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Efficacy of Histidine–Tryptophan–Ketoglutarate Solution Versus Blood Cardioplegia in Cardiac Surgical Procedures: A Randomized Controlled | Parallel Group Study

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ABSTRACT

Background: In cardiac surgery, myocardial protection is required during cross-clamping followed by reperfusion. The use of cardioplegic solutions helps preserve myocardial energy stores, hindering electrolyte disturbances and acidosis during periods of myocardial ischaemia. This study aimed to compare the efficacy and safety between the histidine–tryptophan–ketoglutarate (HTK) solution and blood cardioplegia in various cardiac surgeries.

Methods: Three-hundred-twenty patients aged 30-70 years old undergoing various cardiac surgeries were randomized into the HTK group and the blood cardioplegia group. The ventilation time, total bypass time, cross-clamp time, length of intensive care unit (ICU) or hospital stay, and postoperative complications were analyzed.

Results: The total bypass time and cross-clamp time were significantly shorter in the HTK group than in the blood cardioplegia group ($P < 0.001$). Segmental wall motion abnormalities (SWMA) at postoperative echocardiography were significantly higher in in the blood cardioplegia group ($P = 0.008$). The number of patients requiring DC Shock was significantly higher in the HTK group ($P < 0.001$). The number of patients requiring inotropic support was significantly higher in the blood cardioplegia group ($P < 0.001$). The length of ICU, hospital stay, and ventilation time were significantly longer in the blood cardioplegia group than in the HTK group ($P = 0.004$, $P < 0.001$, $P < 0.001$, respectively). The number of patients requiring prolonged ventilation was significantly higher in the blood cardioplegia group compared with the HTK group ($P = 0.022$). There was no significant difference between the study groups regarding electrocardiographic changes, 30-day mortality, and 30-day readmission.

Conclusion: The use of HTK cardioplegia was associated with significantly shorter cross-clamp time, bypass time, duration of mechanical ventilation, length of ICU stay, and length of hospital stay. It is associated with less incidence of postoperative segmental wall abnormalities and less need for inotropic support than blood cardioplegia. Custodiol cardioplegia is a safe and feasible option that can be used as an effective substitute for blood cardioplegia to enhance myocardial protection.

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INTRODUCTION

Cardioplegic arrest is one of the most well-known myocardial protection strategies for patients posted for cardiac surgery [Korun 2013]. The main concern in ischemia-reperfusion injury is to improve the tolerance of the myocardium to ischaemia particularly in high-risk patients during cardiac surgery because it is associated with a higher incidence of morbidity and mortality [Liu 2008]. However, the myocardial protection strategies for cardiac surgery still remain controversial [Huang 2011; Viana 2013]. The histidine–tryptophan–ketoglutarate (HTK) solution (Custodiol) was initially presented by Preusse et al. [Preusse 1981]. It is composed of histidine, tryptophan, and ketoglutarate, and its effect depends on intracellular electrolytes [Braathen 2011]. In addition to the buffering effect of histidine, it increases the efficiency of anaerobic glycolysis [Braathen 2011]. Tryptophan maintains the stability of the cell membrane, and the beneficial effect of mannitol is to decrease cellular oedema [Braathen 2011]. Ketoglutarate is a cofounder of nicotinamide adenine dinucleotide that preserves the endothelium of the coronary artery, thus promoting its recovery [Saitoh 2000; Yang 2004]. The Custodiol HTK solution for cardiac arrest is administered as one single dose, and it sufficiently provides more than 2 h of myocardial protection for cardiac arrest [Braathen 2011]. Alternatively, blood cardioplegia is considered an effective technique for myocardial protection based on the fact that blood, compared with crystalloid solutions, can improve postoperative outcomes, due to its structure being closer to the normal physiology [Nardi 2018].

Each liter of Custodiol HTK cardioplegic solution is composed of the following: Na+ (15 mmol/l), K+ (9 mmol/l), Mg++ (4 mmol/l), Ca++ (0.015 mmol/l), histidine (198 mmol/l), tryptophan (2 mmol/l), ketoglutarate (1mmol/1), and mannitol (30 mmol/l) with a pH of 7.02-7.20 [Nardi 2018]. Blood cardioplegia components consists of the following: Na+ (118

mEq/l), K+ (18 mEq/l), Mg++ (1.6 mEq/l), and Ca++ (0.3-0.5 mEq/l) with a pH of 7.6-7.8 [Ishikawa 2010].

Careaga et al. [Careaga 2001] reported that the usage of HTK solution was associated with a lower incidence of arrhythmias, shortening the length of the intensive care unit (ICU) stay and reducing the need for inotropic support postoperatively. One single dose of cardioplegia is a feasible choice particularly in complex cardiac surgeries to avoid disturbance of the technical sequence of the procedure. This prospective study was conducted to compare HTK cardioplegia with blood cardioplegia in terms of the total bypass time, ventilation time, length of ICU stay, mortality rate, and incidence of postoperative complications.

MATERIALS AND METHODS

Ethical considerations: The Ethics Committee of Ain Shams University approved this randomized prospective controlled parallel group study to be conducted at the Cardiothoracic Academy for 5 months from December 2019 to April 2020 (FMASU R61/2019). This study was registered at ClinicalTrials.gov (registration number: NCT04203680) in December 2019.

Patients: This study consisted of 320 patients aged 30-70 years old posted for various cardiac surgeries. Written informed consent was signed by all patients. The exclusion criteria included (1) unstable angina (class III or IV), (2) poor left ventricular function (left ventricular ejection fraction <40%), (3) acute myocardial infarction, (4) history of renal failure, (5) emergency cardiac surgery.

Study protocol: A detailed medical history, including medications used, symptoms and risk factors for ischaemic heart disease (smoking, diabetes mellitus, hypertension), and the New York Heart Association classification, was taken and full assessment was performed on the night of the surgical procedure. Anaesthesia management was standardized for all patients. Premedication with midazolam was limited to a maximum of 0.05 mg/kg. Anaesthesia was inducted with 12 µg/kg fentanyl, 5-7 mg/kg thiopental sodium, and 0.15 mg/kg pancuronium and was maintained with 1-2.0% isoflurane. The heart rate and blood pressure were maintained within 20% of the baseline values. Anticoagulation was achieved with heparin 300 U/kg administered into the right atrium to maintain an activated clotting time above 480 seconds. Cardiopulmonary bypass (CPB) was established using non-occlusive roller pumps, membrane oxygenators, and arterial line filtration. The CPB circuit was primed with 1.8 l lactated Ringer's solution and 50 ml of 20% mannitol. CPB management included systemic hypothermia during aortic cross-clamping, targeted mean perfusion pressure between 60 and 80 mmHg, and pump flow rates of 2.2 l/min/m2. Intraoperatively, the patients were monitored using electrocardiography, pulse oximetry, invasive blood pressure monitoring, arterial blood gases, central venous line catheters, and temperature probes. The median sternotomy surgical approach was performed.

Patients were randomly allocated into two groups (HTK group and blood cardioplegia group), according to a computer-generated randomisation code, with an allocation ratio of 1:1. Randomisation was done by a statistician who was not involved in the study using the SAS statistical package version 9.3 (SAS Institute, Cary, NC, USA). Opaque sealed envelopes were prepared, according to the randomisation schedule and were opened by a clinician not involved in any part of the study.

In the HTK group, patients received a single dose of 30 ml/kg of HTK cardioplegic solution over 6-7 minutes at 4°C through the antegrade route within 12-15 min at an initial perfusion pressure of 80-100 mmHg that was then decreased to 40-60 mmHg after myocardial arrest.

In the blood cardioplegia group, patients received 1liter of blood induction cardioplegic solution at ratio 4:1 through the antegrade route at 29°C or lower at a pressure of 80-100 mmHg. Blood maintenance cardioplegia was repeated every 30-45mins. Another warm blood retrograde dose was administered before myocardial reperfusion.

The study medications were calculated and prepared by ICU residents, who were not a part of the research team.

Prior to weaning from CPB, patients were rewarmed to 36-37°C. After weaning from CPB, heparin was neutralized with protamine sulphate 1 mg/100 U heparin to achieve an activated clotting time within 10% of baseline. All patients were then transferred to the ICU after surgery.

Outcome measures: The primary outcome of the study was the 30-day mortality rate (%). Secondary outcomes included cardiac enzyme levels [troponin > 20 mg/l, creatinine kinase-myocardial band > 30 U/l] 12 and 24 h postoperatively, segmental wall motion abnormalities (SWMAs), and at least two new Q waves on two consecutive electrocardiograms and pericardial effusion, electrocardiographic changes such as ventricular fibrillations or ventricular arrhythmia, cross-clamp and total bypass time, length of ICU stay, length of hospital stay, requirement for inotropic support, 30-day readmission, intra-aortic balloon use and the incidence of late postoperative complications, such as renal failure [serum creatinine >0.2 mmol/l, doubling of preoperative serum creatinine and need for renal replacement therapy].

Statistical analysis: Using the Power Analysis and Sample Size software (PASS; NCSS, LLC, East Kaysville, UT, USA), it was determined that 320 patients, 160 per arm, was needed after considering a 5% dropout (power of 80%, alpha error at 5%) and to detect the non-inferiority margin difference between the group proportions of 2%. The blood cardioplegia group is assumed to be 6% under the hypothesis of non-inferiority. These calculations were based on a previous study [Viana 2013] that showed that the mortality rate in the HTK group was 4%, whereas that in the blood cardioplegia group was 1%.

Data were analyzed using SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA). Normally distributed numerical data were presented as mean and standard deviation, and skewed data were presented as median and interquartile range. Qualitative data were presented as number and percentage or ratio. Normally distributed numerical data were compared using the unpaired t-test. Skewed numerical data were compared using the Mann–Whitney test, and categorical data

were compared using Fisher's exact test. *P*-values <0.05 were considered statistically significant.

RESULTS

This study was conducted at the Cardiothoracic Academy from December 2019 to April 2020. A total of 320 patients were assessed for eligibility, and all were enrolled in our study with no single case of protocol violation as shown in the CONSORT flow diagram. (Figure 1) They were randomized and their data were analyzed.

The two groups were similar in terms of their demographic and preoperative data. (Table 1)

The total bypass time was significantly longer in the blood cardioplegia group than the HTK group ($P < 0.001$). The cross-clamp time was significantly longer in the blood cardioplegia group compared with the HTK group ($P < 0.001$). NYHA class was significantly higher in the blood cardioplegia group compared with the HTK group ($P = 0.037$).

Preoperative and postoperative ejection fractions were comparable between the two study groups ($P = 0.380$ and $P = 0.885$, respectively). (Table 2) There was no significant difference between the two groups, in terms of the SWMA at preoperative echocardiography ($P = 0.073$). In contrast, SWMAs at postoperative echocardiography were significantly higher in the blood cardioplegia group than the HTK group ($P = 0.008$). The incidence of pericardial effusion was similar between the two groups ($P = 0.090$).

Similarly, the number of patients requiring DC Shock was significantly higher in the HTK group than in the blood cardioplegia group ($P < 0.001$). Conversely, the number of patients requiring inotropic support was significantly higher in the blood cardioplegia group than in the HTK group ($P < 0.001$). (Table 3)

The lengths of ICU and hospital stay were significantly longer in the blood cardioplegia group than in the HTK group ($P = 0.004$ and $P < 0.001$, respectively). (Table 4) The ventilation time was significantly longer in the blood cardioplegia group than in the HTK group ($P < 0.001$).

Table 1. Comparison between the two study groups in terms of patient demographics

Patient demographics	HTK group (*N* = 160)	Blood cardioplegia (*N* = 160)	Tests	
			t/X^2	*P*-value
Age (years)	44.19±11.63	43.11±10.76	0.868	0.386
Sex				
Female	42 (26.3%)	40 (25%)	0.066	0.798
Male	118 (73.8%)	120 (75%)		
Smoking	56 (35%)	40 (25%)	3.810	0.051
Diabetes mellitus	72 (45%)	56 (35%)	3.333	0.068
Hypertension	80 (50%)	72 (45%)	0.802	0.370
NYHA class				
1	8 (5%)	8 (5%)	8.471	0.037*
2	56 (35%)	80 (50%)		
3	80 (50%)	56 (35%)		
4	16 (10%)	16 (10%)		
Concomitant CABG and valve	39(24.4%)	57(35.6%)	4.821	0.028*
Mitral valve replacement	45(28.1%)	43(26.9%)	0.063	0.802
Double valve surgery	31(19.4%)	47(29.4%)	4.340	0.037*
Aortic valve replacement	30(18.8%)	14(8.8%)	6.746	0.009*
Isolated CABG	12(7.5%)	13(8.1%)	0.043	0.835
Euro SCORE	4.21±2.67	7.06±2.38	10.079	<0.001**
Aortic cross clamp time (min)	101.53±37.50	147.92±32.25	11.864	<0.001**
Bypass time (min)	141.06±41.1	197.74±37.47	12.891	<0.001**

All data were presented as percentage except age, weight, bypass time, Euro SCORE and cross-clamp time were presented as Mean±SD. NYHA, New York Heart Association Functional Classification.

P-values <0.05 were considered statistically significant.

Table 2. Comparison between the two study groups in terms of preoperative and postoperative echocardiography

	HTK group (*N* = 160)	Blood cardioplegia (*N* = 160)	Tests	
			t/X^2	*P*-value
Preoperative Echo				
EF%	46.66±2.63	46.41±2.58	0.880	0.380
SWMA preoperative Echo				
No abnormality	24 (15%)	40 (25%)		
Akinesia	96 (60%)	88 (55%)	5.237	0.073
Dyskinesia	40 (25%)	32 (20%)		
Postoperative Echo				
EF%	41.21±2.81	41.17±2.59	0.145	0.885
SWMA postoperative Echo				
No abnormality	16 (10%)	8 (5%)		
Akinesia	72 (45%)	64 (40%)	11.865	0.008*
Hypokinesia	24 (15%)	48 (30%)		
Dyskinesia	48 (30%)	40 (25%)		
Pericardial effusion	8 (5%)	16 (10%)	2.883	0.090

All data were presented as percentage. EF, ejection fraction; SWMA, systolic wall motion abnormalities

Table 3. Comparison between the two study groups in terms of intraoperative results

Intraoperative results	HTK group (*N* = 160)	Blood cardioplegia (*N* = 160)	Chi-square	
			t/X^2	*P*-value
CPB weaning				
DC Shock	96 (60%)	56 (35%)	20.050	<0.001**
Inotropes	64 (40%)	104 (65%)		

All data were presented as percentage. CPB, cardio-pulmonary bypass

There was no significant difference between the two groups, in terms of electrocardiographic changes ($P = 0.176$) and cardiac enzyme levels 12 and 24 h postoperatively ($P = 0.317$ and $P = 0.239$, respectively) (Table 4). The incidence of renal failure was similar in the blood cardioplegia group and the HTK group ($P = 0.702$). (Table 5) There was no significant difference between the study groups regarding intra-aortic balloon usage ($P = 1.00$) (Table 5). The number of patients requiring prolonged mechanical ventilation was significantly higher in the blood cardioplegia group compared with the HTK group ($P = 0.022$). There was no significant difference between the study groups regarding 30-day mortality and 30-day readmission ($P = 0.556$ and $P = 0.644$, respectively).

DISCUSSION

Blood cardioplegia is a popular method of myocardial preservation but it is administered repeatedly every 15-30 minutes, which causes interruption of the cardiac procedure. HTK solution is preferable, especially in lengthy cardiac procedures, as it is given as a single dose.

The results of this prospective study revealed that the administration of Custodiol HTK solution as a single initial dose for patients undergoing cardiac surgeries was associated with shorter cross-clamp time, bypass time, and the duration of mechanical ventilation; it also was associated with shorter ICU stay and length of hospital stay and less incidence of postoperative SWMA. The 30-day mortality, 30- day readmission and incidence of postoperative complications were comparable

Table 4. Comparison between the two study groups in terms of postoperative results

Postoperative result	HTK group (*N* = 160)	Blood cardioplegia (*N* = 160)	Tests		95% CI
			t/X^2	*P*-value	
Ventilation time (h)	5.97±0.69	9.07±1.27	27.174	<0.001**	-3.324/-2.876
ICU stay (days)	2.05±0.22	2.14±0.35	2.862	0.004*	-0.158/-0.029
Hospital stay (days)	5.48±0.94	5.99±0.91	4.930	<0.001*	-0.717/-0.308
ECG changes	16 (10%)	24 (15%)	1.829	0.176	0.320/1.236
Cardiac enzyme level after 12 h					
Increased	40 (25%)	48 (30%)	1.003	0.317	0.786/2.259
Decreased	120 (75%)	112 (70%)			
Cardiac enzyme level after 24 h					
Increased	24 (15%)	32 (20%)	1.385	0.239	0.394/1.263
Decreased	136 (85%)	128 (80%)			

All data were presented as Mean±SD except ECG changes and cardiac enzymes which were presented as percentage. ICU, intensive care unit; ECG, electrocardiogram

Table 5. Comparison between the two study groups in terms of postoperative complications

Postoperative complications	HTK group (*N* = 160)	0.96 in	Chi-square test
	t/X^2		*P*-value
30-day mortality rate	5(3.1%)	7(4.4%)	0.346	0.556
30-day readmission	9(5.6%)	11(6.9%)	0.213	0.664
Prolonged ventilation (number of patients)	7(4.4%)	18(11.3%)	5.250	0.022*
30-day mortality	5(3.1%)	7(4.4%)	0.346	0.556
30-day readmission	9(5.6%)	11(6.9%)	0.213	0.644
Intra-aortic balloon insertion	1(0.6%)	1(0.6%)	0.000	1.000
Renal failure	3(1.9%)	4(2.5%)	0.146	0.702

All data were presented as percentage

between the two groups, except that the occurrence of prolonged ventilation time was significantly higher in the blood cardioplegia group. After review of literature, a study by Viana et al. [Viana 2013] comparing Custodiol and blood cardioplegia in all cardiac surgical procedures, it was observed that the 30-day mortality was similar between the two study groups (blood cardioplegia vs. Custodiol; 3% and 6%, respectively, *P* = 0.079). There was no significant difference between the two groups, in terms of the incidence of postoperative stroke, renal failure, and 30-day readmission. However, the ventilation time was significantly longer in the HTK group. These findings are consistent with the results of the current study except for ventilation time, which was shorter in the HTK group [Viana 2013].

Consistent with the results of this study, Sakata et al. investigated the use of Custodiol HTK solution in valve surgery and concluded that it was associated with less inotropic drug requirements than those used in cold blood cardioplegia [Sakata 1998].

In contrast with the results of the current study, a study by Mahrous et al. [Mahrous 2016] included pediatric patients undergoing total corrective cardiac surgery with either HTK solution or blood cardioplegia. They observed that the troponin I level was significantly higher in the HTK group than in the blood cardioplegia group 4 h after CPB but in this study, there was no significant difference between the study groups, regarding the cardiac enzymes level.

Different from the present study, a retrospective study by Bojan et al. compared HTK solution (Custodiol) with blood cardioplegia in neonates with arterial switch operations; they found that the troponin I level was higher during the first week

of surgery in the HTK group than in the blood cardioplegia group [Bojan 2013]. They concluded that Custodiol provides poorer myocardial protection than blood cardioplegia.

Hamed et al. designed a prospective study to compare three cardioplegic solutions, including HTK solution, blood cardioplegia, and crystalloid cardioplegia, in pediatric patients posted for cardiac surgery for acyanotic heart disease [Hamed 2018]. They found that the mechanical ventilation time, extubation time, and length of ICU stay were significantly longer in the blood cardioplegia group than in the HTK group ($P < 0.001$); these results are similar to those of the current study.

Ali et al. [Ali 2019] compared Custodiol with blood cardioplegia in patients with poor left ventricular function posted for CABG surgery and reported that, in contrast to the findings of this study, the length of ICU stay, ventilation time, and need for inotropic support were comparable between the two study groups, while the mortality rate was similar to the mortality rate in this study.

It remains questionable which type of cardioplegia is more beneficial. Nevertheless, the choice of cardioplegic method should be based on the patient's condition and the type of cardiac procedure to be performed to ensure optimal myocardial protection and to improve the postoperative outcomes and reduce complications [Weisel 2013].

Prathanee et al. used Custodiol cardioplegia and blood cardioplegia in patients undergoing isolated CABG surgery [Prathanee 2015]. They found that the incidence of postoperative complications was insignificant in both study groups. However, they noticed that the incidence of ventricular fibrillation was significantly higher in the HTK group. In the current study, the incidence of postoperative complications were comparable except for prolonged ventilation time, which was significantly higher in the blood cardioplegia group.

Hachida et al. reported that HTK promotes anaerobic glycolysis during the period of ischaemia by HTK preserving cardiac contractility [Hachida 1997]. Takeuchi et al. stated that administration of the histidine-containing cardioplegia solution enhances high-energy phosphate stores recovery and the contractility of the hypertrophied myocardium [Takeuchi 2002].

A study by Braathen and his colleagues reported that HTK administration is as effective as antegrade cold blood cardioplegia as regarding myocardial protection in patients undergoing elective mitral surgery [Braathen 2011].

Fannelop et al. found that cold blood cardioplegia significantly protected the myocardium thus preserving the left ventricular function compared with HTK following declamping [Fannelop 2009].

According to a study by Von Oppell, HTK solution is superior for hypothermic endothelial cell preservation because of its low chloride in the intracellular solutions in addition to its content of histidine, tryptophan, and KH-2-oxygluterate [Von Oppell 1990].

A prospective Australian cardiac center data base reviewed by Viana et al. [Viana 2013], comparing myocardial protection offered by HTK cardioplegia versus blood cardioplegia for patients undergoing complex cardiac surgery, reported that a single dose of the HTK solution was sufficient in protecting the myocardium for long period of time without the need to interrupt the surgical procedure and improving the clinical outcomes similar to blood cardioplegia [Viana 2013].

A cohort study by Pizano et al. [Pizano 2018], discussing the efficacy of HTK versus blood cardioplegia in patients undergoing cardiac surgery, revealed that cross-clamp time and bypass time were significantly shorter in the HTK group compared with the blood cardioplegia group, $P < 0.001$. On the other hand, the incidence of prolonged ventilation, 30-day mortality, and hospital readmission were comparable between the study groups. They concluded that HTK was equivalent to blood cardioplegia regarding early postoperative outcomes [Pizano 2018].

LIMITATIONS

This study was subjected to limitations. Initially, some endpoints were not analyzed, such as the volume of cardioplegic solution given and the incidence of heart block. Another limitation was the lack of double blinding, which could cause bias in the study.

CONCLUSION

The use of HTK cardioplegia was associated with significantly shorter cross-clamp time, bypass time, duration of mechanical ventilation, length of ICU stay, and length of hospital stay. It is associated with less incidence of postoperative segmental wall abnormalities and less need for inotropic support than blood cardioplegia. Custodiol cardioplegia is a safe and feasible option which can be used as an effective substitute for blood cardioplegia to enhance myocardial protection.

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