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Custodiol Histidine-Tryptophan-ketoglutarate Versus Blood Cardioplegia in Totally Thoracoscopic Cardiac Surgery

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Abstract

Objective: The present study aimed to evaluate and compare the myocardial protection performance between Custodial histidine-tryptophan-ketoglutarate cardioplegic solution and blood cardioplegic solution in the context of totally thoracoscopic cardiac surgery.

Methods: A total of 101 patients who underwent thoracoscopic cardiac surgery adopting either blood cardioplegic or histidine-tryptophan-ketoglutarate solution at Guangdong Provincial People's Hospital from January 2021 to December 2021 were retrospectively enrolled. Postoperative outcomes assessed by myocardial enzyme level, the capacity of return to spontaneous rhythm, left ventricle ejection fraction, myocardial infarction, vasoactive-inotropic score, mechanical ventilation time, intensive care unit stay, hospital stay, mechanical circulatory support, and in-hospital mortality were compared between the two groups.

Results: 69 and 32 patients adopted blood cardioplegic and histidine-tryptophan-ketoglutarate solutions, respectively. The cardiac troponin I and creatine kinase-MB at the peak period or at the postoperative period of <24h, 24-48h, and >48h were similar between the two groups (p>0.05). There was also no significance regarding the postoperative left ventricle ejection fraction, vasoactive-inotropic score, and incidence of myocardial infarction (p>0.05). However, blood cardioplegic solution administration resulted in a significantly more occurrence of return to spontaneous rhythm in contrast to the histidine-tryptophan-ketoglutarate solution (p=0.025). Multivariate logistic regression for outcomes revealed that histidine-tryptophan-ketoglutarate administration was associated with a lower possibility to return to spontaneous rhythm (odds ratio (OR)=0.238; confidence interval CI=0.072-0.783;

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p=0.018]. Additionally, increased aortic cross-clamp time per 10 mins was associated with a higher risk of myocardial infarction (OR=1.499; CI=1.161-1.934; p=0.002) while increased total volume was associated with a lower risk of myocardial infarction (OR=0.997; CI=0.994-0.999; p=0.029)

Conclusion: Delivery of histidine-tryptophan-ketoglutarate solution offered equivalent myocardial protection to the delivery of blood cardioplegic solution in patients undergoing totally thoracoscopic cardiac surgery. In this setting, the histidine-tryptophan-ketoglutarate seems to be associated with decreased incidence of postoperative return to spontaneous rhythm.

Keywords: Cardioplegic solution; Histidine-tryptophan-ketoglutarate; Blood cardioplegic solution; Total thoracoscopy; Cardiac surgery.

Introduction

Total thoracoscopy (TTS) for cardiac surgery has recently been of great interest in contrast to the traditional median sternotomy on account of advantageous minimal invasiveness, shorter period of hospital stay as well as comparable long-term outcomes [1,2]. However, the limited surgical exposure and surgeons' movement resulting from the small incision raise concerns that augmented aortic cross-clamp (ACC) time probably aggravates the cardiac ischemic injury and therefore compromise the postoperative outcomes. To address these, tremendous efforts have been made such as the minimization of crowded surgical fields and simplification of surgical procedures [3]. Additionally, the myocardial protection is particularly imperative in this setting. The frequently adopted cardioplegia solutions that enable a pharmacological myocardial arrest in diastole would reduce energy use and thereby minimize the myocardial ischemic injury [4]. Buckberg Blood cardioplegic [BCP] solution in a (1:4) dilution with whole blood has been the standard solution extensively applied in adult cardiac surgery for decades because of its more oxygen-carrying capacity and physiological properties [5,7]. But the multiple-dose administration may interrupt the operation flow. In contrast, Custodial histidine-tryptophan-ketoglutarate (HTK) which is an intracellular crystalloid cardioplegic solution, allows a single-dose administration. It also emerged as a promising cardioplegic agent in children and adults since first fabricated by Bretschneider in the (1970) s [8,9]. Both have been demonstrated with comparable safety and effectiveness in isolated aortic valve replacement and elective mitral valve surgery [10,11]. However, the direct comparison between these two cardioplegic solutions in a spectrum of TTS for cardiac surgery is scanty. Therefore, this study was undertaken to compare the myocardial protection performance in the context of totally thoracoscopic cardiac surgery between BCP and HTK solutions.

Methods

Study design: A total of 101 patients undergoing thoracoscopic cardiac surgery using either BCP or HTK solution between January 2021 to December 2021 at Guangdong Provincial People's Hospital were retrospectively enrolled. The demographic data, medical history, surgery information, anesthesia record, and perfusion record were all reviewed and collected. The present study was approved by the Guangdong Provincial People's Hospital ethics committee.

Surgical technique: Conventional general anesthesia was applied to all patients. The route for TTS was established by the right lateral 3rd to 4th intercostal space or right anterior 2nd to 3rd intercostal space. To achieve cardiopulmonary bypass (CPB), cannulation of the femoral artery and vein was first performed. The right internal jugular vein was directly cannulated for drainage of the superior vena cava. All cardiac procedures were performed under mild hypothermia or normothermia. After CPB establishment and ACC, cardioplegic solutions were infused in antegrade, retrograde, or both fashions. The details of cardioplegic solution administration varied individually. In general, the BCP in a 4:1 blood dilution was administrated with an initial dose of 1200-1500 ml and a maintained dose of approximately 500 ml given every 15-20 minutes thereafter. In contrast, HTK was administrated in a single-dose manner with 2000 ml and most commonly in an antegrade direction. If the ACC time is over 2 hours, an additional dose of 500-1000 ml would be used. The use of inotropes, insulin requirement, fluid administration, and intraoperative transfusion would be carried out and decided by the whole surgical team following the institutional protocols.

Study endpoints: The primary outcome reflecting postoperative myocardial injuries included postoperative levels of cardiac Troponin T (cTnT) and creatine kinase-MB [CKMB] at different periods, the capacity of return to spontaneous rhythm, postoperative left ventricle ejection fraction (LVEF) as well as vasoactive-inotropic score (VIS). Myocardial infarction (MI) was defined as the postoperative CKMB of more than 100 ug/L as previously described [12]. The VIS was calculated according to the following formula: VIS = 10,000 × vasopressin (mU/kg/min) + 10 × milrinone (mg/kg/min) + 100 × norepinephrine (mg/kg/min) + 100 × epinephrine (mg/kg/min) + dobutamine (mg/kg/min) + dopamine (mg/kg/min) [13]. The secondary endpoints included mechanical ventilation time, intensive care unit (ICU) stay, hospital stay, mechanical circulatory support [MCS], and in-hospital mortality.

Statistical analysis: Continuous data were presented as mean ± standard deviation if normally distributed or median with interquartile range if non-normally distributed. Categorical data were presented as the frequency with percentage. The results between the two groups were compared using the Student t-test, Mann-Whitney U test, chi-square test, and Fisher exact test as appropriate. Multivariate logistic regression for postoperative outcomes including MI and return to spontaneous rhythm was performed with the following independent variables: age, female gender, body mass index (BMI), atrial fibrillation, LVEF, HTK, ACC time, and total volume. All statistical analysis were performed using the IBM SPSS Statistics version 26.0 and R statistical software version 4.1.3. A p-value less than 0.05 were considered to be significant.

Results

Baseline characteristics: In the present study, 69 patients underwent totally thoracoscopic cardiac surgery with BCP perfusion while 32 patients with HTK perfusion. The baseline characteristics

were summarized in Table 1. The two groups were comparable as a consequence of no significant difference in age, female gender, BMI, atrial fibrillation, hypertension, diabetes, dyslipidemia, cerebrovascular event, creatine (Cr), cTnT, CKMB, LVEF, European System for Cardiac Operative Risk Evaluation (euroSCORE) (p>0.05).

Perioperative data: As shown in Table 2, the pre-perfusion blood gas analysis (BGA) including the K^+, Hematocrit (Hct), and Lactate were similar between the two groups. However, 98.55% were delivered in an antegrade fashion in the BCP group, significantly higher than 84.38% in the HTK group (p<0.05). There were significantly higher total doses but lower total volume in the BCP group in contrast to the HTK group (p<0.05). No significant differences regarding the surgical procedures, CPB time, and ACC time was observed between the two groups (p>0.05).

Outcomes: In Table 3, a significantly more proportion of patients perfused by BCP could return to spontaneous rhythm than by HTK (84.58% for the BCP group vs 62.50% for the HTK group) (p=0.025). The median level of both Hct and lactate was significantly lower in the BCP group than that in the HTK group (p<0.05). However, both the postoperative peak cTnT/CKMB (Table 3) and the postoperative cTnT/CKMB levels at the period of <24h, 24-48h, and >48h (Figure 1) were similar between the two groups. There was no significant difference in the postoperative LVEF, VIS, mechanical ventilation time, ICU stay, MI, need for MCS, and in-hospital mortality (p>0.05). In (Figure 2), multivariate logistics regression revealed that the type of cardioplegic solutions was not associated with MI but associated with a return to spontaneous rhythm. Specifically, HTK perfusion was associated with a lower possibility to return to spontaneous rhythm (odds ratio (OR)=0.238; confidence interval (CI)=0.072-0.783; p=0.018). Additionally, increased ACC time (per 10 mins) was associated with a higher risk of MI (OR=1.499; CI=1.161-1.934; p=0.002) while increased total volume was associated with a lower risk of MI (OR=0.997; CI=0.994-0.999; p=0.029).

Table 1: Baseline characteristics.

	BCP (n=69)	HTK (n=32)	p
Age (y)	50.44±14.52	51.63±12.79	0.693
Female gender	39 (56.52%)	16 (50.00%)	0.540
BMI (kg/m^2)	22.77 (20.80-27.06)	23.64 (20.05-25.29)	0.737
Atrial fibrillation	21 (30.43%)	9 (28.13%)	0.813
Hypertension	8 (11.59%)	4 (12.50%)	>0.999
Diabetes	1 (1.45%)	2 (6.25%)	0.489
Dyslipidemia	3 (4.35%)	2 (6.25%)	1.000
Cerebrovascular event	5 (7.25%)	0 (0)	0.285
Cr (mmol/L)	70.80 (59.38-84.38)	76.75 (61.04-81.22)	0.867
cTnT (ug/L)	7.50 (2.50-11.75)	8.60 (6.18-11.80)	0.358
CKMB (u/L)	5.00 (5.00-11.07)	5.44 (5.00-11.23)	0.627
LVEF (%)	65.43±6.20	64.27±6.55	0.390
euroSCORE	4.00 (3.00-6.00)	4.00 (3.00-6.15)	

BCP: Blood Cardioplegia; HTK: Histidine-Tryptophan-Ketoglutarate; BMI: Body Mass Index; Cr: Creatine; cTnT: Cardiac Troponin T; CKMB: Creatine Kinase-MB; LVEF: Left Ventricle Ejection Fraction; euroSCORE: European System for Cardiac Operative Risk Evaluation.

Table 2: Operative profile.

	BCP (n=69)	HTK (n=32)	p
Pre-BGA			
K^+ (mmol/L)	3.60 (3.30-3.90)	3.50 (3.33-3.98)	0.798
Hct (%)	35.00 (29.00-37.50)	36.50 (30.25-41.00)	0.213
Lactate (mmol/L)	0.80 (0.70-1.10)	0.80 (0.70-1.18)	0.789
Delivery			0.016
Antegrade	68 (98.55%)	27 (84.38%)	
Retrograde	1 (1.45%)	3 (9.38%)	
Antegrade and retrograde	0 (0)	2 (6.25%)	
Cardioplegia			
Total doses	2 (1-2)	1 (1-1)	0.000
Total volume (ml)	1900 (1500-2100)	2000 (2000-2000)	0.004
Surgical procedures			0.262
AV	4 (5.80%)	3 (9.37%)	
MV	35 (50.72%)	17 (53.13%)	
TV	2 (2.90%)	0 (0)	
ASD	1 (1.45%)	0 (0)	
AV+MV	1 (1.45%)	3 (9.37%)	
MV+TV	23 (33.33%)	7 (21.88%)	
AV+MV+TV	1 (1.45%)	2 (6.25%)	
ASD+TV	2 (2.90%)	0 (0)	
CPB time (min)	150.79±44.18	154.00±50.44	0.746
ACC time (min)	88.57±34.19	95.84±33.73	0.320

BCP: Blood Cardioplegia; HTK: Histidine-Tryptophan-Ketoglutarate; BGA: Blood Gas Analysis; Hct: Hematocrit; AV: Aortic Valve; MV: Mitral Valve; TV: Tricuspid Valve; ASD: Atrial Septal Defect; CPB: Cardiopulmonary Bypass; ACC: Aortic Cross-Clamp.

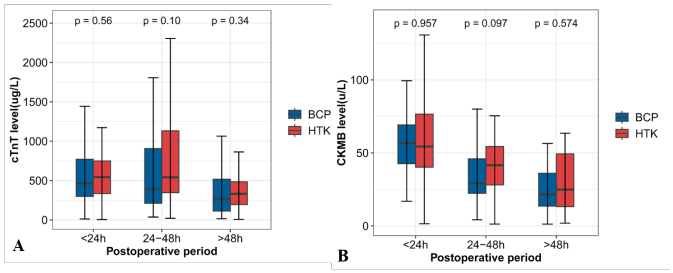

Figure 1: Comparison of cTnT **(A)** and CKMB level **(B)** between the BCP group and HTK group among different postoperative periods. A. No significant difference in cTnT level was detected between the BCP group and HTK group among <24h, 24-48h, and >48h after the totally thoracoscopic cardiac surgery (p>0.05). B. No significant difference in cTnT level was detected between the BCP group and HTK group among <24h, 24-48h, and >48h after the totally thoracoscopic cardiac surgery (p>0.05).
Cr: creatine; cTnT: Cardiac Troponin T; CKMB: Creatine Kinase-MB; BCP: Blood Cardioplegic; BCP: Blood cardioplegia; HTK: Histidine-tryptophan-ketoglutarate.

Table 3: Early postoperative outcomes.

	BCP (n=69)	HTK (n=32)	p
Return to spontaneous rhythm	58 (84.58%)	20 (62.50%)	0.025
Post-BGA			
K^+ (mmol/L)	5.10 (4.50-5.76)	5.40 (4.90-5.85)	0.155
Hct (%)	25.00 (24.00-28.50)	28.00 (24.25-31.50)	0.045
Lactate (mmol/L)	1.10 (1.00-1.50)	1.40 (1.20-2.30)	0.005
LVEF (%)	62.00 (56.29-65.00)	60.00 (53.43-63.88)	0.462
Peak cTnT (ug/L)	479.20 (315.10-1004.10)	609.10 (323.25-1106.10)	0.919
Peak CKMB (u/L)	56.00 (41.40-71.10)	51.25 (32.17-76.50)	0.414
VIS	5.00 (3.00-6.75)	5.00 (2.00-8.75)	0.878
Mechanical ventilation time (h)	9.92 (4.17-18.75)	7.50 (4.17-17.71)	0.677
ICU stay (h)	44.58 (22.75-69.50)	39.85 (21.10-67.98)	0.348
Hospital stay (d)	6.00 (5.00-8.00)	7.00 (5.00-8.00)	0.415
MI	6 (8.70%)	6 (18.75)	0.262
MCS	2 (2.90%)	0 (0)	0.837
In-hospital mortality	2 (2.90%)	0 (0)	0.837

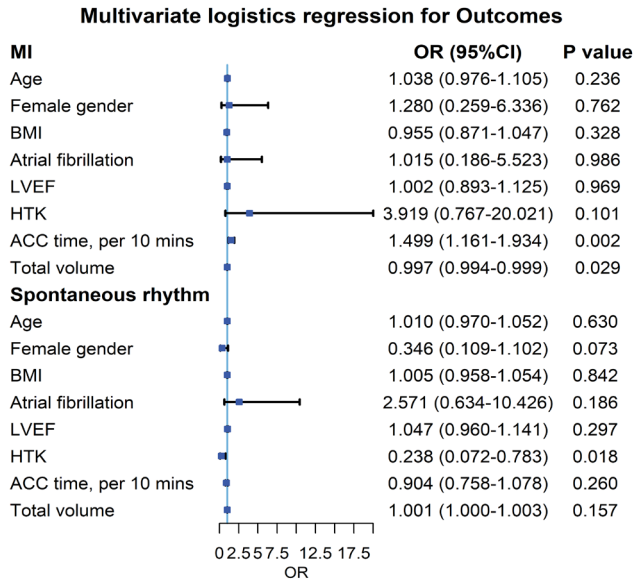

Figure 2: Multivariate logistics regression for postoperative MI and return to spontaneous rhythm. ACC time was identified as a risk factor for postoperative MI, while total volume was identified as a protective factor for postoperative MI. HTK was identified to be associated with lower possibility of return to spontaneous rhythm. BMI, body mass index; LVEF, left ventricle ejection fraction; HTK, histidine-tryptophan-ketoglutarate; ACC: Aortic Cross-Clamp; OR: Odds Ratio; CI: Confidence Interval.

Discussion

The present study found that the myocardial protection performance was equivalent between HTK and BCP groups in the context of cardiac surgery by TTS, as a consequence of the similar level of myocardial enzymes at any postoperative time point, LVEF, VIS, and incidence of MI. Additionally, the administration of HTK resulted in comparable short-term clinical outcomes in terms of mechanical ventilation time, ICU stay, hospital stay, MCS, and in-hospital mortality versus BCP. However, the HTK solution seems to compromise the capacity of postoperative return to spontaneous rhythm. HTK is an intracellular crystalloid cardioplegic solution with tryptophan to stabilize the cell membrane, ketoglutarate to promote ATP energy generation during reperfusion, histidine as a buffer, and mannitol to ameliorate the cellular edema [14,16]. It can cause heart arrest by inhibiting the rapid phase of the action potential, theoretically protecting the myocardial ischemia for up to 120 minutes. Indeed, our study demonstrated comparable myocardial protection as well as short-term outcomes on HTK administration in contrast to the standard BCP administration in a spectrum of totally thoracoscopic cardiac surgery, which is consistent with the previous studies in other situations. Viana et al. compared the use of HTK versus standard tepid blood cardioplegia in complex cardiac procedures, suggesting that the myocardial protection was comparable between the two groups in this setting [9]. Hoyer et al. assessed the impact of BCP and HTK administration on short- and long-term outcomes in isolated aortic valve replacement, also showing equivalent outcomes [10]. Therefore, our findings verified the safety and efficacy of HTK as an alternative cardioplegic agent to BCP in cardiac procedures by TTS. Of note, patients receiving HTK solutions were not prone to return to spontaneous rhythm after cross-clamp removal in our study. In other words, more proportional spontaneous ventricular fibrillation occurred in the HTK group, which was lined with the previous study [11]. This may at least in part be attributed to the conduction disturbances of low adenosine triphosphate levels, electrolyte concentration alteration across the cell membranes, oxidative stress, and insufficient myocardial protection resulting from heterogeneous reperfusion. Regardless, the increased spontaneous ventricular fibrillation in the HTK group seems not adversely impact the myocardial enzyme release and short-term outcomes. The total volume of cardioplegic solution was significantly higher in the HTK group than that in the BCP group. HTK acting as single-dose formula requires more volume to ensure relatively myocar-

dial homogenous distribution of cardioplegia as well as complete cooling. In this study, the volumes were applied following the recommendations from HTK manufactured company determined by the experienced perfusionist. There were several inherent limitations in this study. The retrospective and single institution in nature limits its generalizability. A prospective multi-center investigation comparing HTK and BCP is warranted. Additionally, the number of enrolled patients was not sufficient to verify any small but significant difference in our primary endpoints such as LVEF and VIS. What's more, we did not capture perioperative serum sodium levels since the administration of HTK was demonstrated to be associated with an increased risk of hyponatremia and postoperative seizure [4]. Finally, continuous follow-up is required to assess the long-term impact of the cardioplegic solution type.

Conclusion

HTK administration during the totally thoracoscopic cardiac surgery provides comparable myocardial protection and short-term outcomes to the BCP administration. But HTK seems to compromise the capacity of postoperative return to spontaneous rhythm. A randomized prospective study comparing safety and efficacy between these two groups is warranted.

Declarations

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Conflicts of interest: The authors declared no conflicts of interest.

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