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Use of Histidine-Tryptophan-Ketoglutarate Solution for Coronary Perfusion in Cardiopulmonary Bypass Can Reduce the Risk of Renal Replacement Therapy for Post-Operative Acute Renal Failure

[1]Xiaolin Wang, [1]Lei Chen, [2]Junjie Yang, [1]Fei Hua, [1]Yunsheng Yu,
[1]Yanqiu Hu, [1]Wenxue Ye, [1]Haoyue Huang, [1]Yihuan Chen,
[1]Hong Nin, [1]Qingwei Ding and [1]Zhenya Shen
[1]Department of Cardiovascular Surgery, The First Affiliated Hospital,
[2]Department of Institute for Cardiovascular Science, Soochow University,
Suzhou, People's Republic of China

Abstract: To evaluate the impact of Histidine-Tryptophan-Ketoglutarate solution (HTK solution, Koehler Chemie, Germany) for coronary perfusion in cardiopulmonary bypass on the risk of post-operative Acute Renal Failure (ARF) requiring Renal Replacement Therapy (RRT). The data of patients aged over 18 were retrospectively analyzed for the Cardiopulmonary Bypasses (CPB) performed in our Heart Center from April 2012 to October 2013. According to Simplified Renal Index (SRI) Scoring System, the patients were divided into two groups: the experiment group (using HTK solution and the control group (using cold blood cardioplegia solution). The actual occurrence rate of RRT for the postoperative ARF was analyzed for both groups. Furthermore, the pre and post-operative Glomerular Filtration Rate (GFR) were also compared between the two groups. According to SRI Scoring System, 512 patients were selected: 239 cases in the experiment group and 273 cases in the control group. The probability of RRT for post-operative ARF was 0.42% in the experiment group and was 4.03% in the control group ($p<0.05$). Comparing the experiment group and the control group with a score of ≥3 (48 cases in the experiment group and 44 cases in the control group), the occurrence rate in the control group (22.73%) was significant higher than that in the experiment group (2.08%). The pre and post-operative GFR levels in patients with a score of ≥3 were continuously monitored. No obvious statistical difference ($p>0.05$) was observed pre-operation (HTK: 72.6±32.93; cold blood: 72.73±29.31), on the 1st post-operative day (HTK: 62.38±26.76; cold blood: 58.89±23.22) and at the discharge day (HTK: 86.40±19.99; cold blood: 81.51±33.95). However, the GFR level of HTK solution group was significantly higher than that of cold blood group on the second (HTK: 73.13±26.01; cold blood: 61.10±23.40; $p<0.05$) and the 3rd post-operative days (HTK: 84.99±25.07; cold blood: 69.62±32.50; $p<0.05$). The SRI Scoring System was able to distinguish the low or high risk patients before cardiac surgery. For patients with an SRI score of ≥3 using the HTK solution for coronary perfusion could effectively reduce the risk of RRT for post-operative ARF and protect renal function.

Key words: Cardiopulmonary bypass, SRI Scoring System, HTK solution, ARF, renal function

INTRODUCTION

With the rapid development of cardiac surgery, various post-operative complications need to be solved. Acute Renal Failure (ARF) is one of the most common complications after the cardiac surgery with approximately 3.7% of the patients requiring a Renal Replacement Therapy (RRT) (Zanardo *et al*., 1994; Mangos *et al*., 1995; Wijeysundera *et al*., 2007). Patients with ARF and RRT have generally a poor prognosis and their mortality rate is over 50% (Hein *et al*., 2006). It has been reported that ARF after cardiac surgery was directly associated with mortality rate and was even an independent risk factor for post-operative death. The RRT for ARF not only brings a series of complications but also greatly increases the hospital stays in ICU (Chertow *et al*., 1998; Mangano *et al*., 1998; Antunes *et al*., 2004) as well as hospitalization expenses. Therefore, it is very important to pay more attention on the prediction and prevention of the post-operative ARF. The HTK solution has been widely used in the clinical setting for the coronary perfusion in the Cardiopulmonary Bypass (CPB). It could provide positive effects for myocardium (Liu *et al*., 2008, 2009; Scrascia *et al*., 2011), lung (Buggeskov *et al*.,

Corresponding Author: Zhenya Shen, Department of Cardiovascular Surgery, The First Affiliated Hospital, Soochow University, Suzhou, People's Republic of China

2013), liver (Moray *et al*., 2006) and other organs however, there have been limited number of studies on the protective effects of the HTK solution on renal function.

Through multicenter studies with a large number of samples (Wijeysundera *et al*., 2007) screened out the factors that could possible affect the occurrence of post-operative ARF including: the pre-operative GFR levels, diabetes mellitus requiring medication, LVEF, past-operation history, cardiac surgeries excluding coronary artery bypass and surgery repair of atrial septal defect, non-selective operations usage of IABP (Intra-Aortic Balloon Pump) pre-operatively. With the use of this SRI Scoring System, low (scored 0-1) intermediate (scored 2-4) and high (scored>4) risk patients could be distinguished before the surgery to evaluate which group might have needed the RRT after the operation. In this study, researchers used this model to retrospectively grade the patients in the Heart Center and compared the patients who used the HTK solution or cold blood cardioplegia solution, to analyze the risk of ARF requiring RRT. Furthermore, researchers compared the pre and post-operative creatinine and Glomerular Filtration Rate (GFR).

MATERIALS AND METHODS

Patient preparation: According to the inclusion criteria of SRI Scoring System (Wijeysundera *et al*., 2007), data from patients (≥18 years old) who underwent a cardiac surgery under CPB from April 2012 to October 2013 were selected. The exclusion criteria included: severe renal insufficiency which was defined as a pre-operative RRT or creatinine clearance rate (Ccr) of >300 μmol L^{-1} before operation, heart surgery such as heart transplantation and installation of heart assist device. According to the SRI Scoring System (Wijeysundera *et al*., 2007) (Table 1), 512 patients were selected, the numbers of patients with different grades were 66 cases scored 0 point, 195 cases scored 1 point, 159 cases scored 2 points, 51 cases scored 3 points, 34 cases scored 4 points, 6 cases scored 5 points, 1 case scored ≥6 points. The patients were divided into two groups: the experiment group (using HTK solution; 239 cases) and the control group (using cold blood cardiopelgia solution; 273 cases).

Table 1: SRI Scoring System

Variables	Score
Pre-operative estimated GFR 31-60 mL min^{-1}*	1
Pre-operative estimated GFR ≤31 mLmin^{-1}*	2
Diabetes mellitus requiring medication	1
Left ventricle Ejection Fraction (LEF) ≤40%	1
Previous cardiac surgery	1
Procedures other than isolated coronary artery bypass graft or isolated atrial septal defect repair	1
Nonelective procedure	1
Pre-operative intra-aortic balloon pump	1

Calculated by Cockcroft and Gault (1976) formula

Collection of clinical data: The pre-intra and post-operative data were collected including: age, gender, diabetes, original renal function (serum creatinine on the day prior to the operation, the 1st post-operative day, the 2nd post-operative day, the 3rd post-operative day and the discharge day as well as GRF), pre-operative heart condition (previous cardiac surgery, LVEF, pre-operative intra-aortic balloon pump), surgery methods, selective or non-selective operations, cardiopulmonary bypass time, aortic cross-clamp time and RRT therapy for ARF (Table 2). Diagnostic criteria of the post-operative ARF (Burns *et al*., 2005) was that the creatinine level increased by 25% within 5 days after the operation as compared to the preoperative baseline or over 0.5 mg dL^{-1} (44 μmol L^{-1}). The requirement of RRT for post-operative ARF was strictly determined by clinicians according to the general conditions of patients including anuria, metabolic disorders and humoral overload.

Operative treatment: All patients were informed that HTK solutions have been safely used clinically (Burns *et al*., 2005; Moray *et al*., 2006). The experimental group used the HTK solution for a single antegrade coronary perfusion at the aortic root (Burns *et al*., 2005). The perfusion volume was 1,500-2,000 mL with the perfusion time of 6-8 min, the perfusion temperature of 5-8°C and the initial perfusion pressure of 100-110 mmHg (aortic root pressure). The perfusion pressure after the heart arrest remained at 40-50 mmHg. The re-perfusion was necessary

Table 2: Pre and intra-operative information statistics

Items	Experimental group (n = 239)	Control group (n = 273)
Age (years±SD)	57.75±9.52	60.54±7.60
Female (%)	103 (43.34)	115 (42.12)
Complications (%)		
Diabetes (need drug therapy)[a]	39 (16.31)	43 (15.75)
Pre-operative renal function (GFR (%)[a])		
31-60 mL min^{-1}	57 (23.84)	67 (24.54)
≤30 mL min^{-1}	5 (2.09)	7 (2.56)
Preoperative cardiac situation (%)		
Previous cardiac surgery[a]	8 (3.35)	9 (3.30)
LVEF≤0.40[a]	6 (2.51)	9 (3.30)
Pre-operative intra-aortic balloon pump[a]	1 (0.42)	2 (0.73)
Procedures other than isolated[a] coronary artery bypass graft	218 (91.21)	241 (88.28)
Valvular surgery alone	160 (66.95)	186 (68.13)
Other surgery	58 (24.27)	64 (23.44)
Non-selective operation (%)[a]	98 (41.00)	110 (40.29)
Limited operation	93 (38.91)	105 (38.46)
Emergency operation	5 (2.09)	5 (1.83)
Cardiopulmonary bypass time (min±SD)	126.43±41.36	125.26±42.52
Aortic cross-clamp time (min±SD)	93.00±25.30	92.55±21.81

[a]Items of SRI Score System

if the extracorporeal time was expected over 180 min. The perfusion volume was 300 mL with the perfusion temperature of 5-8°C, the perfusion time of 2-3 min. The perfusion pressure was described as the coronary pressure at the last one minute after the first heart arrest. The HTK solution was pumped back into the circulatory system using the resorptive method and ultrafiltration was performed during the operation. Water electrolytes and acid base balance were maintained and hyponatremia was prevented.

The control group used cold blood cardioplegia solution for multiple coronary perfusion at the aortic root (Giordano *et al*., 2013) where the initial perfusion volume was 15 mL kg^{-1}, the perfusion time was 3-4 min, the perfusion pressure was 160-200 mmHg and the perfusion temperature was 26-29°C. The perfusion tube was then placed at 4°C cold water at 30 min intervals to maintain the 8 mL kg^{-1} level with the perfusion time of 2 min. Finally, warm blood without potassium was used to re-perfuse for 3-6 min before opening of the aortic cross clamp. Cold blood with the antegrade and retrograde perfusion methods was used for patients with aortic incompetence.

Statistical analysis: Quantitative data were presented as mean±SD. The Student's t-test and Chi-square test (correction of continuity, Fisher's Exact Method) were used for statistical analysis. The incidence rate of RRT for ARF after the operation and the estimated GFR changes were compared between both groups to ensure whether there was any statistical difference in order to evaluate the clinical effect of the HTK solution. The data was analyzed using SPSS 19.0 Software (SPSS Inc., Chicago, IL, USA) and differences were considered statistically significant when $p<0.05$.

RESULTS AND DISCUSSION

Medical record data distribution: According to the inclusion and exclusion criteria of SRI Scoring System, various pre-operative indexes of SRI Scoring System were selected and the medical record distribution as well as the operation situation of both groups were statistically analyzed (Table 2). The probability of RRT for post-operative ARF was obviously increased in patients who scored ≥3 than in those who scored≤2.

Among all the enrolled patients (Table 3), 420 patients were scored ≤2. According to the native characteristics of SRI, the probability of renal insufficiency after the operation was very low (0.11%) (Wijeysundera *et al*., 2007). For the patients undergoing RRT, the occurrence rate was 0 for the patients with a score of 0 and 1, 0.63% for the patients with a score of 2 (1 case), 3.92% for the patients with a score of 3 (2 cases), 14.71% for the patients with a score of 4 (5 cases), 50% for the patients with a score of 5 (3 cases), 100% for the patients with a score of 6 (1 case). Above all, the probability of RRT for ARF was very low for patients with a score of ≤2 while obviously increased when it was scored ≥3.

Table 3: Comparison of occurrence rate of post-operative ARF between HTK group and cold blood group

	Experimental group		Control group	
SRI score	Cases	Actual cases of RRT	Cases	Actual cases of RRT
0	20	0	46	0
1	83	0	112	0
2	88	0	71	1
3	27	0	24	2
4	18	0	16	5
5	3	1	3	2
≥6	0	0	1	1

The renal protection by HTK solution: The total occurrence rate was 0.42% in the experimental group, 4.03% in the control group. There are significant differences between two groups ($p<0.05$). Meanwhile, researchers found that patients requiring RRT for ARF centered on the population with a score of ≥3. Therefore, researchers further analyzed patients who score ≥3. The occurrence rate was 22.73% in the control group, 2.08% in the experimental group. There were significant differences between two groups ($p<0.05$). It is strongly suggested that use of HTK solution for coronary perfusion could reduce the risk of RRT for ARF (Table 3).

The GFR changes were compared at different time points before and after the operation between the two groups with a score of ≥3 (Fig. 1). No obvious statistical difference ($p>0.05$) of GFR levels was observed preoperatively (experimental group: 72.6±32.93; control group: 72.73±29.31) on the 1st post-operative day (experimental group: 62.38±26.76; control group: 58.89±23.22) as well as the discharge day (experimental group: 86.40±19.99; control group: 81.51±33.95). However, the GFR level of the HTK solution group was significantly higher than that of the control group on the 2nd (experimental group: 73.13±26.01; control group: 61.10±23.40; $p<0.05$) and the third (experimental group: 84.99±25.07; control group: 69.62±32.50; $p<0.05$) postoperative days which further confirmed the positive effects of the HTK solution.

At present, ARF is one of the most common complications after the cardiovascular surgery. For severe patients, RRT not only largely increases the hospital stay in ICU (Chertow *et al*., 1998; Mangano *et al*., 1998; Antunes *et al*., 2004) but also increase the risk of other complications. The HTK solution has been widely used in

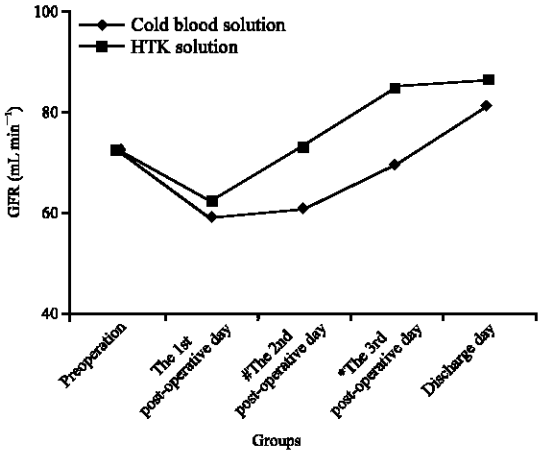

Fig. 1: The GFR level changes at different time points; #* HTK perfusion group was significantly higher than the cold blood perfusion group on the 2nd post-operative day ($p<0.05$) and the 3rd post-operative day ($p<0.05$)

the clinical setting as the coronary perfused solution in heart surgeries. It has been reported that it provides good protection for the organs especially myocardium, lung and liver (Moray *et al*., 2006; Feng *et al*., 2007; Liu *et al*., 2008; Scrascia *et al*., 2011; Buggeskov *et al*., 2013). Meanwhile, researchers also found that the RRT occurrence rate was substantially decreased in the actual clinical application after using the HTK perfusion solution.

A number of clinical studies have compared the effectiveness of prediction models for post-operative ARF. Simplified Renal Index score, Cleveland Clinic score, Thakar score, Meta score and AKICS are superior in the way of accuracy and distinguishability. Among them, SRI Scoring System established by Wijeysundera only needs 8 pre-operative indexes which is most practical clinically. SRI System showed good accuracy and distinguishability in the clinical studies undertaken in many American, Canadian and European medical centers (Knapik *et al*., 2008; Vives *et al*., 2011). The study focused on the prediction of high-risk patients requiring RRT for ARF and determination of the usage of HTK perfusion solution or not so, researcher selected SRI Scoring System to analyze patients pre-operatively.

In this study, researchers found that the probability of RRT for ARF in patients who scored ≥3 was obviously increased compared with patients who scored lower. After further analysis of those patients who scored ≥3, researchers found that the rate of RRT was only 2.08% in the experimental group and 22.73% in the control group.

There was a significant difference between both groups ($p<0.05$). Researchers further detected the pre and post-GFR of the patients and found that the GFR of the HTK solution group was significantly higher than that of the cold blood group in the 2nd and 3rd operative days ($p<0.05$). Therefore, the HTK solution was more effective than the cold blood cardioplegia solution to decrease the ARF rate and to better protect the renal protection.

There could have been several reasons for this observation: the HTK solution has been previously used as an organic preservation solution. A number of studies demonstrated that it had a very good effect in the preservation and application of the extracorporeal organs (Feng *et al*., 2007; Klaus *et al*., 2007; Liu *et al*., 2009) during the operation. The HTK solution can be perfused into kidneys through the blood circulation. Furthermore, its temperature balance, strong histidine/histidine acetate buffer system, ionic equilibrium ability (hypokalemia, hyponatremia, microcalcium), oxygen metabolism balance (low oxygen consumption) and high oxyradical scavenging capacity could decrease the organizational damage during the operation (Bretschneider *et al*., 1975; Gebhard *et al*., 1983; Wilson *et al*., 1990), protect the kidney from the injuries such as low oxygen, hypoperfusion and reperfusion during a complicated operation with a long operative time, especially cardiovascular surgery, multiple perfusions might be needed using cold blood cardioplegia solution. However, a single perfusion is usually enough for the HTK solution. In addition, large number of studies have reported protective effects for HTK on the myocardium (Burns *et al*., 2005; Liu *et al*., 2008; Buggeskov *et al*., 2013). Both aspects could help to maintain a good cardiac function after the operation, to ensure a stable peripheral circulation, to maintain the renal blood perfusion, to stabilize the RAAS System (Renin-Angiotensin-Aldosterone System) (Ahmed, 2002; Wolf and Ritz, 2005) and to decrease the post-operative renal injury.

The operations were complicated for most of the patients enrolled in this study. Furthermore, the operative time was relatively long where the average aortic cross-clamp time was 93.00±25.30 min. Fifteen patients had an operation on their great artery (Satdhabudha and Luengtaviboon, 2002; Schachner *et al*., 2005) including five patients who underwent a deep hypothermic circulatory arrest. Of those five, two patients were treated by cold blood perfusion during the operation (SRI scores were 4-5, respectively) and three patients were treated by the HTK perfusion (SRI scores were 3-5, respectively). The two cold blood perfused patients had post-operative ARF and RRT while the three HTK perfused patients didn't have ARF. It could be referred that the HTK solution was able to decrease the trend of the post-operative ARF risk although the sample size was small.

CONCLUSION

According to the enrolled cases composition by SRI, patients with a score of ≥3 accounted for 17% of the total study population. Combined with the experimental results, it was speculated that about 17% of the patients who used the HTK solution might have had a significantly decreased rate of post-operative ARF. In addition, the SRI Scoring System was simple and convenient, so it had a good clinical application value. Above all, SRI System could be used for screening patients prepared for cardiopulmonary bypass. With the warning criteria of score 3, HTK solution perfusion is suggested for patients who scored ≥3 to reduce the risk of RRT for ARF and protect renal function.

LIMITATIONS

There are limitations in the study. First, the necessity of RRT is mainly determined by the general diagnosis of clinicians including anuria, metabolic disorders and humoral overload while the experience of clinicians cannot be quantified. Second, high risk population was fewer than low risk population which means the enrolled patients were relatively small. In addition, the data compiled in this study was the result of a single medical center. Therefore, it is necessary to collaborate with other medical centers to further validate the results. Moreover, the occurrence of ARF in cardiopulmonary bypass is a result of multiple factors. The usage of HTK solution could protect renal function and reduce the risk of RRT in a certain degree but cannot be used as a precaution method. Further, deep study is needed on the precaution of post-operative ARF.

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