Original Article

Myocardial Protection by Retrograde Application of HTK Solution Compare with Cold Blood Cardioplegic Solution during Heart Valve Surgery

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Objective: Cardioplegic solution is one important principle for adequate myocardial protection in cardiac surgery. Bretschneider's histidine-tryptophan-ketoglutarate (HTK) solution is an intracellular solution while blood cardioplegia solution is an extracellular solution. Both have been used to preserve the myocardium. The present study compared between the two cardioplegic solutions for incidence of ventricular fibrillation after aortic clamp removal in double valve replacement (DVR) and tricuspid annuloplasty (TVA) to assess the effectiveness for myocardial protection.

Materials and Methods: A retrospective study was conducted among patients who underwent DVR with TVA operations between January 1, 2013 and June 30, 2017 and divided in two groups at Queen Sirikit Heart Center of the Northeast. The medical records were searched for detailed demographics, preoperative status, operative technique, and post-operative hospital course.

Results: Thirty-six patients were included in the present study, 18 patients received HTK solution, the others received blood cardioplegia. The demographic data presented no statistical difference between the two groups. Incidence of ventricular fibrillation after aortic clamp removal occurred in 10 patients (55.6%) in the HTK group, which was more than the cold blood group [five patients (27.78%)]. Cardiopulmonary bypass (CPB) and aortic cross clamp time in the cold blood group was significantly longer than in the HTK group ($p<0.001$). The peak of Trop-T and CK-MB within six hours after surgery tended to be downward after 24 hours and was not related to perioperative myocardial ischemia in the HTK group. No statistically difference was observed in postoperative outcome, ICU stay, or hospital stay.

Conclusion: The use of HTK solution has no significant different outcome compared to conventional cold blood cardioplegia via retrograde route in DVR with TVA operation. There was no significantly different incidence of ventricular fibrillation and there was no evidence of postoperative myocardial infarction. CPB and aortic cross clamp time in the HTK group were shorter than in the cold blood cardioplegia significantly.

Keywords: Cardioplegia, HTK, Custodiol, Ventricular fibrillation

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The ischemic condition after cardiac arrest during cardiac surgery can cause the impairment of myocardial function. After myocardial revascularization, the process may induce ischemic reperfusion injury, which may disturb hemodynamics of patients such as arrhythmia, myocardial stunning, low cardiac output syndrome, and perioperative myocardial infarction (MI)[1].

With effective myocardial protection, the heart can return to its normal function after the cardiac surgery. Appropriated buffering of the cardioplegic solution is a one of basic principles for myocardial protection[2].

Single-dose cardioplegia is an option in cardiac procedures as re-administration of cardioplegia may interrupt the technical flow of the surgery. Bretschneider's histidine-tryptophan-ketoglutarate (HTK) solution can preserve the myocardium for up

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to four hours without re-administration. The safety of the HTK solution has been assessed, and a higher incidence of ventricular fibrillation was documented compared to standard cold blood cardioplegia[1-8].

Double valve replacement (DVR) and tricuspid annuloplasty (TVA) presented with long cardiopulmonary bypass time. Many surgeons are concerned about ventricular fibrillation after using of HTK, but one of advantage of this solution was single administration via coronary sinus that could preserve myocardium for two to four hours without re-administration[3,5,6].

Currently, many studies still presented controversy between HTK and blood cardioplegic solution via retrograde route. No study presented the result in DVR and TVA with this technique.

Thus, the purposes of the current study were to compare the incidence of ventricular fibrillation after aortic cross clamp removal and the level of cardiac enzyme between the two types of cardioplegia, and to assess the postoperative outcomes of each solutions.

Materials and Methods

The authors performed a retrospective cohort study of the in-patients at Queen Sirikit Heart Center of the Northeast, Faculty of Medicine, Khon Kaen University who were operated by DVR and TVA between January 1, 2013 and June 30, 2017, and compared between HTK solutions and cold blood cardioplegia.

The database records detailed patient demographics, pre-operative status, operative technique, post-operative hospital course included incidence of ventricular fibrillation after removing aortic cross clamp, serum level of Trop-T and CK-MB, new post-operative stroke, acute kidney injury, serum creatinine level, new onset of heart failure, perioperative MI, infection, intensive care unit (ICU), and hospital stay. Thirty-day mortality information was also obtained. The present study was approved by the Office of Khon Kaen University Ethics Committee in human research (HE601396).

Surgical technique

Hemodynamic monitoring was carried out via a radial arterial line, and central venous pressure monitoring via the internal jugular vein or subclavian vein. Other monitoring included end-tidal CO_2, electrocardiogram (ECG), and urinary volume. Conventional general anesthesia was used for all patients.

The surgical approach was performed via a standard median sternotomy. The cardiopulmonary bypass was established by an arterial cannula in the ascending aorta. Venous drainage was obtained with bicaval cannulation. Cardioplegia was performed by retrograde technique or surgeon preference.

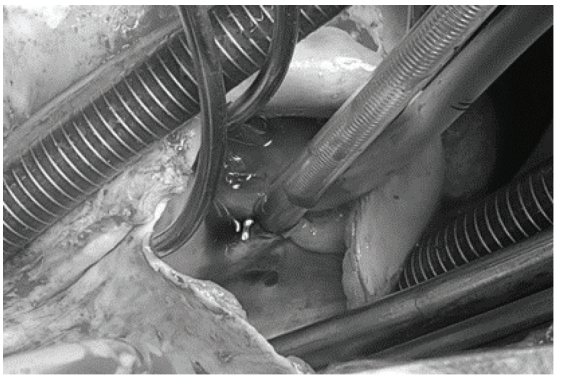

Figure 1. Retrograde cannulation via coronary sinus in HTK group.

HTK=histidine-tryptophan-ketoglutarate

Blinded retrograde cardioplegic canulation may sub-optimize the myocardial protection of the right ventricle. In the HTK group, the right atriotomy and purse string around the coronary sinus was done to prevent a dislodge of the cardioplegic catheter. The cannula was cannulated and snared under direct vision (Figure 1), then inflation of the balloon with 3 mL of the air was performed and the catheter was pull back until the balloon attached to the purse string for precise position to the coronary sinus with optimal right ventricular perfusion.

In both groups, the cardioplegia was given retrogradely after the aortic cross-clamping. Cold HTK solution (4°C) was administered once with an initial perfusion pressure of 120 mmHg. After onset of cardiac arrest, the perfusion pressure was then reduced to 60 mmHg for six to eight minutes. In the other group, mixing oxygenated blood with cold crystalloid cardioplegia (4°C) at a ratio of four to one, was administered at dose of 20 mL/kg, with a repeat dose of 10 mg/kg every 20 to 25 minutes.

The primary study endpoint in both groups was the incidence of ventricular fibrillation after removal of the aortic cross-clamp presented at ECG monitoring and interpreted by surgeons and anesthesiologist. The secondary outcomes were MI, stroke, acute renal failure, and 30-day mortality.

The definition of post-operative MI was fulfilled if there were at least two of the followings, (a) an increase in cardiac biomarker more than 10-fold of the

Table 1. Demographic data

Demographic data	Cold blood (n=18) n (%)	HTK (n=18) n (%)	p-value
Sex			0.738
Male	8 (44.44)	9 (50.00)	
Female	10 (55.56)	9 (50.00)	
Age (years); mean±SD	52.17±6.67	52.61±5.55	0.829
Diabetes	0 (0.00)	1 (5.56)	>0.999
Hypertension	1 (5.56)	2 (11.11)	>0.999
Hypercholesterolemia	1 (5.56)	0 (0.00)	0.486
Preoperative heart failure	3 (16.67)	6 (33.33)	0.443
Neurological disease			0.387
TIA	0 (0.00)	1 (5.56)	
CVA	1 (5.56)	1 (5.56)	
GFR staging			0.243
Stage I (≥90 mL/minute)	2 (11.11)	4 (22.22)	
Stage II (60 to 89 mL/minute)	11 (61.11)	6 (33.33)	
Stage III (30 to 59 mL/minute)	5 (27.78)	8 (44.44)	
Ejection fraction (%); mean±SD	63.46±12.97	56.98±15.40	0.181

HTK=histidine-tryptophan-ketoglutarate; TIA=transient ischemic attack; CVA=cerebrovascular accident; GFR=glomerular filtration rate; SD=standard deviation

Table 2. Cardiopulmonary support

Cardiopulmonary support	Cold blood (n=18) Mean±SD	HTK (n=18) Mean±SD	p-value
CPB time (minute)	186.28±42.00	122.06±11.91	<0.001
Cross-clamp time (minute)	136.78±32.51	93.33±9.04	<0.001

HTK=histidine-tryptophan-ketoglutarate; CPB=cardiopulmonary bypass; SD=standard deviation

ninety-ninth percentile of a normal reference range at Queen Sirikit Heart Center of the Northeast laboratory (Troponin T greater than 30 ng/mL in association with elevated CK-MB), (b) new post-operative Q wave on at least two serial ECGs, or (c) new ventricular wall motion abnormalities.

The definition of acute renal failure was fulfilled when any of the followings were present, (a) serum creatinine increased more than 0.3 mg/dL from baseline within 48 hour post-operatively, or (b) urine output less than 0.5 mL/kg/hour for six hours or more.

Statistical analysis

Patient demographic data, operative variables, and post-operative outcomes were compared between the HTK and the blood cardioplegia groups. Categorical variables were expressed as frequencies and compared using Pearson chi-squared tests. Continuous variables were expressed as the mean ± standard deviation (SD) and compared using the unpaired t-test. A p-value of less than 0.05 was considered statistically significant. The analyses were carried out by IBM SPSS Statistics, version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Thirty-six patients were included in the present study. Eighteen patients received the HTK solution and 18 patients received the cold blood cardioplegia. Demographic data are presented in Table 1, and there was no statistical difference between the two groups.

The cold blood cardioplegia group presented longer time for cardiopulmonary bypass and aortic cross clamp than the HTK solution group with statistical significance (Table 2).

The incidence of ventricular fibrillation after

Table 3. Ventricular fibrillation After cross clamp removal

Event after cross clamp removal	Cold blood (n=18) n (%)	HTK (n=18) n (%)	p-value
Ventricular fibrillation	5 (27.78)	10 (55.56)	0.176

HTK=histidine-tryptophan-ketoglutarate

Table 4. Postoperative course

Postoperative course	Cold blood (n=18) n (%)	HTK (n=18) n (%)	p-value
Temporary pacemaker	9 (50.00)	3 (16.67)	0.075
Stroke	0 (0.00)	0 (0.00)	-
Acute kidney injury	5 (27.78)	4 (22.22)	>0.999
Highest serum creatinine within 48 hours; mean±SD	0.97±0.26	0.94±0.59	0.874
Pneumonia	5 (27.78)	2 (11.11)	0.402
ICU stay (hours); median (range)	43 (20 to 70)	46 (21 to 115)	0.366
Hospital stay (days); median (range)	14 (8 to 26)	16.5 (10 to 65)	0.199

HTK=histidine-tryptophan-ketoglutarate; ICU=intensive care unit; SD=standard deviation

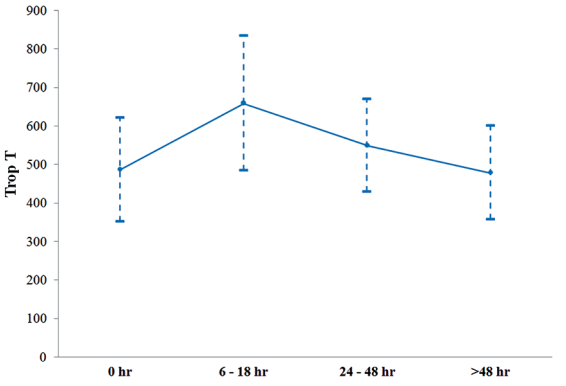

Figure 2. Troponin level in HTK group (ng/mL).
HTK=histidine-tryptophan-ketoglutarate

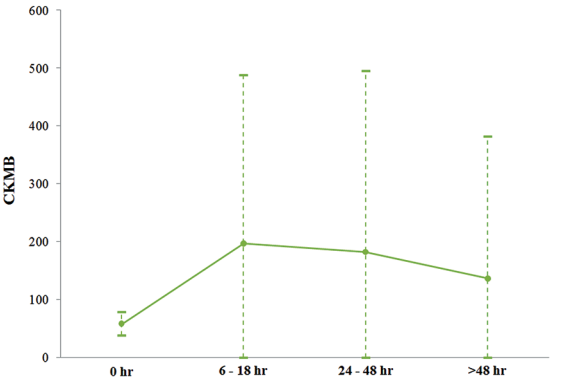

Figure 3. CK-MB level in HTK group (ng/mL).
HTK=histidine-tryptophan-ketoglutarate

aortic cross clamp removal occurred in ten patients (55.6%) of the HTK group, which is more than the five patients (27.78%) in the cold blood cardioplegia group, but without statistical significance (p=0.176) (Table 3).

Cardiac enzymes (Troponin-T and CK-MB) were examined in 18 patients immediately after surgery and once daily on the first to third day post-operatively. Cardiac enzymes were elevated on the first day after surgery but did not reach the diagnostic criteria for post-operative MI, and gradually decreased on the following days (Figure 2, 3).

Three patients from the HTK group and nine from the blood cardioplegia group needed a temporary pacemaker. There was no evidence of post-operative MI in both groups. Postoperative stroke, acute kidney injury, post-operative creatinine in 48 hours after surgery, and new heart failure presented with no difference between the two groups. The length of ICU and hospital stay were not different between the two groups (Table 4). No thirty-day mortality occurred.

Discussion

Bretschneider's HTK is a solution based on the intracellular level of electrolytes, proposed by Bretschneider in the 1970s. Histidine acts as a buffer, potassium hydrogen 2-ketoglutarate helps to increase ATP production during reperfusion, and tryptophan

helps stabilize the cell membrane[1-3].

In the current study, the incidence of ventricular fibrillation after aortic cross-clamp removal was higher in the HTK group but not statistically significant, which was consistent with other studies[1,3,4,6].

Silarat et al studied the incidence of ventricular fibrillation in mitral valve repair patients and hypothesized that the HTK solution does not contain procaine, an anti-arrhythmic medication found in the preparation for cold blood cardioplegia[8]. Unclear evidence of ventricular fibrillation after the reperfusion period was observed. Blood cardioplegia has procaine component with antiarrhythmic effect by inhibited sodium flux over cell membrane and inactivation of enzyme phospholipase A (destructive properties on cell membrane)[8].

Comparable with Chanmayka et al study in DVR and TVA by retrograde HTK solution he found nine patients (40.9%) that had ventricular fibrillation[7].

According to Braathen B study in elective mitral valve surgery, antegrade cardioplegia also presented the same incidence of ventricular fibrillation with 27 patients (70%) in the HTK group and five patients (13%) in the cold blood cardioplegia group ($p<0.001$)[3].

Cardiac enzymes (Troponin-T and CK-MB) were examined immediately after surgery and once daily on the first to third day post-operatively. Cardiac enzymes were elevated on the first day after surgery but did not reach the diagnostic criteria for post-operative MI and moreover, gradually decreased on the following days.

The present study is comparable to Braathen et al study in elective mitral valve, which shows the same results. There was no difference between groups at 7, 20, 44, and 68 hours. Peak of Trop-T in the HTK group was 1.13±0.12 microgram/L and in the cold blood cardioplegia group was 1.05±0.11 microgram/L ($p=0.6$) with tend to be downward. The peak of CK-MB in the HTK was 56.2±4.7 microgram/L and in the cold blood group was 55.9±4.9 microgram/L ($p=0.8$) and tended to be downward[3].

Even though antegrade cardioplegia was convenient with rapid administration, incomplete distribution could occur in some conditions such as aortic insufficiency or coronary occlusive disease. The benefit of retrograde cardioplegia with the proper cannulation technique was minimal operative interruption and the postoperative right ventricular function showed no difference from the antegrade routes[9,10].

Cardiopulmonary bypass and aortic cross clamp time in the HTK group presented shorter than in the cold blood cardioplegia significantly. The benefit of HTK solution was a single administration via coronary sinus that could preserve myocardium for two to four hours without re-administration[3,5,6] resulting in an aortic cross clamp time in the HTK group (93.33±9.04 minutes) that was shorter than in the cold blood cardioplegia group (136.78±32.51 minutes) with statistical significance ($p<0.001$). Furthermore, the cardiopulmonary bypass time was also shorter (HTK group 122.06±11.91 minutes versus cold blood cardioplegia group 186.28±42 minutes, $p<0.001$).

El-Hamamsy et al[11] study in DVR found that the duration of the surgery in the HTK group was shorter than in the cold blood cardioplegia group.

The other operative outcomes were not statistically different between the groups. The ICU length of stay was not different between the groups. The cardiac enzyme level was elevated on the first day after surgery, but this decreased on the following day, which is similar with the study of Braathen et al who studied the use of single-dose HTK solution compared to repeated cold blood cardioplegia in elective mitral valve surgery[3]. They documented the troponin T and CK-MB levels of both groups and found no significant difference. They also noted that spontaneous ventricular fibrillation after aortic cross-clamp removal was observed more often in the HTK group. The ventricular fibrillation may not have catastrophic consequences.

Limitation

A main limitation of the present study was its retrospective nature. Some patients used a combined cardioplegic route depending on aortic valve condition, surgeon preference, or quality of the arrested heart before surgery. The authors were unable to analyze the cardiac enzyme levels in the blood cardioplegic group as these data were not routinely collected at the authors center. At the time, there was lack of protocol for echocardiographic evaluation of post-operative LV function, and there was no definite protocol for cardiac enzyme study after a heart valve operation. There was also no clear record of volume of cardioplegia delivered. Moreover, intra-operative transesophageal echocardiography was not routinely used, nor were laboratory results routinely collected at the time of cross-clamp removal. A final limitation was the number of patients undergoing each operation, which was quite small thus, affecting the ability to perform the power of the subgroup analysis.

Conclusion

The outcomes for DVR and TVA were not significantly different between the HTK solution group and the cold blood cardioplegia group. The ventricular fibrillation that occurred after the aortic cross-clamp removal tended to be temporary and there was no evidence of peri-operative MI related to the use of cardioplegia. Cardiopulmonary bypass and aortic cross clamp time in the HTK group was shorter than in the cold blood cardioplegia significantly. No difference was observed in postoperative outcome, ICU, and hospital length of stay.

What is already known on this topic?

Myocardial protection is an important issue in cardiac surgery, which involves a period of ischemia followed by reperfusion. Inadequate myocardial preservation may result in devastating events following the cardiac procedure.

What this study adds?

Retrograde application of HTK solution did not show significant different outcomes as compared to conventional retrograde application of cold blood cardioplegia in DVR and TVA. Ventricular fibrillation occurred after the aortic cross clamp removal but tended to be temporary and there was no evidence of postoperative MI.

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Conflicts of interest

The authors declare no conflict of interest.

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