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Comparison between Bretschneider -HTK solution and antegrade cold blood cardioplegia as a method for myocardial protection in thoracic aortic surgery

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***Abstract*---**Background: Cardiac surgeons demand a cardioplegic solution providing extended durations of myocardial protection due to the increasing complexity of cardiac surgical procedures, especially thoracic aortic operations which require extended myocardial ischemic periods. The goal of this study was to assess the safety and efficacy of cold crystalloid single dosage Histidine Tryptophan Ketogultarate (Custodiol) cardioplegia to cold blood multidose cardioplegia in aortic surgery patients. Methods: Our study included 100 elective and emergency aortic surgery patients. Fifty patients received Custodiol cardioplegic solution (group A) and fifty received cold blood cardioplegia (group B). We evaluated post-operative cardiac Troponin I release, postoperative morbidities and mortality. Results: Troponin I peak release, duration of inotropic support & intensive care unit stay were more in the cold blood group. Hemofiltration and intraoperative requirement of blood products transfusion were more in the Custodiol group. No differences were found regarding cross-clamp time, arrhythmias, postoperative ejection fraction and in-hospital mortality. Conclusion: In patients having thoracic aortic surgery, custodiol and cold blood cardioplegic treatments give good myocardial protection.

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Custodiol usage was linked to lower troponin levels, shorter inotropic support periods, and shorter ICU stays. In terms of early mortality and morbidity, there was no statistically significant difference between the two groups.

***Keywords*---**myocardial protection, cardioplegia, aortic surgery, troponin.

Introduction

The most efficient strategy for myocardial protection during ischemic diastolic cardiac arrest is still a matter of debate, especially in thoracic aortic surgical procedures requiring a prolonged cross-clamp time. The combined effect of hypothermia and potassium-induced cardiac arrest represent the cornerstone of cold crystalloid cardioplegia strategy [1,2]. Later on, blood became utilized as a vehicle for potassium delivery and myocardial protection with warm blood cardioplegia providing good results in coronary bypass surgeries [3-5]. In thoracic aorta surgery, a single-dose strategy providing 2–3 hours of myocardial protection may be an attractive alternative especially in acute Stanford type A aortic dissection. Normothermic cardioplegia is not considered to be a valid option in these surgeries, since systemic cooling and hypothermic circulatory arrest (HCA) is often needed. Currently, the HTK solution is frequently utilized for organ preservation in transplantation, but is also used as a cardioplegic solution that allows single-dose administration in cardiac surgical procedures with prolonged ischemic times [6-8]. The efficacy of this crystalloid cardioplegia in thoracic aortic operations will be assessed here in our study.

The fundamental pillars of adequate myocardial protection are rapid induction of arrest, mild or moderate hypothermia, appropriate buffering of the cardioplegic solution and avoidance of myocardial edema [9]. Buffering of the cardioplegic solution is necessary to neutralize the intracellular acidosis associated with surgically induced myocardial ischemia. This may be provided by the blood component in cold blood cardioplegic solution as well as Histidine in HTK cardioplegia. Maintenance of the tissue pH of 6.8 or greater offers adequate myocardial protection and is important in preventing intracellular acidosis from reaching irreversible levels [10].

During cardiac surgery, cardiac troponin may be utilised as a marker of myocardial damage. The cardiac troponin complex (troponin I, T, and C), which is located on the actin filament, is required for heart muscle contraction mediation. In myocardial tissue, there is just one cardiac troponin I (cTnI) isoform [11]. There are four troponin T isoforms found in human myocardium, but only one is unique to the normal adult heart. As a result, cTnT measurement has cardiac specificity similar to cTnI testing. In ischemic heart disease and after cardiac surgery, cardiac troponin has diagnostic and prognostic utility [12].

Aim of work: to compare the efficacy of single dose HTK cardioplegic solution to multiple dose antegrade cold blood cardioplegia for myocardial protection in patients undergoing surgical repair of thoracic aortic (ascending & arch) pathologies.

Patients and methodology

The cardiothoracic surgery department of Kasr AlAiny Hospitals (Cairo University) was used for this study, which ran from April 2019 to November 2020. 100 patients who underwent thoracic aortic surgery, including those with aneurysms and dissection, were studied. In addition to the permission of the local ethics commission, each patient signed a written consent form.

Inclusion criteria: Patients undergoing surgery on thoracic aorta (ascending and/or arch) including aortic aneurysm and aortic dissection
Exclusion criteria: Patients with known ischemic heart disease, mitral valve disease, acute myocardial infarction, or redo patients were not allowed to participate in the research.
Sample size and Randomization:100 patients; 50 in each group. Patients meeting the inclusion criteria were randomly assigned to receive either: Group A (n=50) HTK solution (Custodiol; Bretschneider) or Group B (n=50) antegrade cold blood cardioplegia.

Primary outcomes

- Evaluating post-operative cardiac Troponin I (cTnI) release

Secondary outcomes

- Early mortality and morbidities

Patient Approach

Preoperative

Detailed history taking and clinical examination was performed. Full preoperative laboratory workup as well as ECG (electrocardiogram), CT (computed tomography) Aortography were also performed.

Intra-operative management

Two central venous lines were placed into both internal jugular veins after anaesthesia was administered. There were also catheters implanted in the urinary and nasopharyngeal systems. These two techniques were used often by anesthesiologists to monitor the patient's heart rate and blood flow. There was no evidence of intraoperative malperfusion for all patients who had TEE measurements of the descending aorta's real lumen vs false lumen area ratio. The pericardium was then cut open with a midline sternotomy. The distal ascending aorta, femoral or axillary artery, depending on the amount of aortic disease, was utilised for arterial cannulation. In the case of venous drainage, a right atrial cannulation was used. Through the right superior pulmonary vein, a left ventricular vent catheter was inserted. Reconstruction or partial replacement of the aortic arch will be conducted after aortic dissection, hence the femoral or axillary artery was utilised for arterial cannulation.

Perfusion and myocardial protection

Cardiopulmonary bypass and systemic cooling were initiated upon cannulation. The aorta was cross-clamped, and antegrade cardioplegic solutions were administered to preserve the myocardium. At a temperature of roughly 4°C, the anesthesiologist administered 600mL of cold blood cardioplegia into the heart's coronary vessels (the aortic root or the coronary ostia) for two minutes. Every 20-30 minutes, a maintenance dosage was administered (300mL for 1 minute). A single dose of Custodiol cardioplegia solution was supplied at 4-8°c and delivered antegrade by the coronary ostia or the aortic root in cases of Custodiol cardioplegia (depending on presence of aortic regurgitation). The HTK solution was administered in doses of 20-25 mL per kilogramme of body weight to the patients. Over the course of 15 minutes, a starting dosage of 1750-2000 mL was provided. To provide a uniform distribution of sodium and buffers at low concentrations, a somewhat lengthy administration period is necessary.

Surgical technique

To get a closer look at the organ, the aortic root was cut just above the sinotubular junction. Traction was provided by using Commissural stitches (Prolene 3/0 with Teflon pledgets). An examination of the sinuses and the aortic valve was carried out in order to perform a supra-coronary conduit by replacing the ascending aorta above the sources of the coronaries without dissection or dilating the sinuses and the valve was not damaged. After that, the aortic valve is thoroughly evaluated for any damage. If the valve and aorta are not appropriate for reconstruction, the procedure is continued as a Bentall and De Bono composite replacement. Aortic root replacement with the Tirone David procedure may continue if all sinuses have been dissected or dilated with the presence of aortic regurgitation. It was decided to execute the arch operation under hypothermic circulatory arrest, with either ante- or retrograde cerebral perfusion. In order to execute a partial or complete arch replacement, the patient must be cooled progressively until their core temperature is between 24 and 26 degrees Celsius. Ten minutes before the start of HCA, the patient's head was chilled with ice packing and circulation was halted, the aorta declamped, and the surgeon began performing a distal anastomosis while anaesthetic medicines, such as thiopental, corticosteroids, and mannitol, were administered.

Data collection

A) Preoperative data: Demographics, patients characteristics, aortic pathology
B) Operative data
- Bypass time, cross clamp time, surgery performed, cannulation site and recovery of spontaneous rhythm after weaning from bypass
- Intra operative laboratory variables; serum sodium and lactate production measured through arterial blood gas analysis which were taken immediately after induction of anesthesia (baseline value) and approximately every 30 min after starting cardiopulmonary bypass (CPB)

C) Postoperative data

Measurements of Troponin I was done through a venous blood sample collected 24 hours postoperatively. Electrocardiogram (ECG) was routinely done, upon arrival of the patient to the ICU, and repeated whenever indicated to detect new ECG changes in the form of ischemia, and arrhythmias. Post-operative mechanical ventilation time, duration of the inotropic support and ICU stay were recorded. Post-operative blood loss, blood transfusion and re-exploration for excessive bleeding were documented as well as early mortality. Echocardiography as well as follow up of renal functions were also performed.

Statistical analysis

The collected data was analyzed using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non- parametric Mann-Whitney test. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered as statistically significant.

Results

In our study preoperative, operative and postoperative data were analyzed for 100 patients undergoing thoracic aortic surgical procedures. All group A patients received a single dose HTK cardioplegia solution according to body weight (20ml/kg body weight with a maximum of 2 liters) while group B patients received an initial dose of 600ml followed by subsequent doses of 300ml cold blood cardiolegia every 20-30 minutes. Preoperative characteristics are shown in table 1. In group A 45 patients had risk factors and comorbidities to develop aortic disease; 25 had hypertension, 15 had marfan syndrome and 10 had bicuspid aortic valve while in group B 40 patients had risk factors; 21 were hypertensive, 11 had Marfan syndrome and 8 had bicuspid aortic valve. There was no stastistically significant difference between the two groups regarding age, gender, co-morbidities or aortic pathology.

Table 1: Preoperative parameters in the two groups

	Group A (HTK)	Group B (cold blood)	p value
Age	50.3 ±10.4	49.4 ± 10.5	0.627
Gender (Male)	32 (64%)	37 (74%)	0.280
Comorbidities	45 (90%)	40 (80%)	0.161
Aortic dissection	18 (36%)	16 (32%)	
Aortic aneurysm	32 (64%)	34 (68%)	0.673

Statistical significance is defined as p 0.05 for continuous variables and p 0.05 for categorical variables.

Regarding intraoperative findings (as shown in table 2), there was no statistically significant difference between both groups regarding choice of surgical technique, cannulation site, cross clamp time, CPB time or the utilization of hypothermic circulatory arrest (HCA). The number of patients requiring hemofiltration on CPB was higher in the HTK group (62% compared to 36% with a p value 0.009). No statistically significant difference was found between the two groups regarding intraoperative blood transfusion, hyponatremia or serum lactate. 19 patients in group A develop arrhythmias after removal of aortic cross clamp, 11 had ventricular fibrillation (VF) , 4 had atrial fibrillation (AF) that required direct current (DC) shock to return to the spontaneous rhythm and 4 had heart block which necessitated temporary pacing. However there were 23 patients in group B suffering from such arrhythmias; 14 had ventricular fibrillation (VF), 3 had AF, 4 had heart block requiring temporary pacing and 2 with complete heart block who required permenant pacemaker insertion in the ICU. The p value was 0.418 denoting no statistical significance.

Table (2) Intraoperative findings in the 2 groups

		Group A (HTK)	Group B (cold blood)	p value
CPB time		160 ± 27.7	169.7 ±26.5	0.094
Cross clamp time		127.1 ±22	136.9 ± 22.1	0.052
Cannulation site	Aorta Femoral Axillary	26 (52%) 17 (34%) 7 (14%)	30 (60%) 13 (26%) 7 (14%)	0.664
HCA		13 (26%)	19 (38%)	0.198
Surgical procedure	Bentall Tirone David Supracoronary	14 (28%) 12 (24%) 24 (48%)	18 (36%) 14 (28%) 18 (36%)	0.470
Hemofiltration		31 (62%)	18 (36%)	0.009
Blood transfusion		26 (52%)	16 (32%)	0.043
Hyponatremia		21 (42%)	13 (26%)	0.091
Lactate (mmol/L)		4.7 ±1.3	4.4 ±1.5	0.140
Arrhythmias		19 (38%)	23 (46%)	0.418

Statistical significance is defined as p 0.05 for continuous variables and p 0.05 for categorical variables.
CPB: cardiopulmonary bypass
HCA: hypothermic circulatory arrest

Table (3) summarizes postoperative findings. The troponin levels measured in the intensive care unit (ICU) 24 hours postoperatively were statistically significantly higher in group B with the mean value in group A being 56.5 ±19.1ng/ml compared to 82.7 ±19.2ng/ml in group (B) with p value of <0.001. ICU stay and duration of inotropic support postoperatively were both also higher in group B (p value 0.001). Inotropic support refers to the use any inotropic drug in the immediate postoperative ICU period (the inotropic drug of choice in this study was adrenaline). Postoperative echocardiography: was done on the first postoperative day and before discharge from hospital and an impaired ejection fraction was considered when its value was reduced below 50% in any postoperative measurement. Both groups were comparable regarding postoperative impairment of myocardial contractility. Mortality was 6 cases (12%) in group A compared to 8 (16%) in group B (no statistical significance). In group A, 3 patients died from complications of massive blood transfusion due to intra & postoperative bleeding, 2 from stroke complications and 1 from arrhythmia while in group B, 4 patients died from complication of massive blood transfusion, 2 from the complications of stroke, 1 from arrhythmia and the last one from low cardiac output syndrome (LCOS). No statistically significant difference was found between the 2 groups regarding postoperative morbidities as bleeding, arrhythmias, stroke and renal impairment.

Table (3) Postoperative findings in the 2 groups

	Group A (HTK)	Group B (cold blood)	p value
Duration of inotropic support (days)	1.9 ±1.2	2.9 ±1.0	<0.001
Troponin (ng/ ml)	56.5 ±19.1	82.7 ±19.2	<0.001
Mechanical ventilation (hours)	14.1 ±5.5	15 ±4.9	0.225
ICU stay (days)	3.1 ±1.1	4.1 ±1.2	<0.001
Impaired postoperative Ejection fraction	9 (18%)	14 (28%)	0.235
Arrhythmia	11 (22%)	14 (28%)	0.488
Bleeding and re-exploration	12 (24%)	10 (20%)	0.629
Blood transfusion	19 (38%)	13 (26%)	0.198
Renal impairment	8 (16%)	9 (18%)	0.790
Stroke	3 (6%)	5 (10%)	0.715
Mortality	6 (12%)	8 (16%)	0.564

Statistical significance is defined as p 0.05 for continuous variables and p 0.05 for categorical variables.
ICU: Intensive Care Unit

Discussion

Thoracic aortic surgical procedures are long and complex interventions requiring prolonged ischemic times and extensive myocardial protection. In this study we compared myocardial protection obtained with cold blood intermittent cardioplegia with single dose HTK solution. Multiple dose cardioplegia is not optimum in these lengthy procedures with frequent interruption of surgery as well as the repeated risk of coronary ostial injury especially in acute aortic dissection patients [13]. Anaerobic glycolysis is improved by the buffering action of histidine in Custodiol, which has considerable benefits for improving clinical results. Nicotinamide adenine dinucleotide (NAD) is synthesised from ketoglutarate, an intermediate in the Krebs cycle. The cell membrane is stabilised by Tryptophan, while cellular oedema is reduced by Mannitol [14].

In our study we compared HTK with intermittent antegrade cold blood cardioplegia in myocardial protection during aortic surgeries. There was no statistically significant difference between the two groups regarding age, gender distribution, aortic pathology or risk factors for aortic disease. Intraoperatively both groups were comparable regarding cross clamp and total bypass time. This is similar to Scrascia and colleagues' [13] results which was a study for aortic surgery cases using both cardioplegia techniques. Viana [14] showed significantly shorter bypass and cross clamp times in the blood cardioplegia group but this study included an array of different complex cardiac operations and was not limited to aortic surgery.

There was no statistically significant difference between the two groups regarding the surgical procedure performed, cannulation sites or the use of HCA (hypothermic circulatory arrest) during surgery.This may be attributed to the similarity in aortic pathologies between the two groups hence the similarity in operative strategies. The number of patients requiring hemofiltration on CPB was higher in the HTK group (62% compared to 36% with a p value 0.009). Scrascia [13] and Rimphanitchayakit [15] both agreed with our study regarding the higher percentage of patients requiring hemofiltration in the HTK group and this may be explained by the larger volumes of cardioplegia solution utilized in the HTK group. Hyponatremia occurred in both groups but was more in HTK group, however it did not reach statistical significance. This is probably due to increased hemofiltration rate in the HTK group which compensated for the larger volume given on CPB. Also the intraoperative transfusion of blood products was statistically significantly higher in the HTK group. This could be due to the requirement of packed RBCs (red blood cells) to correct the drop in hematocrit value associated with initiation of CPB and after giving large volume HTK cardioplegia solution. Lactate release in our study did not show any statistical difference between both groups which is probably explained by the comparability of mean bypass and clamp times in both groups and other surgical details. Intraoperative arrhythmias were similar in both groups as was shown by Rimphanitchayakit [15] where the incidence of VF was insignificantly higher in the HTK group but in disagreement with Viana [14], El-Hammasy [16] and Braathen [17] in which patients in the HTK group were more likely to experience new-onset ventricular tachycardia or fibrillation.

We measured troponin levels 24 hours postoperatively. The mean level was 56.5 $\pm$19.1 ng/dl in the HTK group compared to 82.7 $\pm$19.2 ng/dl in the cold blood cardioplegia group (p value <0.001). Scrascia and colleagues [13] also showed lower Troponin levels in their study but they further analyzed the data in the 2 groups according to cross clamp time. They found that troponin release was significantly lower in HTK group in cases with prolonged cross clamp time exceeding 160 minutes. The explanation for this finding is not entirely clear but may signify better protection with the HTK solution on the cellular level. That may be related to its components or inadequate cold blood cardioplegia delivery for prolonged thoracic aorta procedures with long clamp times. De Haan and colleagues [18] found no statistically significant difference in release of cardiac enzymes but they depended on the measurement of CK-Mb (Creatine kinase-Myoglobin binding) instead of troponin. The postoperative CK-Mb level was clearly correlated with the aortic cross-clamp time; the longer the clamp time the higher the postoperative CK-Mb level. The lower mean troponin levels in the HTK group in our study were further highlighted by the duration of inotropic support postoperatively which was statistically significantly lower in patients in group (A) as the mean value in group A was 1.92 days compared to 2.86 days in group B (p value <0.001). This was also reflected on a lower mean ICU stay in the HTK group. These theoretical indicators of improved myocardial protection in the HTK group were not observed in postoperative ejection fraction which was comparable between both groups.

The mortality in both groups did not show a statistically significant difference as there were 6 in group A (12%) and 8 in group B (16%). This may be explained by the comparability of intraoperative procedures, bypass, cross clamp times, incidence of stroke, renal impairment, as well as bleeding and reexploration between the two groups. Many studies Pizano [19], De Haan [18], Scrascia [13], Moursi [20] and Rimphanitchayakit [15] all showed that mortality was not statistically significantly different between the two groups. Both Custodiol and cold blood cardioplegia are safe and effective techniques in providing myocardial protection during thoracic aortic surgeries. We concluded from our study that HTK use was associated with less troponin release, less inotropic support duration in ICU and shorter ICU stay. However its use resulted in higher requirements of hemofiltration and intraoperative transfusion of blood products than cold blood cardioplegia. Both techniques were comparable regarding early mortality and morbidities as well as postoperative ejection fraction. Limitations to our study included the number of cases enrolled in the study as well as the lack of baseline troponin levels or multiple intra and postoperative measurements. The study also included heterogenous aortic surgery cases including emergency dissection patients which may have affected the overall results of the study.

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Informed consent: Written informed consent was obtained from all individual participants included in the study.

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