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Clinical comparative analysis of histidine-tryptophan-ketoglutarate solution and St. Thomas crystalloid cardioplegia: A 12-year study from a single institution

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Abstract. Cardioplegic reperfusion during a long-term ischemic period interrupts cardiac surgery and increases cellular edema due to repeated administration. The present clinical study compared the protective effects of histidine-ketoglutarate-tryptophan (HTK) solution and St. Thomas crystalloid cardioplegia. Clinical experiences of the myocardial protection induced by one single perfusion with HTK were reviewed in high-risk patients with severe pulmonary arterial hypertension associated with complex congenital heart disease. This retrospective study included 88 high-risk patients (aortic cross-clamp time, >120 min) between March 2001 and July 2012. The cohort was divided into two groups according to the technique used. Either myocardial protection was performed with one single perfusion with HTK solution (HTK group) or with conventional St. Thomas crystalloid cardioplegia (St group). The duration of cardiopulmonary bypass did not differ between the two groups. The mortality, morbidity, intensive care unit (ICU) stay, postoperative hospitalization, and transfusions of HTK group are significantly lower than those of the St group (P<0.05). Univariate and multivariate analysis demonstrated that HTK is a statistically significant independent predictor of decreased early mortality and morbidity (P<0.05). In conclusion, the present findings suggested that HTK solution decreases mortality, morbidity, ICU stay, postoperative hospitalization, and transfusions in high-risk patients with severe pulmonary arterial hypertension associated with complex congenital heart disease.

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Introduction

With the development of cardiac surgery, an increasing number of high-risk patients with complex congenital heart disease have undergone cardiac surgery (1,2). Ischemia-reperfusion injury during cardiac surgery is associated with increased mortality and morbidity. The improvement of myocardium tolerance to ischemia for high-risk patients with complex congenital heart disease is a key issue (3). However, the optimal myocardial protection strategy for high-risk patients with complex congenital heart disease remains controversial (1,4). There are two main groups of cardioplegic solutions; one is based on extracellular components with high potassium, magnesium and bicarbonate levels and the other is based on intracellular electrolytes. The histidine-ketoglutarate-tryptophan (HTK) solution, which is based on intracellular electrolytes, was introduced by Preusse *et al* in 1981 (5). A single-dose strategy for myocardial protection, which avoids interrupting the procedure to re-administer cardioplegia, is preferable during lengthy surgery.

Histidine, tryptophane and ketoglutarate are the components of HTK solution. Histidine has a buffer effect and may enhance the efficiency of anaerobic glycolysis, tryptophane stabilizes the cell membrane and the addition of mannitol decreases cellular oedema, whereas ketoglutarate is a precursor of nicotinamide adenine dinucleotide (6). Several studies have demonstrated the efficacy of the HTK solution based on biochemical markers or physiological evaluation in experimental models (7-9). HTK solution helps to preserve myocardial adenosine triphosphate stores, improve post-arrest contractile function and minimize myocardial necrosis (10,11). HTK solution has also been shown to preserve the coronary artery endothelium, which may help to improve functional cardiac recovery (12,13). Careaga *et al* (14) reported that patients treated with HTK solution had a lower incidence of arrhythmias, length-of-stay in the intensive care unit (ICU) and inotropic support, postoperatively.

It was hypothesized that a single-dose of HTK may provide superior myocardial protection than cold crystalloid cardioplegia in high-risk patients. The present clinical study compared the protective effects of HTK Solution and St. Thomas crystalloid cardioplegia in high-risk patients with severe pulmonary arterial hypertension associated with complex congenital heart disease.

Materials and methods

Patients. Cardiac catheterization data was collected from patients under general anesthesia. Severe pulmonary arterial hypertension was defined as mean pulmonary pressure >50 mmHg or systolic pulmonary/systemic pressure ratio >0.8. A total of 88 high-risk patients (47 males, 48 females; aortic cross-clamp time, >120 min) aged >6 months (3.17±3.36 years) with dextro-transposition of the great arteries (d-TGA) and nonrestrictive ventricular septal defect or Taussig-Bing anomaly and severe pulmonary arterial hypertension who underwent arterial switch surgery (two ventricles repair) at Fuwai Hospital between March 2001 and July 2012 were included in the study. Patients were divided into two groups: HTK group (myocardial protection was performed with a single perfusion of HTK solution) and the St group (control group; myocardial protection with conventional St. Thomas cold potassium cardioplegia) (Table I). Inclusion criteria included: Patients aged >6 months who were diagnosed as d-TGA and nonrestrictive ventricular septal defect or Taussig-Bing anomaly and severe pulmonary arterial hypertension. Exclusion criteria included: Patients aged <6 months; mean pulmonary arterial pressure <50 mmHg or systolic pulmonary/systemic pressure ratio <0.8; or 21 trisomy. Diagnosis (according to the International Congenital Heart Surgery Nomenclature) was made on the basis of echocardiographic and cardiac angiographic findings and was confirmed during surgery. Hospital charts, echocardiographic and cardiac catheterization data and operative reports were reviewed. Cardiac catheterization was performed under general anesthesia. Preoperative pulmonary artery pressure and pulmonary vascular resistance were measured according to the conventional cardiac catheterization protocol and Fick method (15,16) The Medical Ethics Committee of Fuwai Cardiovascular Disease Hospital approved the study protocol, and approval was granted to waive the requirement for patient consent for publishing follow-up data about the present patients.

Data collection. Clinical records of 88 high-risk patients included in the present study were retrospectively reviewed. If a patient succumbed to their symptoms, their death certificate and the medical records of the hospital and physician were reviewed. In the present study, early mortality was defined as mortality prior to hospital discharge or within 30 days of arterial switch surgery.

Anesthesia management. Prior to surgery, anesthesia was induced with intravenous ketamine (1.5 mg/kg; Xi'an HanFeng Pharmaceutical Co. Ltd., Xi'an, China), fentanyl (30 μg/kg; Yichang Humanwell Pharmaceutical Co. Ltd., Yichang, China), and pancuronium (0.15 mg/k; Organon International, Oss, Netherlands). During surgery, fentanyl (0.3 μg·kg-1·min-1; Yichang Humanwell Pharmaceutical Co. Ltd.) was used for maintenance. An arterial line in the radial artery or femoral artery was used for hemodynamic monitoring. Specifically, a central venous pressure catheter was installed via the subclavian vein, and a urinary catheter was installed.

Table I. Compositions of the two cardioplegic solutions.

Substrate (mM)	HTK[a]	St. Thomas[b]
K^+	10	16
Na^+	15	116
Ca^{2+}	0.02	1.2
Mg^{2+}	4	16
Sodium bicarbonate	0	10
Histidine	180	0
Tryptophan	2	0
α-ketoglutarate	1	0
Mannitol	30	0
Theoric osmolality (mOsm/l)	310	318

[a]Intracellular solution; [b]extracellular solution. HTK, histidine-ketoglutarate-tryptophan; St. Thomas, St. Thomas crystalloid cardioplegia.

Cardiopulmonary bypass. Cardiopulmonary bypass was performed using a Dideco 901 or 902 hollow fiber oxygenator (Sorin Group, Mirandola, Italy), and a roller pump (Jostra GmbH, Munich, Germany) with non-pulsatile flow. A tubing pack, which contained a crystalloid cardioplegia delivery system (Beijing Perfect Chemical Material Co. Ltd., Beijing, China) and an arterial clotting time was maintained above 400 sec during cardiopulmonary bypass. Heparin (Shanghai No. 1 Biochemical Pharmaceutical Co., Ltd., Shanghai, China) was neutralized with protamine chloride (4 mg/kg) after cardiopulmonary bypass.

Infusion of cardioplegia. Under cardiopulmonary bypass and aortic cross-clamping, cardioplegic arrest was induced. HTK solution (4-8˚C) was perfused as a single dose (40-50 ml/kg) via the aortic root at an initial perfusion pressure of 80-100 mmHg. Infusion was maintained at 40-60 mmHg over 5-7 min. St. Thomas solution (4-8˚C; initial dose, 20 ml/kg; maintenance dose, 10 ml/kg) was perfused (antegrade) every 30 min at a pressure of 100-120 mmHg. Cardiopulmonary bypass time and aortic cross-clamping time were recorded. The presence of arrhythmias during reperfusion after aortic cross-clamping and during the postoperative period was evaluated.

Surgical technique. Median sternotomy and hypothermic cardiopulmonary bypass with ultrafiltration technique were routinely used. Cardioplegia solution was administered (HTK solution: 40-50 ml/kg; St. Thomas solution: Initial dose 20 ml/kg, maintenance dose 10 ml/kg). Surgery was performed on cardiopulmonary bypass at low flow (50 ml/kg/min) with a rectal temperature of 18-22˚C. Ventricular and atrial septal defect and patent ductus arteriosus were completely closed. The aorta was transected and the aortic root was fully dissected. A large aortic button containing the coronary orifice was harvested. The pulmonary

Table II. Demographic and operative data.

Variable	HTK group (n=70)	St group (n=18)	P-value
Patients, n	70	18	
Male, n (%)	35	12	0.833
Age, years	3.4±0.4	2.2±0.5	0.176
Weight, kg	12.0±0.9	10.2±1.2	0.347
c/t ratio	0.6±0.01	0.6±0.01	0.614
CPB time, min	239.9±6.8	233.4±11.4	0.654
Aortic cross-clamp time, min	170.8±4.2	158.8±5.8	0.181
SPO_2	74.9±1.9	73.4±3.2	0.719
Pre-op mPAP	65.3±1.6	61.2±3.1	0.246
Post-op mPAP	31.9±1.3	31.8±2.2	0.965
Pre-op PVR	524.4±134.9	439.4±120.3	0.769
Ultrafiltration, ml	831.9±148.7	545.6±62.4	0.336
Chest drainage, ml	401.6±89.2	367.1±71.5	0.848

Data are presented as the mean ± standard error of the mean, unless otherwise stated. HTK, histidine-ketoglutarate-tryptophan solution; St, St. Thomas crystalloid cardioplegia; c/t ratio, cardiothoracic ratio; CPB time, time of cardiopulmonary bypass; SPO2, pulse oxygen saturation; Pre-op mPAP, preoperative mean pulmonary arterial pressure; Post-op mPAP, postoperative mean pulmonary arterial pressure; Pre-op PVR, preoperative pulmonary vascular resistance.

Table III. Hospital mortality and morbidity.

Variable	HTK group, n=70. n (%)	St group, n=18. n (%)	P-value
Mortality	2 (2.8)	4 (22.2)	0.015
Cause			
Severe arrhythmia	1 (1.4)	2 (11.1)	0.105
PH crisis	1 (1.4)	0	1.000
MOF	0	2 (11.1)	0.040
Morbidity	14 (20)	12 (66.7)	<0.001
Cause			
PH crisis	1 (1.4)	0	1.000
LOS	1 (1.4)	1 (5.6)	0.369
Arrhythmia	0	1 (5.6)	0.205
Respiratory failure	0	1 (5.6)	0.205
Pneumonia	5 (7.1)	1 (5.6)	1.000
Pneumothorax	0	1 (5.6)	0.205
pleural effusion	5 (7.1)	1 (5.6)	1.000
Hemorrhage	2 (2.9)	2 (11.1)	0.184
Sepsis	0	1 (5.6)	0.205
Gastrointestinal	0	1 (5.6)	0.205
MOF	0	2 (11.1)	0.040

HTK, histidine-ketoglutarate-tryptophan solution; St, St. Thomas crystalloid cardioplegia; PH, pulmonary arterial hypertension; LOS, low-output syndrome; MOF, multiple organ failure.

trunk was transected, pulmonary branches dissected, and the Lecompte maneuver (17) was performed. The coronary artery was reimplanted to an appropriate site of the neo-aorta. Pulmonary artery reconstruction was performed using a fresh autologous pantaloon-shaped pericardial patch. Associated anomalies were corrected simultaneously. Associated anomalies include patent ductus arteriosus, atrial septal defect, mild left ventricular outflow tract obstruction, mild right ventricular outflow tract obstruction, mitral insufficiency, tricuspid insufficiency, pulmonary veinstenosis, aortic arch coarctation, major aortopulmonary collaterals and anomalous origin of the right pulmonary artery from the ascending aorta. Postoperative pulmonary artery pressure measurements were recorded in the operating room at the end of the surgery.

Follow-up. All survivors were followed-up to the end date of the study (July 2012). All patients at the outpatient department were subjected to electrocardiogram, X-ray chest film and echocardiogram analysis. Patients were followed-up at the outpatient department once every three months. At the final follow-up, patients were contacted by telephone or were directly interviewed at the outpatient department.

Statistical analysis. All analyses were performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard error of the mean and were compared by a two-tailed Student's t-test. Survival rates were estimated using the Kaplan-Meier method. Comparison of multiple mean values was performed by analysis of variance. Discrete variables were expressed as percentages and compared by Fisher's exact test or Pearson's χ^2 test, as required. End-points of the study included prevalence and cause of hospital mortality, prevalence and cause of hospital morbidity, resource utilization (assisted ventilation, intensive care and blood transfusions) and postoperative hospital stay. Associations with perioperative risk factors were assessed by means of contingency table methods and logistic regression analysis. To explore the simultaneous effects of perioperative characteristics on early mortality, variables that were significant at the 0.1 level in univariate analysis were included in a multivariate logistic regression model. $P<0.05$ was considered to indicate a statistically significant difference.

Table IV. Resource utilization.

Variable	HTK group (n=70)	St group (n=18)	P-value
Ventilation, h	112.6±29.6	219.2±61.8	0.118
ICU stay, days	10.5±1.4	20.1±4.4	0.009
Post-op hospitalization, days	19.1±1.5	26.1±4.3	0.063
Transfusions, ml	772.1±88.7	1352.9±214.7	0.007

Data are presented as the mean ± standard error of the mean. HTK, histidine-ketoglutarate-tryptophan solution; St, St. Thomas crystalloid cardioplegia; ICU, intensive care unit; Post-op hospitalization, postoperative hospitalization.

Table V. Alterations in serum sodium in the histidine-ketoglutarate-tryptophan group.

Variable	Prior to CPB	After clamping	After declamping	After CPB	In PICU
Hct (%)	37±3	26±4	29±1	34±3	35±5
Na^+ (mmol/l)	136.8+2.5	132.6±3.1[a]	134.6±2.1	137.6±2.3	139.8±2.1
Lac (mmol/l)	0.9±0.2	1.5±0.3	2.1±1.5	2.3±1.6	1.8±1.3
Osm (mOsm/kg)	272.8±4.3	266.8±7.3	272.6±5.1	277.8±5.1	282.8±5.3

Data are presented as the mean ± standard error of the mean. CPB, cardiopulmonary bypass; Hct, hematocrits; Lac, lactate; Osm, osmotic pressure; PICU, pediatric intensive care unit. [a]P<0.001.

Table VI. Spontaneous defibrillation.

Group	n	Spontaneous defibrillation, n (%)	P-value
HTK	70	65 (92.9)	0.027
St	18	13 (72.2)	

HTK, histidine-ketoglutarate-tryptophan solution; St, St. Thomas crystalloid cardioplegia;.

Results

Patients. Table II shows the demographic and operative data. Preoperative cardiac catheterization data were available for all patients. No significant differences were observed between any of the variables.

Mortality and morbidity. The mortality rate during surgery was 6/88. Mortality in the HTK group was significantly lower than that of the St group (2.8 vs. 22.2%; P=0.015), suggesting that HTK solution may decrease mortality. Multiple organ failure in HTK group was significantly lower than that in St group (0.0 vs. 11.1%; P=0.040), suggesting that the effect of organ preservation of HTK solution is better than that of St. Thomas crystalloid cardioplegia. The incidence of morbidity in HTK group was significantly lower in than that in St group (20 vs. 66.7%; P<0.001; Table III), suggesting that HTK solution has better clinical effect than St. Thomas crystalloid cardioplegia.

Resource utilization. In the HTK group, the duration of ICU stay was significantly shorter than that of the St group (10.5±1.4 vs. 20.1±4.4 days; P=0.009), suggesting that the clinical effect of HTK solution is better than that of St. Thomas crystalloid cardioplegia. The mean volume of transfusions for patients was significantly reduced in the HTK group (772.1±88.7 vs. 1352.9±214.7 ml; P=0.007; Table IV); however, the reason for this remains to be elucidated.

Alterations in serum sodium in HTK group. Table V shows the changes of serum sodium observed in the HTK group. The results indicated that serum sodium in the HTK group decreased after clamping (P<0.001; Table V).

Spontaneous defibrillation. Following reperfusion, rates of spontaneous defibrillation in the HTK group were significantly higher than those of the St group (92.9 vs. 72.2%; P=0.027) (Table VI), indicating that the myocardial protection effect of HTK solution is superior to that of St. Thomas crystalloid cardioplegia.

Follow-up results. Follow-up was successfully completed by 90.2% (74/82) of patients. The mean duration of follow-up was 58.8±26.8 months; two late deaths (deaths that occurred >2 months post-surgery) occurred due to sudden death with no known reason. The overall survival rate of patients in the present study was 97.3% (72/74). The latest follow-up data showed that 2.8% of survivors were in New York Heart Association Class II and 97.2% were in Class I, showing that the midterm results of the operation are excellent.

Analysis of risk factors associated with early mortality and morbidity. Both univariate and multivariate analysis showed that HTK was associated with decreased early mortality [odds ratio (OR=0.103, P=0.013 and OR=0.135, P=0.045, respectively) and morbidity (OR=0.132, P<0.001 and OR=0.097, P<0.001, respectively; Table VII). This strongly indicates that the myocardial protection effect of HTK solution is superior to that of St. Thomas crystalloid cardioplegia.

Discussion

Mortality and morbidity rates for high-risk patients with complex congenital heart disease are relatively high; therefore, although it remains difficult, the optimal myocardial protection strategy for high-risk patients should be urgently determined (6,18). Data collected from instances in which HTK solution has been used for high-risk patients with complex congenital heart disease remains rare (19-22).

A study of Fuwai Hospital compared the myocardial protective effect induced by HTK solution and conventional St. Thomas crystalloid cardioplegia on the long-term ischemic period (cross-clamping time, >90 min) during severe complex pediatric cardiac surgery without pulmonary arterial hypertension. The results demonstrated that mortality rates and the levels of CK in the HTK solution group were significantly lower, as compared with these values in the St. Thomas crystalloid cardioplegia group (P<0.05). Patients with severe pulmonary arterial hypertension associated with congenital heart disease are difficult to treat in clinic practice. Older patients

Table VII. Analysis of RF for early mortality and morbidity.

Model	OR	95% CI	P-value
Univariate analysis of risk factors for mortality			
HTK	0.103	0.017-0.618	0.013
Multivariate analysis of risk factors for mortality			
HTK	0.135	0.019-0.954	0.045
Sex	2.389	0.338-16.867	0.383
Age	0.574	0.558-1.382	0.668
Univariate analysis of risk factors for morbidity			
HTK	0.132	0.042-0.409	0.000
Multivariate analysis of risk factors for morbidity			
HTK	0.097	0.028-0.336	0.000
Sex	0.553	0.179-1.706	0.303
Age	1.208	1.037-1.407	0.015

OR, odds ratio; CI, confidence interval; UVA, univariate analysis; multivariate analysis; RF, risk factors; HTK, histidine-ketoglutarate-tryptophan solution.

(aged >6 months) with complex congenital heart disease with severe pulmonary arterial hypertension are at a higher risk of developing postoperative pulmonary arterial hypertension (23). Postoperative pulmonary arterial hypertension is a major determinant of perioperative morbidity and mortality (24,25).

Conventional St. Thomas cold potassium cardioplegia solution is routinely used at Fuwai Hospital, and HTK solution is used in patients with complex congenital heart disease. A comparison of the myocardial protection of a single dose of HTK solution and St. Thomas crystalloid cardioplegia in high-risk patients with severe pulmonary arterial hypertension associated with complex congenital heart disease may have more power to detect significant differences in myocardial protection between HTK solution and St. Thomas crystalloid cardioplegia. Older patients (aged >6 months) with complex congenital heart disease with severe pulmonary arterial hypertension were included in the present study, whereas patients without severe pulmonary arterial hypertension were excluded.

In the present 12-year retrospective analysis of Fuwai Hospital, the mortality rate and incidence of morbidity in the HTK group was significantly lower than that of the St group, and the ICU stays of patients in the HTK group were significantly shorter than those in the St group. The mean volume of transfusions for patients was significantly less in the HTK group, as compared with the St group. Following reperfusion, rates of spontaneous defibrillation in the HTK group were significantly higher than those observed in the St group. Univariate and multivariate analyses showed that HTK was associated with decreased early mortality and morbidity.

The present study demonstrated that HTK solution is more effective than the St. Thomas crystalloid cardioplegia at protecting the myocardium from ischemia. However, subsequent prospective randomized controlled trials in a uniform group of high-risk patients are required to detect equivalence or important differences.

Blood cardioplegia has typically been used as the standard to protect the myocardium. Conventional St. Thomas crystalloid cardioplegia and blood cardioplegia must be repeated every 20-30 min and the surgical procedure must be suspended during infusion. An uninterrupted surgical field is desirable, and single-dose cardioplegia may be preferable in more complex cardiac procedures to avoid disturbing the technical flow of the surgery. Del Nido cardioplegia was formulated to act as single-dose administration in pediatric patients (26,27). Del Nido cardioplegia has not been widely used in Fuwai Hospital.

HTK induces fluctuations in sodium concentration, thus particular attention should be paid to low Na^+ levels. Hyponatremia becomes deleterious if osmolarity simultaneously becomes hypoosmolar. Aspirating HTK solution into a blood cell saver as much as possible avoids large volumes of HTK solution entering the cardiopulmonary bypass circuit, which would otherwise induce severe hyponatremia. Clinicians must avoid overtreatment of low sodium content to prevent severe neurologic complications. The application of small volumes (25-100 ml) of NaCl (5.85%) or $NaHCO_3$ (8.4%) to the circuit is recommended in adults during cardioplegic delivery to counteract low blood sodium content (28).

In conclusion, the present study showed that HTK solution decreases mortality, morbidity, ICU stay, postoperative hospitalization, and transfusions in high-risk patients with complex congenital heart disease. A prospective randomized controlled trial is required to determine the superior myocardial protective effects of HTK solution, as compared with conventional St. Thomas crystalloid cardioplegia.

Acknowledgments

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