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Myocardial Protection in Donor Heart Preservation: A Comparison Between Bretschneider's Histidine–Tryptophan–Ketoglutarate Solution and Cold Blood Cardioplegia

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ABSTRACT

Background. Optimal myocardial protection for donated hearts is crucial to improve outcomes of heart transplantation and reduce morbidity and mortality. This study aimed to compare the efficacy of myocardial protection using single dose of Bretschneider's histidine–tryptophan–ketoglutarate (HTK) solution and repeated doses of cold blood cardioplegia (CBC) in donor heart preservation.

Methods. Sixty-seven patients undergoing heart transplantation in Tri-Service General Hospital, Taipei, Taiwan between 2002 and 2012 were enrolled in this study. Patients were divided into an HTK group and a CBC group based on the preservation solution used to protect the donated hearts. The perioperative variables and postoperative outcomes were retrospectively reviewed.

Results. There were no statistic differences about demographic data in donors and recipients between the 2 groups. There were no significant differences in postoperative cardiac enzymes, hemodynamic data, length of stay in intensive care, or 30-day mortality between the groups. The HTK group showed a trend of shorter pumping time ($P = .091$). Multivariate analyses reveal that the HTK group had higher postoperative inotropic score ($P < .001$) and shorter pumping time ($P = .02$).

Conclusions. Single dose of Bretschneider's HTK solution could effectively reduce pumping time and afford similar myocardial protection compared with repeated doses of CBC in the preservation of donated hearts.

CARDIAC TRANSPLANTATION is a widely accepted treatment for end-stage heart failure. Advanced immunosuppression, monitoring of rejection, and prevention of postoperative infection after the procedure are reasons for the improvement. Preservation solutions play a large role in myocardial protection during ischemic arrest following distant organ procurement. The cold blood cardioplegia (CBC) made by St Thomas' Hospital solution mixed with blood in a 1:4 ratio has been used with favorable results in our center. However, this solution should be given repeatedly every 20 to 25 minutes during the anastomosis of the heart, which can interrupt heart transplantation several times. Moreover, repeat reperfusion increases the risk of air embolism. Improvement in organ preservation and subsequent surgical outcomes remains an important issue.

The histidine–tryptophan–ketoglutarate (HTK) solution, proposed by Bretschneider in the 1970s, has been widely used in liver, pancreas, and kidney preservation. In contrast, cardioplegia with HTK solution has been widely used clinically for open heart surgery and is comparable with CBC [1–5]. Reichenspurner et al studied the effect of HTK myocardial protection on 600 patients undergoing heart transplantation and demonstrated that the HTK could preserve the donor heart with good results, provided ischemic times were less than 4 hours [6]. It is simple to use with only a single dose and is claimed to provide myocardial

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0041-1345/14/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.11.056

protection for more than 2 hours. However, no studies have compared the effects of HTK and CBC on donor heart preservation. Thus, the main aim of this study was to compare Bretschneider's HTK solution and CBC with respect to the efficacy of myocardial protection in donor heart preservation.

PATIENTS AND METHODS

Population

After approval by an institutional review board, the medical records of 67 adult heart transplants performed between December 1, 2002, and November 30, 2012, were retrospectively reviewed. The HTK group included 18 recipients whose donated heart had been preserved in HTK solution and the CBC group included 49 patients whose heart had been preserved in CBC solution. Demographic data were analyzed for the 2 groups including age, sex, body weight, height, cause of heart failure, other systemic diseases, preoperative left ventricular ejection fraction (LVEF), and preoperative pulmonary vascular resistance index.

Donor Evaluation

The donor's demographic data (age, body weight, and height) and LVEF examined by echocardiography were evaluated. The procurement of the heart was performed according to standard procedures. After aortic cross-clamping, St Thomas' Hospital (StH) solution was infused at a dose of 30 to 40 mL/kg proximal to the aortic cross-clamp site. The StH solution was kept at a temperature of 4°C with copious amounts of cold saline for rapid cooling. In the HTK group, a further 30 to 40 mL/kg of cold HTK solution was infused at low perfusion pressure after procurement, and the donor heart was placed in a sterile bag containing the HTK solution. In the CBC group, another 15 mL/kg cold StH solution was infused and the heart was placed in StH solution. The heart was covered with ice-cold saline for topical cooling and packed in a transport container with ice [7].

Peri- and Postoperative Management

Before donor heart implantation in the recipient, the heart was perfused with either HTK or CBC. The HTK group hearts were perfused with HTK solution (30–40 mL/kg) at a hydrostatic pressure of 50 mm Hg for 6 to 8 minutes [7]. The CBC group hearts were perfused with StH solution mixed with blood in the ratio 1:4 (15 mL/kg) and repetitive doses given (7 to 8 mL/kg) every 20 to 30 minutes. During the perioperative period, all patients received inotropic support, usually starting at the dosage that the organ donor received immediately on procurement. For the first 48 hours after surgery, all patients received isoproterenol for chronotropic support to keep the heart rate at 100 to 120 beats per minute. The standard immunosuppression regimen consisted of 500 mg methylprednisolone before starting reperfusion, 250 mg immediately at the end of the operation, and 2 further doses of 125 mg at 8 and 16 hours after surgery. Oral mycophenolate (1 g/d, adjusted to keep white blood cell counts at 5000–7000/μL) was started 12 to 24 hours after HT, prednisolone was started at 0.4 mg/kg after the final dose of methylprednisolone, and cyclosporine (5–10 mg/kg/d) was started after the third postoperative day. Intravenous rabbit antithymocyte globulin (3–5 mg/kg/d) was administered for the first 3 to 7 days.

Table 1. Summary of Donor Data

Clinical Variable	HTK ($n = 18$)	STH ($n = 49$)	P Value
Age (mean ± SD)	37.4 ± 12.7	39.7 ± 12.3	.513
Body weight (kg)	70.4 ± 9.4	67.8 ± 10.6	.362
Body height (cm)	168.6 ± 5.7	165.7 ± 14.9	.417
LVEF (%)	61.6 ± 6.6	60.8 ± 6.4	.656

Data are shown as mean ± standard deviation.
Abbreviations: SD, standard deviation; LVEF, left ventricular ejection fraction; HTK, histidine–tryptophan–ketoglutarate solution; STH, St Thomas' Hospital solution.

Clinical Outcome

To evaluate the clinical results, we analyzed the ischemic time, cardiopulmonary bypass time, intensive care unit (ICU) stay, hospital stay, and 30-day mortality in each group. Blood samples for biochemical assessment including creatine kinase (CK), and its MB coenzyme (CKMB), troponin I were taken 0.5 and 24 hours after surgery. Patients in either the HTK or CBC group who died within 30 days were excluded from the comparisons of ICU stay, hospital stay, and cardiac enzyme concentration.

Hemodynamic Assessment

Patients in either group who died within 30 days were excluded from hemodynamic assessment. The inotropic scores (dopamine μg/kg/min × 1 + dobutamine μg/kg/min × 1 + milrinone μg/kg/min × 15 + epinephrine μg/kg/min × 100) at 0.5 and 24 hours after surgery were calculated. A Swan–Ganz catheter and 20-gauge arterial line were used for hemodynamic monitoring. Cardiac output, cardiac index, pulmonary capillary wedge pressure, and systemic and pulmonary vascular resistance index were recorded at 0.5 and 24 hours after surgery. Echocardiography assessment of cardiac function by LVEF was performed on days 3 and 7 after the operation.

Statistical Analysis

Statistical analysis was performed with the statistical software SPSS (SPSS Inc., Chicago, IL) for Windows version 17.0. Student t test and χ^2 test were used to determine the statistical significance of differences between the 2 groups. Quantitative data are shown as mean ± standard deviation. The significance level was at $P \leq .05$.

RESULTS

Donor Data

The donor data are presented in Table 1. Age, body weight, height, and LVEF were similar in the 2 groups.

Recipient Data

All recipient data are summarized in Table 2. Age, sex, body weight, height, and cause of heart failure were similar in the 2 groups. The preoperative LVEF was 19.5% ± 7.1% in the HTK group and 19.13% ± 7.7% in the StH group ($P = .852$). The preoperative pulmonary vascular resistance index was similar in both groups: 310.3 ± 101.7 versus 305.1 ± 173.3 dynes $cm^{-5} \cdot m^{-2}$ for the HTK and STH groups, respectively.

Clinical Outcomes

In HTK group, 2 patients died within 30 days after surgery (11.1%), with the causes of death being right heart failure

Table 2. Summary of Recipient Data

Clinical Variable	HTK ($n = 18$)	STH ($n = 49$)	*P* Value
Age (y)	50.7 ± 11.5	50.6 ± 12.5	.973
Body weight (kg)	72.3 ± 19.7	65.5 ± 11.9	.092
Body height (cm)	167 ± 7.5	165 ± 8.37	.239
Sex			
Male	14	38	
Female	4	11	
Cause of heart failure			
DCM	12	36	
ICM	6	11	
Others	6	2	
LVEF	19.5 ± 7.1	19.13 ± 7.7	.852
Pulmonary vascular resistance index	310.3 ± 101.7	305.1 ± 173.3	.91

Data are shown as mean ± standard deviation.
Abbreviations: DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; HTK, histidine–tryptophan–ketoglutarate solution; STH, St Thomas' Hospital solution.

($n = 1$) and pneumonia with septic shock ($n = 1$). Analysis of pumping time, heart ischemic time, and short-term outcomes in all recipients showed that the HTK group had a trend of shorter pumping time ($P = .091$) but did not differ significantly (Table 3). In the CBC group, 4 patients died within the first 30 postoperative days (8.2%), with the causes of death being acute rejection ($n = 2$), right heart failure ($n = 1$), and pneumonia with septic shock ($n = 1$). The clinical outcomes of the surviving patients are summarized in Table 4. The CK/CKMB/troponin I value (units) showed no significant difference between the HTK and STH groups. The mean ICU stays were 8.2 ± 3.8 days for the HTK group and 12.2 ± 9.9 days for the CBC group ($P = .13$). The mean hospital stays were 37.1 ± 16.6 days for the HTK group and 44.5 ± 31.8 days for the CBC group ($P = .379$).

Hemodynamic Assessment

The inotropic scores at 0.5 and 24 hours after surgery were 19.4 ± 15.5 and 12.7 ± 7.7 in the HTK group compared with 7.1 ± 6.3 and 5.9 ± 4.6 in the CBC group ($P = .07$ and .03). Analysis of hemodynamic data including cardiac output, cardiac index, and central venous pressure, pulmonary capillary wedge pressure, systemic vascular resistance, and pulmonary vascular resistance index for 0.5 and 24 hours after surgery revealed no significant differences (Table 5). Cardiac function assessed by echocardiography on postoperative days 3 and 7 was similar in both groups with respect to LVEF.

Multivariate analyses show the significant reduced pumping time in HTK group ($P = .002$). In addition, the HTK group still had higher operative inotropic score than the CBC group ($P < .001$) after operation (Table 6).

Table 3. Intraoperative Variables and Short-Term Outcomes

Variable	HTK ($n = 18$)	STH ($n = 49$)	*P* Value
Pumping time (min)	158.3 ± 32.0	173.9 ± 33.2	.09
Heart ischemic time (min)	152.3 ± 74.6	159.6 ± 78.2	.73
Short-term outcomes (%)			
Resternotomy	2 (11.1)	6 (12.2)	>.99
Pulmonary complication (pneumonia or ARDS)	3 (16.6)	4 (8.2)	.375
30-d mortality	2 (11.1)	4 (8.2)	>.99

Data are shown as mean ± standard deviation.
Abbreviations: ARDS, acute respiratory distress syndrome; HTK, histidine–tryptophan–ketoglutarate solution; STH, St Thomas' Hospital solution.

DISCUSSION

Both the extracellular and intracellular types of crystalloid cardioplegia have revolutionized cardiac surgery and become the gold standard for cardiac preservation [8,9]. StH solution, a crystalloid extracellular solution, induces rapid cardiac arrest by high potassium and magnesium concentrations as well as by the membrane-stabilizing effect of procaine hydrochloride. The HTK solution, an intracellular type, contains lower concentrations of sodium and calcium and induces cardiac arrest by deprivation of extracellular sodium for action potential. Because a low sodium concentration results in the opening of calcium channels, leading to increased cytosolic calcium and aggravating cellular injury, the calcium concentration is decreased. Ketoglutarate provides high-energy production via adenosine triphosphate during reperfusion and tryptophan stabilizes cell membranes. Mannitol acts in osmotic regulation of the cell membrane [10–12]. The major advantages of HTK

Table 4. Clinical Outcomes of Survive Patients

Variable	Postoperative	HTK ($n = 16$)	STH ($n = 45$)	*P* Value
CK	0.5 h	744.6 ± 316.7	1038 ± 1433.2	.423
	24 h	1554.1 ± 1455.6	1499.1 ± 1528.5	.901
CKMB	0.5 h	122.8 ± 43.9	133 ± 99.5	.695
	24 h	85.8 ± 39.9	88.1 ± 37.2	.834
Troponin-I	0.5 h	11.5 ± 6.7	13.3 ± 16.7	.687
	24 h	20.7 ± 11.9	25.3 ± 23.7	.461
LVEF%	3 d	62.1 ± 7.2	59.9 ± 7.4	.300
	7 d	62.0 ± 4.4	60.7 ± 7.3	.502
ICU stay (d)		8.2 ± 3.8	12.2 ± 9.9	.13
Hospital stay (d)		37.1 ± 16.6	44.5 ± 31.8	.379

Data are shown as mean ± standard deviation.
Abbreviations: CK, creatine kinase; CKMB, creatine kinase MB coenzyme; LVEF, left ventricular ejection fraction; HTK, histidine–tryptophan–ketoglutarate solution; STH, St Thomas' Hospital solution.

Table 5. Hemodynamic Data of Surviving Patients

Variable	Postoperative (h)	HTK ($n = 16$)	STH ($n = 45$)	*P* Value
Inotropic score	0.5	19.4 ± 15.5	7.1 ± 6.3	.07
	24	12.7 ± 7.7	5.9 ± 4.6	.03
CO	0.5	6.7 ± 2.2	6.1 ± 1.8	.321
	24	6.7 ± 2.5	6.2 ± 1.7	.407
CI ($L \cdot min^{-1} \cdot m^{-2}$)	0.5	3.7 ± 1.0	3.5 ± 1.0	.570
	24	3.7 ± 1.1	3.6 ± 1.0	.743
CVP (mm Hg)	0.5	15.9 ± 5.4	15.1 ± 5.3	.24
	24	15.4 ± 4.7	13.7 ± 4.8	.22
PCWP (mm Hg)	0.5	18.6 ± 5.5	16.4 ± 4.3	.103
	24	20.3 ± 6.9	18.6 ± 16.2	.688
SVRI ($dyne \cdot s \cdot cm^{-5} \cdot m^{-2}$)	0.5	1821.6 ± 873.2	1784.1 ± 736.4	.868
	24	1659.5 ± 648.2	1686 ± 651.4	.887
PVRI ($dyne \cdot s \cdot cm^{-5} \cdot m^{-2}$)	0.5	294.7 ± 214.2	303 ± 105.8	.841
	24	235.6 ± 113.1	251.7 ± 116.7	.635

Data are shown as mean ± standard deviation.
Abbreviations: CO, cardiac output; CI, cardiac index; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; HTK, histidine–tryptophan–ketoglutarate solution; STH, St Thomas' Hospital solution.

solution are derived mainly from histidine, which acts as a buffer, enhancing the efficiency of anaerobic glycolysis. Kresh et al found that a histidine protein-type buffer solution was superior to bicarbonate-based and tromethamine-based hyperkalemic crystalloid cardioplegic solutions for stabilizing intracellular pH and postoperative biochemical and mechanical data [13]. Takeuchi et al also demonstrated that a histidine-based crystalloid cardioplegic solution with high buffer capacity afforded effective myocardial preservation and a wider safety margin for prolonged myocardial protection in open heart surgery [14]. Heinemeyer et al reported that the intracellular pH of ventricular muscle in HTK solution remained unchanged for 180 minutes during ischemia [10].

The HTK solution is widely used for heart preservation in Europe. This solution has shown good cardiac preservation, provided that the ischemic time does not exceed 4 hours [6,15]. The HTK solution is superior to the StH solution owing to its histidine buffer system, which has higher buffering capacity over a wider pH range [13]. If the ischemic time was greater than 4 hours, postoperative CK, CKMB, and troponin I were higher, but the values were still within the acceptable range [13]. Wei et al reported a case with successful heart transplantation after 13 hours of ischemia [16], demonstrating the outstanding long-term preservation efficacy of the HTK solution.

The levels of CK, CKMB, and troponin I were measured to evaluate the myocardial damage after the surgery. We found that the levels of cardiac enzymes increased markedly in the early postoperative days. The levels were equal between the HTK and StH group at 30 minutes and 24 hours after surgery, showing that the HTK solution had equal effective as the StH solution in preserving the ischemic myocardium. Many studies have indicated that the HTK solution promotes anaerobic glycolysis during ischemia, resulting in better recovery of postischemic biochemical and hemodynamic parameters in the dilated heart [17,18].

The StH solution should be perfused every 20 to 25 minutes, and the surgical procedure has to be interrupted during infusion. Because a single dose of HTK offers adequate myocardial protection for 120 minutes, the HTK solution may be used in complicated cardiac surgery without interruption. In this study, although the number of patients in the HTK group was small, they showed a trend of shorter pumping time ($P = .09$). After multivariate analysis, the pumping time in surviving patients was reduced significantly ($P = .002$) in the HTK group. In addition, the higher inotropic score in the HTK group after operation was significantly different compared with the CBC group. There were no differences in postoperative cardiac enzymes, hemodynamic parameters, ICU stay, hospital stay, 30-day mortality, or other clinical outcomes.

Many studies have evaluated the effect of HTK solution as a cardioplegic additive in open heart surgery. Liu et al indicated that an HTK solution group had shorter cross-clamping times and a higher rebeating rate during reperfusion than an StH group in pediatric heart surgery [19]. Careaga et al concluded that the HTK cardioplegic solution decreases the incidence of arrhythmias, inotropic support, and ICU stay in open heart surgery compared with conventional crystalloid cardioplegia [11]. Braathen et al found that there were no significant differences in creatine kinase MB or troponin T at baseline, 7 hours, and 1, 2, and 3 days

Table 6. Multivariate Analysis of Surviving Patients

Clinical Variable	HTK ($n = 16$)	STH ($n = 45$)	*P* Value
Inotropic score at 24 h postoperatively	19.4 ± 15.5	7.1 ± 6.3	<.001
Pumping time (min)	158.3 ± 32.0	173.9 ± 33.2	.002
LVEF (%) at 7 d postoperatively	62.0 ± 4.4	60.7 ± 7.3	.806
Age (y)	50.7 ± 11.5	50.6 ± 12.5	.648

Data are shown as mean ± standard deviation.
Abbreviations: LVEF, left ventricular ejection fraction; HTK, histidine–tryptophan–ketoglutarate solution; STH, St Thomas' Hospital solution.

after elective mitral valve surgery [5] in a comparison of HTK and CBC groups.

The present study had several limitations. First, it was a retrospective study and lacked long-term outcome data. Second, the case numbers of this study was small. Third, as the time went by, we had intended to use HTK, rather than CBC. Due to advances in surgical technique, it may influence surgical outcomes (morbidity, hospital stay, etc). A prospective randomized studied including more cases should be designed to clarify this issue.

In summary, our study demonstrated that one single dose of HTK solution could effective reduce pumping time. Although the HTK group needed higher doses of inotropic agent after surgery, there were no differences in postoperative cardiac enzymes, hemodynamic parameters, ICU stay, hospital stay, 30-day mortality, and other clinical outcomes compared to the CBC group. A single dose of HTK solution or repeated doses of CBC solution afford similar myocardial protection in the preservation of donated hearts.

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