannula was inserted then induction of anesthesia was induced by thiopental 5 mg.kg^{-1} . Patients received IV fentanyl 2 mcg.kg^{-1} and atracurium 0.5 mg.kg^{-1} as a muscle relaxant to facilitate intubation. Patients were mechanically ventilated with 50% O_2 and the end-tidal CO_2 was monitored with capnography and maintained between 30 and 35 mmHg. Anesthesia was maintained by sevoflurane, atracurium infusion at a rate of $5-12 \text{ mcg.kg.min}^{-1}$ and fentanyl $0.05 \text{ mcg.kg.min}^{-1}$. A radial artery catheter (22G) was inserted to monitor the arterial blood pressure and blood gas sampling during the entire procedure. A central venous catheter was inserted under complete aseptic conditions; urinary catheter was also placed to monitor urine output. Core body temperature was monitored through nasopharyngeal probe hypothermia was prevented before and after CPB by using warmer. Anticoagulation was established, while the aortic purse string sutures were placed before cannulation, with an initial bolus $300-400 \text{ IU.kg}^{-1}$ of heparin sodium to get activated clotting

time (ACT) higher than 480 sec. After cannulation of the ascending aorta, superior vena cava and inferior vena cava, CPB started. Systemic body temperature was maintained at ($25^\circ-28^\circ\text{C}$). After aortic cross-clamping, the cardioplegic solution was administered at a pressure of 50-70mmHg. In group A, patients received 30 ml.kg^{-1} of HTK cardioplegic solution once. The cardioplegic solution was administered at a temperature of $4-8^\circ\text{C}$.

In group B, patients received 20 ml.kg^{-1} of cold oxygenated blood cardioplegia (crystalloid solutions+blood till Hct become 25%) or mixed at a ratio of 1:4 (cardioplegic solution: blood) and then $10 \text{ ml.kg.dose}^{-1}$ every 30 min. The cardioplegic solution may have small variations in individual variables. The cardioplegic solution was administered at a temperature of $4-8^\circ\text{C}$. In group C, patients received 20 ml.kg^{-1} of St.Thomas crystalloid cardioplegia then $10 \text{ ml.kg.dose}^{-1}$ every 30 min. The cardioplegic solution was administered at a temperature of $4-8^\circ\text{C}$. Cardioplegia solutions were given over 5-7 min. and aortic root pressure was kept between 40-50 mm Hg.

Before weaning from CPB, all patients were rewarmed to 37°C then weaning was started followed by removal of venous cannulae and filtration. After that, heparin was neutralized with protamine sulfate to regain normal ACT.

The following parameters were measured: hemodynamic parameters including heart rate, arterial blood pressure (systolic, diastolic and mean), peripheral oxygen saturation were measured continuously during the whole duration of surgery and ICU stay and were recorded pre induction, post induction and every 30 min during the duration of surgery. Arterial blood gases (ABG) and central venous pressure (CVP) were measured as a baseline, before and after CPB, at the end of the operation and every 6 h in the ICU or when indicated.

- Venous blood samples were collected for measurement of cardiac marker proteins [creatin kinase MB (CK-MB) and troponin T levels] 6h, 12h, 24h postoperatively. The upper normal reference limit of serum cardiac troponin T is less than 0.1 ng.ml^{-1} and that of serum CK-MB is less than 5 ng.ml^{-1} .

- Duration of CPB, aortic cross clamping and the whole surgical duration.

- Use of inotropic support, requirement for defibrillations, postoperative pacemaker requirements.

- Mechanical ventilation time, length of ICU stay.

Statistical Analysis

Sample size was calculated using G power program 3.1.7 (Universitat Kiel, Germany), Data was collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 under windows7. Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data, and inferential statistic test: For quantitative parametric data: one way ANOVA test in comparing more than two independent groups of quantitative data. For quantitative non parametric data: Non Paired variables \rightarrow Kruskal Wallis test used in comparing more than two independent groups. Mann-Whitney test in comparing two independent groups. Paired variables \rightarrow Wilcoxon tests used in comparing two groups of dependent data. Friedman test used in comparing more than two groups of dependent data. Paired t-test in

comparing two dependent quantitative data. For qualitative data: Chi square test to compare two of more than two qualitative groups. The level $P \leq 0.05$ was considered the cut-off value for significance.

Results

Our study included 60 children aged 3-10 years of either sex in Cairo National heart institute, randomly allocated to three groups: Group A (20 patients) received HTK cardioplegia. Group B (20 patients) received blood cardioplegia. Group C (20 patients) received St.Thomas cardioplegia.

Regarding the demographic data there was no statistically significant difference between the study groups (Table 1).

The hemodynamic variables measured before and all over the duration of operation showed no statistically significant differences between the study groups (Figures 1 and 2).

Regarding duration of CPB, aortic cross clamping time and the whole surgical duration, there was no significant statistical difference between the study groups (P value >0.05). On the other hand, there was statistical significant difference with p -value=0.001 between different study groups regarding extubation time, time of mechanical ventilation, and length of ICU stay with highest mean among group (B) (Table 2).

There was statistically significant difference with p -value <0.05 between the different study groups regarding the use of inotropic support with highest percentage (100%) of use in group A, followed by (90%) for group C and lowest percentage for group B, (Figure 2).

Troponin(t) levels recorded 6 and 12 h after the operation were not statistically significant different among the study groups however that recorded 24 h after the operation was significant between them with the highest level in the group (B) ($28.1\text{ng/ml} \pm 2.4$) and the lowest one in the group (C) ($24.5\text{ng/ml} \pm 3$) (Figure 3).

There was statistically significant difference with p -value <0.05 between the different study groups regarding CK-MB level after 12 h with there was no statistical significant difference with p -value >0.05 between the different study groups regarding CK-MB level after 6 and 24 h postoperative (Figure 5).

Variables		Group A (n=20)	Group B (n=20)	Group C (n=20)	p-value
		Mean \pm SD	Mean \pm SD	Mean \pm SD	
Age (years)		4.6 \pm 1.5	4.7 \pm 1.6	5.4 \pm 2.1	0.4
Weight (kg)		17.4 \pm 3.9	17.3 \pm 3.5	18.4 \pm 4.8	0.7
Height (cm)		106.9 \pm 12	108.1 \pm 12.8	109.6 \pm 13.4	0.8
Sex	male	9 (45%)	9 (45%)	10 (50%)	0.9
	female	11 (55%)	11 (55%)	10 (50%)	

Group A: HTK cardioplegia; Group B: Blood Cardioplegia; Group C: St Thomas cardioplegia; SD: Standard Deviation.

Table 1: Demographic data in the different study groups.

	Group A (n=20)		Group B (n=20)		Group C (n=20)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Duration of CPB (min)	95.7	11.8	94.6	12.3	90.1	15.3	0.4
Duration of surgery (h)	4.2	0.8	4.4	0.9	4.3	0.8	0.9
Cross clamp time (min)	65.3	13.6	61.2	16.3	61.3	18.3	0.7
Extubation time (h)	1.5	0.4	5.1	0.6	3.3	1.2	$<0.001^{**}$ a,b,c
Mechanical ventilation time (h)	5.2	0.8	8.5	1.1	6.9	1.8	$<0.001^{**}$ a,b,c
ICU stay (h)	17.1	3.5	58.8	10.9	55.9	10.6	$<0.001^{**}$ a,c

Group A: HTK cardioplegia; Group B: Blood cardioplegia; Group C: St Thomas cardioplegia; a: Statistical Significance between Group A and B; b: Statistical Significance between Group B and C; c: statistical significance between group A and C; **: High Statistically Significant Difference; ICU: Intensive Care Unit; CPB: Cardiopulmonary Bypass; Min: Minute; h: hours.

Table 2: Duration of CPB, the whole surgical duration, aortic cross clamping time, extubation time, time of mechanical ventilation, and length of ICU stay in the different study groups.

Discussion

In the present study, we compared the myocardial protective effects of 3types of cardioplegia solution: The histidine-tryptophan-ketoglutarate (HTK) solution, blood and St.Thomas cardioplegia in pediatric cardiac surgery.

Comparing the demographic data, hemodynamic variables, arterial blood gases and central venous pressure readings among the study groups was not statistically significant different.

Duration of CPB, aortic cross clamp time and the whole surgical duration were also not statistically significant in the three study groups.

Similar results were found by El-Morsy et al. [13] (who studied the type of cardioplegia and their effect on myocardial and cerebral outcome in pediatric open cardiac surgeries) as regarding CPB duration which was not significant between (HTK group) and (blood cardioplegia group). LIU J et al [14] reported that the duration of CPB did not differ between HTK group and St. Thomas group S and that was similar to our study. On the other hand, the aortic cross-clamping

time in HTK group was shorter than that in St. Thomas group and that was different from our results.

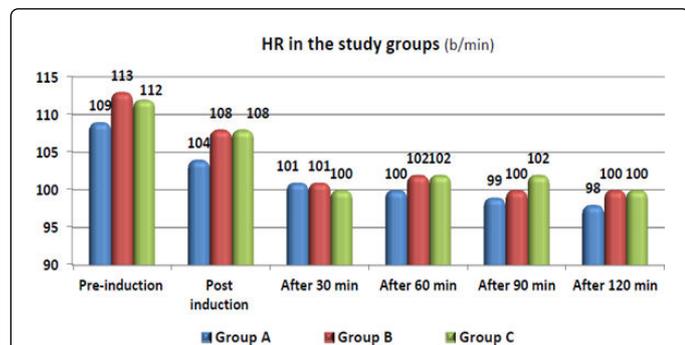


Figure 1: HR in the study groups.

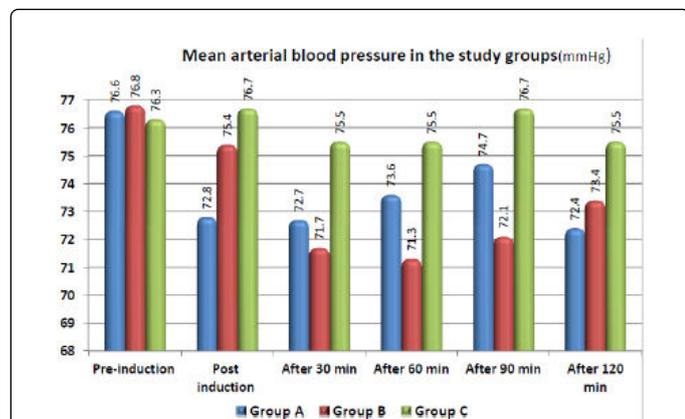


Figure 2: Mean arterial blood pressure in the study groups.

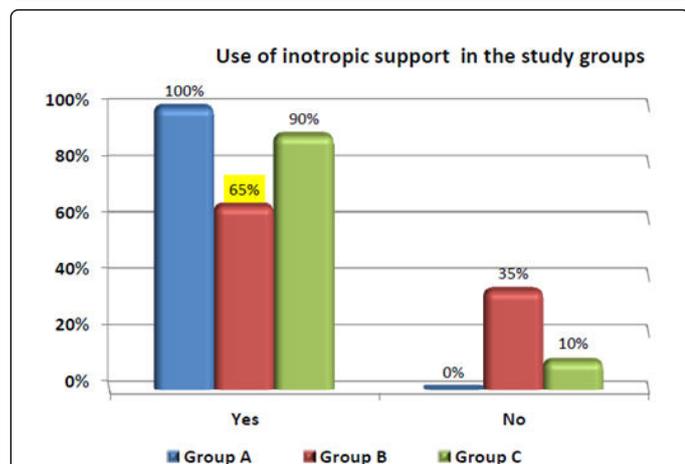


Figure 3: Use of inotropic support in the study groups.

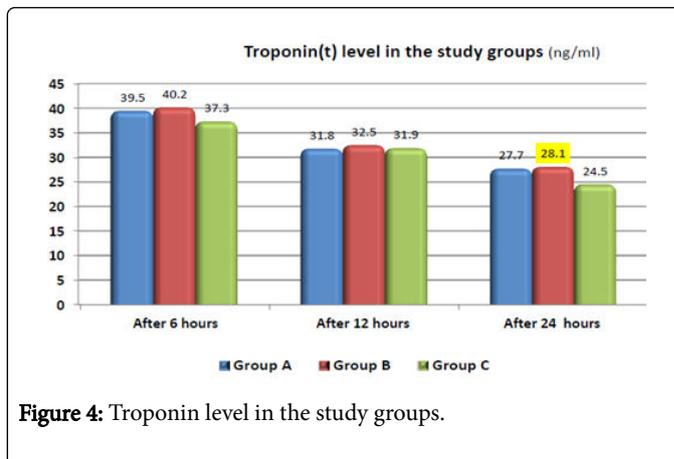


Figure 4: Troponin level in the study groups.

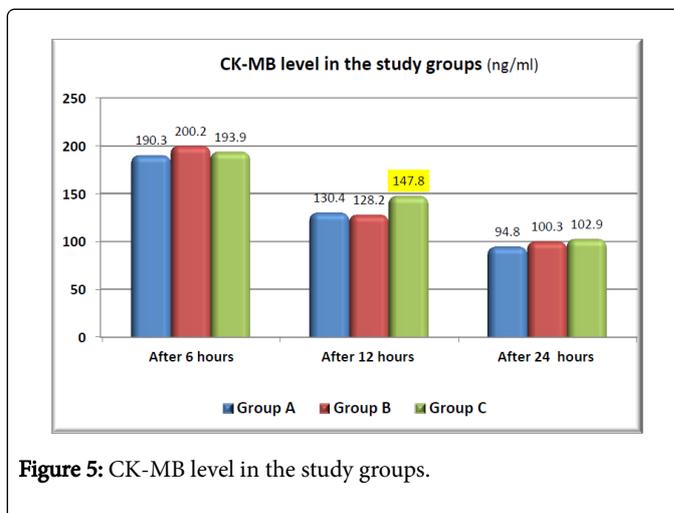


Figure 5: CK-MB level in the study groups.

Regarding extubation time, time of mechanical ventilation, and length of ICU stay, there were statistically significant differences between the three study groups with the longest time was in the group (B) and the shortest one was in the group (A). There were (1.5hrs ± 0.4), (5.2hrs ± 0.8), (17.1hrs ± 0.3) in group (A), (5.1hrs ± 0.6), (8.5hrs ± 1.1), (58.8hrs ± 10.9) in group (B) and (3.3hrs ± 1.2), (6.9hrs ± 1.8), (55.9hrs ± 10.6) in group (C). Li et al. [15] also found in their study that there was shorter length-of-stays in the intensive care unit with less mortality with HTK cardioplegia compared to St. Thomas' cardioplegia. Kuslu et al. [16], (who studied the effects of HTK solution and crystalloid cardioplegia on myocardial protection during pediatric cardiac surgery) found both groups had the same results regarding duration of mechanical ventilation and length of ICU stay and that was different from our study.

The highest percentage of patients needed inotropic support after CPB was reported in group (A) however the lowest one was in group (B), so there were statistical significance differences between the different study groups regarding the need for inotropic support.

Troponin(t) levels recorded 6 and 12 h after the operation were not statistically significant different among the study groups however that recorded 24 h after the operation was significant between them with the highest level in the group (B) (28.1ng/ml ± 2.4) and the lowest one in the group (C) (24.5 ng/ml ± 3).

Regarding CK-MB level, there was statistically significant difference after 12 h between the study groups with the highest mean in group (C) (147.8 ng/ml \pm 28.1) and the lowest one in group (B) (128.2 ng/ml \pm 24.6). On the other hand there was no statistically significant difference between the different study groups regarding CK-MB level after 6 and 24 h postoperative. In each study group there was a gradual statistical decrease in troponin (t) level and CK-MB level after 12 and 24 h, so there was statistically significant difference between troponin and CK-MB levels at 6, 12 and 24 h postoperative in the same group.

The present study demonstrated that there is no superiority of HTK solution (however, there is an implication of better myocardial protection with HTK on longer cross-clamp times), cold blood and crystalloid cardioplegia to each other for myocardial protection during pediatric cardiac surgery, although troponin (t) and CK-MB levels was higher in blood cardioplegia group and crystalloid cardioplegia group respectively. But that was not strong enough for HTK group to have the superiority as it was recorded at one interval among three intervals (12h for troponin (t) and 24 h for CK-MB).

Similarly, a meta-analysis performed by Fang et al [3], found that the cardiac specific isoform of troponin I (cTnI) release postoperatively was not significantly different between blood cardioplegia versus crystalloid cardioplegia with no evidence of improvement in myocardial damage or clinical outcome for either cardioplegia solution. Also, Kuslu et al. [16] found that there was no significant difference between HTK and crystalloid cardioplegia as regarding CK-MB levels. On the other hand, El-Morsy et al. [13] found that cardiac enzymes (CK-MB and troponin (t)) were significantly higher in blood group than HTK group.

Braathen et al. [10] found that patients receiving cold crystalloid cardioplegia had approximately double the circulating levels of CK-MB and troponin-t than patients receiving cold blood cardioplegia, indicating greater myocardial damage, which was against our results as we found that there was nearly no difference between them (except after one interval among three). In their study there was a significant positive correlation between cross-clamp time up to 2 h and cardiac enzymes levels in patients receiving cold cardioplegia only suggesting that the increase in the enzyme levels is explained by the cross clamp time.

Korun [1] and colleagues (who studied the effects of Bretschneider's histidine-tryptophan-ketoglutarate and conventional crystalloid cardioplegia on pediatric myocardium at tissue level), reported no significant difference in clinical outcomes of pediatric patients undergoing surgery for congenital heart disease.

Limitations of the Study

This study had some limitations which include a relatively small sample size in proportion to the importance of the topic. The present study was performed on patients with a simple congenital anomalies (acyanotic congenital heart disease) reflecting a shorter operation time, bypass and aortic cross clamp time. The surgeons were not blind to which type of cardioplegia was being used.

Recommendations

We recommend further studies with a large number of patients, more complicated congenital heart defect, longer aortic cross clamp duration, with better assessment of cardiac functions for long postoperative follow up duration.

Conclusion

Single dose of cold HTK cardioplegia is as effective as repetitive cold blood and crystalloid (St.Thomas) cardioplegia in protecting the myocardium in pediatric cardiac surgery.

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