

선천성 심장기형의 수술 후 Histidine-tryptophan-ketoglutarate 심정지액과 혈성 심정지액의 전자현미경적 심근 구조의 비교 관찰

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Histidine-tryptophan-ketoglutarate Versus Blood Cardioplegic Solutions: A Prospective, Myocardial Ultrastructural Study

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Background: We performed a prospective clinical study to evaluate the ultrastructural integrity of the myocardium after using Histidine-Tryptophan-Ketoglutarate (HTK) solution in comparison with blood cardioplegic solution during congenital heart surgery. **Material and Method:** Twenty two patients with acyanotic heart disease, who were scheduled for elective open heart surgery, were randomized into two groups. The HTK Group (n=11) received HTK cardioplegic solution; the blood group (n=11) received conventional blood cardioplegic solution during surgery. The preoperative diagnoses included ventricular septal defect (n=9) and atrial septal defect (n=2) in each group. A small biopsy specimen was taken from the right ventricle's myocardium, and this was processed for ultrastructural examination at the end of 30 minutes of reperfusion. Semiquantitative electron microscopy was carried out "blindly" in 4 areas per specimen and in 5 test fields per area by 'random systematic sampling' and 'point and intersection counting'. The morphology of the mitochondrial membrane and cristae were then scored. The interstitial edema of the myocardium was also graded. **Result:** The semiquantitative score of the mitochondrial morphology was 19.65 ± 4.75 in the blood group and 25.25 ± 5.85 in the HTK group ($p=0.03$). 6 patients (54.5%) in the blood group and 3 patients (27.3%) in the HTK group were grade 3 or more for the interstitial edema of the myocardium. **Conclusion:** The ultrastructural integrity was preserved even better with HTK solution than with conventional blood cardioplegic solution.

(Korean J Thorac Cardiovasc Surg 2007;40:8-16)

- Key words:**
1. Myocardium
 2. Myocardial reperfusion
 3. Microscopy, electron
 4. Heart defects, congenital

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논문접수일 : 2006년 9월 8일, 심사통과일 : 2006년 11월 1일

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본 논문의 저작권 및 전자매체의 지적소유권은 대한흉부외과학회에 있다.

INTRODUCTION

Myocardial protection during ischemic arrest for open heart surgery is presently an issue of great concern, and this is based on the fact that ischemic injury followed by reperfusion may have a deleterious effect on myocardial function[1,2]. During myocardial ischemia, the cells possess a low tolerance to local acidosis, and the glycogen and ATP levels are rapidly decreased. For these reasons, many cardioplegic solutions have been developed since the 1950's to improve the myocardium's tolerance of ischemia and reperfusion. However, the composition and study protocols for these solutions have produced some controversial results[3,4].

A solution based on the intracellular level of electrolytes is Histidine - Tryptophan - Ketoglutarate (HTK) solution, and this solution has been proposed by Bretschneider since the 1970s. Besides the other ingredients, there is a particularly large quantity of histidine in it and this is a strong biological buffer that counteracts the acidosis caused by metabolites accumulating in the heart during ischemia. This enhances anaerobic energy production and thus, it stabilizes the content of the energy-rich phosphates[5,6], upon which successful reperfusion is highly dependent[7].

Several reports have reported on the efficacy of HTK solution, and these reports have been based on biochemical markers or on physiologic evaluation in experimental models; in addition, this solution is commonly used as a cardioplegia in several countries, but not throughout the world[3,4].

The aim of our clinical study was to answer the question as to whether the application of conventional blood cardioplegic solution or HTK solution leads to a different ultra-structural morphology of the myocardial cells.

MATERIAL AND METHOD

1) Patients and data collection

Between January and June, 2003, 22 patients with acyanotic heart anomalies who were scheduled for elective open heart surgery were prospectively randomized into two groups. In the group HTK (n=11), myocardial protection was performed with HTK solution (CUSTADIOL[®] by Dr.F. Kohler Chemie GmbH), while the second group served as control; in the

Table 1. Composition of different cardioplegic solutions

Substrates	Conventional blood cardioplegia 1,000 mL (S.D 1~4 solution ^b : blood = 1 : 4)	HTK solution 1,000 ml ^c
Sodium Chloride (mmol/L)	6	15
Potassium Chloride ^a (mmol/L)	8	9
Potassium hydrogen 2-ketoglutarate (mmol/L)	—	1
Calcium Chloride (mmol/L)	—	0.015
Magnesium Chloride/6H ₂ O (mmol/L)	—	4
Histidine/Hcl H ₂ O (mmol/L)	—	18
Histidine (mmol/L)	—	180
Tryptophan (mmol/L)	—	2
Ketoglutarate (mmol/L)	—	1
Mannitol (mmol/L)	—	30
Theoric osmolality (mOsm/kg)		310
Bicarbonate ^a (mmol/L)	8	

^aAdded substrates in S.D 1~4 solution; ^bS.D 1~4 solution 1,000 mL[®] by Choongwae pharma corporation consisted of Sodium Chloride 30.8 mmol, glucose 40.0 g and CPDA-1 (citrate phosphated dextrose-adenine) 90 mL was added to S.D 1~4 solution 1,000 mL; ^cHistidine-Tryptophan-Ketoglutarate solution; CUSTADIOL[®] by Dr.F. Kohler Chemie GmbH.

group blood (n=11), conventional cold blood cardioplegic solution was applied, which is routinely used at our hospital (Table 1). All the patients' parents gave their written, informed preoperative consent.

Eighteen of the 22 patients had ventricular septal defects (VSDs) and 4 of 22 patients had atrial septal defects (ASDs). The associated anomalies were partial anomalous pulmonary venous return (PAPVR n=1), subaortic fibrous ridge (n=4), and mild pulmonary valvular stenosis (n=1).

The patient profiles are shown in Table 2 and similar profiles were distributed evenly in the two groups. There were no differences in age and body weight between the two groups. The cardiopulmonary bypass times were 110.09 ± 35.42 minutes in group blood and 111.54 ± 39.51 minutes in group HTK. The aortic clamping times were 73.81 ± 27.83 minutes in group blood and 79.09 ± 33.56 minutes in group HTK (Table 2).

We evaluated the time interval from the asystolic state to

Table 2. Perioperative patients profile^a

	Group blood (n=11)	Group HTK (n=11)	p value ^b
Age (days)	1,011.64±786.40	1,063.00±1,023.41	NS
Body surface area (m ²)	0.58±0.19	0.50±0.22	NS
Weight (kg)	14.18±6.69	11.04±6.08	NS
Diagnosis	VSD (n=9), ASD (n=2)	VSD (n=9), ASD (n=2)	—
Associated anomaly			
PAPVR	1	0	—
Subaortic abnormal ridge	3	1	—
Mild pulmonary valvular stenosis	1	0	—
ACC time (min)	73.81±27.83	79.09±33.56	NS
CPB time (min)	110.09±35.42	111.54±39.51	NS
Morbidity	None	None	—
Mortality	None	None	—

^aData presented as mean±SD; ^bThe significance level is p<0.05; ACC=Aortic cross clamping; ASD=Atrial septal defect; CPB=Cardiopulmonary bypass; NS=Non specific; PAPVR=Partial anomalous pulmonary venous return; VSD=Ventricular septal defect.

resuming a normal sinus rhythm since reperfusion. We also analyzed the time the patient needed artificial ventilation and the length of stay in the postoperative intensive care unit (ICU). Rhythm disturbances were evaluated by continuous electrocardiographic (ECG) monitoring from the time of removal of the aortic clamp to 72 h postoperatively.

Arrhythmias were defined as any premature ventricular beats, ventricular fibrillation and conduction disturbances of the heart requiring treatment with lidocaine or electrical therapy that appear during the reperfusion period or in the postoperative period. We defined the length-of-stay in ICU as the time that the patient arrived at ICU until the time of discharge.

Blood samples for creatinine kinase (CK), creatinine kinase - myocardial bound (CK-MB) and lactic acid dehydrogenase (LDH), and the serum osmolarity measurements were collected 6 and 12 hours after the operations.

2) Clinical criteria for excluding patients

The clinical criteria for excluding patients from the study

were neonates, previous cardiac surgery, an urgent operation due to heart failure, other significant anomalies, a prolonged operation time, an additional operation except for patch repair and any overt air bubble development in the cardioplegic solution delivery tubing during the cardioplegia administration.

3) Operative and cardioplegic technique

All patients were put under general anesthesia, and the surgical approach was done via median sternotomy with a minimal skin incision. For cardiopulmonary bypass (CPB), an arterial cannula was used in the aortic root, whereas venous drainage was obtained via the bicaval venous cannulae that were installed in the right atrium. For administration of the cardioplegic solution, a perfusion needle was inserted into the aortic root near the heart. For patients treated with HTK solution, the effluent from the coronary sinus was discarded with sump suction to avoid excessive hemodilution.

Under CPB and aortic cross-clamping, cardioplegic arrest was induced. In the HTK group, HTK solution was cooled at 4~8°C and perfused via the aortic root at 100 mmHg pressure initially and the infusion pressure was then lowered to about 40~50 mmHg after achieving cardiac arrest. The single dose technique was applied to all patients. The total amount of infused HTK solution was 30 mL/kg in each patient. When the administration of HTK solution was accomplished, the perfusion needle was removed from the operative field. In the blood group, the cold blood cardioplegic solution was cooled to 4~8°C and then it was perfused in an antegrade fashion with 100~120 mmHg pressure every 25 min at an initial dose of 20 mL/kg and 10 mL/kg thereafter.

Moderate hypothermia (28~32°C) of the body core was used in all the surgical procedures. When the surgical maneuver was finished the patient was weaned from CPB; subsequently, the chest wall was reconstructed conventionally after careful hemostasia. Minimum dosages of dopamine were enough for postoperative inotropic support in all patients.

4) Biopsies

A small transmural biopsy specimen of myocardium was taken from the diaphragmatic surface of the right ventricle. This sample was, macroscopically normal and it was pro-

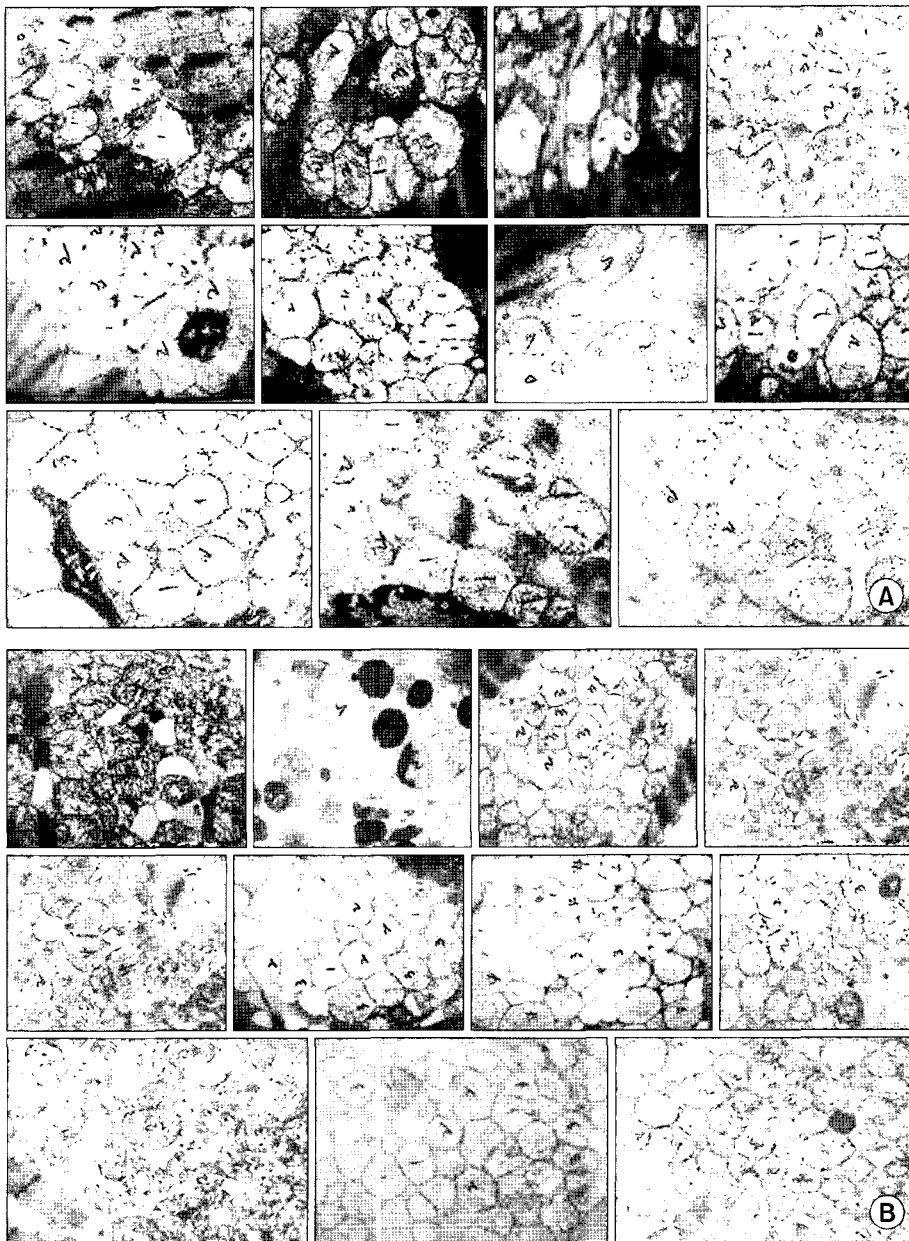


Fig. 1. Electron photomicrographs of the patients. One electron photomicrograph was selected and showed per one patient. Numbers in script type were recorded score of mitochondria by the pathologist. (A) Group blood (n=11). Some mitochondria with destructed cristinae and membrane were viewed. (B) Group HTK (n=11). Most mitochondria demonstrate well preserved cristinae and membrane. HTK, Bretschneider's Histidine - Tryptophan - Ketoglutarate cardioplegic solution.

cessed for ultrastructural examination 30 minutes after reperfusion. All biopsy specimens were taken after confirming the normalized ECG findings. The biopsy sites were oversewn. To date, no complications from this technique have been noted.

5) Electron microscopy

The tissue plug specimens were immediately fixed with 2.5% glutaraldehyde in 0.1 mol/L phosphate buffer, pH 7.4,

for 1 hour and then they were postfixed in 1% OsO₄ in 0.1 mol/L phosphate buffer, pH 7.4, for 1 hour. They were then dehydrated in acetone and embedded in Epon LX 112 fixative. Semi-thin sections stained with toluidine blue were prepared from all tissue samples. The sections were cut with a Reichert Ultracut E-ultramicrotome (Leica, Inc., Buffalo, NY) and then they were prepared and placed on uncoated copper grids, stained with uranyl acetate and lead citrate, and they were examined under a Philips 410 LS transmission

electron microscope (Philips Electronic Instruments, Inc., Mahwah, NJ), with using an acceleration voltage of 60 kV. After examination of the sections for qualitative subcellular alterations, micrographs were taken for morphometric evaluation.

6) Morphometry and scoring

The cardiac pathologist and electron microscopist were blinded as to the sequence of the specimens and to the group which the patients belonged. The morphological preservation of the membrane and cristae of mitochondria within the myocardial cells were examined and scored semiquantitatively. The following procedures were applied: ten copper grids were made in each tissue sample. With a 70-mm camera, 10 micrographs from each grid were taken at a magnification of $\times 15,000$ by 'random systematic sampling' and 'point and intersection counting'. Then 10 mitochondrias were selected randomly from each micrograph and each mitochondria was scored to evaluate semiquantitatively.

This system is predicated on the classical analysis as described by Flameng et al[8] but the detail score grading is modified.

The score ranged from 1 (worst preserved) to 5 (best preserved) according to the morphometry of the mitochondrial membrane and crista. For every mitochondrion, the following grading was used in this study:

Score 1: normal ultrastructure of the cristae and matrix contains small osmiophilic granules.

Score 2: loss of matrix granules and clarification of the matrix without breaking of the cristae

Score 3: loss of matrix granules and uniform clarification of the matrix with disruption of the cristae

Score 4: loss of matrix granules, disruption of cristae and loss of integrity of the mitochondrial membranes

Score 5: this score was given when the mitochondria contained large, dark, amorphous densities irrespective of the other aspects of the mitochondrion.

The final scores (S) were calculated as $S = \frac{1}{10} \sum_{i=1}^{10} MG_i$

Where MG is the sum of the scores for each micrograph that included 10 scored mitochondrias.

The sum of score ranged from 10 to 50 in each micro-

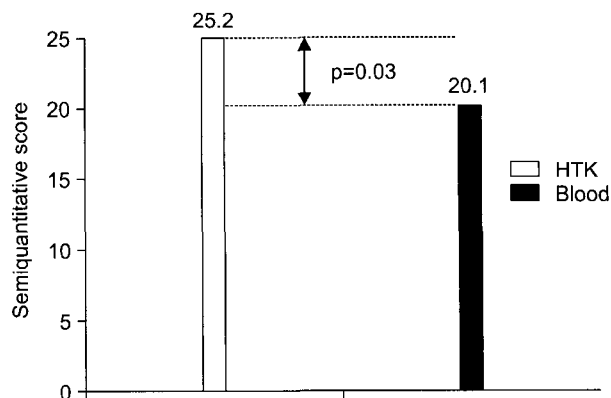


Fig. 2. Semiquantitative score of mitochondrial morphology. The score of mitochondrial morphology of group HTK was significantly higher than group blood. The significance level is $p < 0.05$. HTK, Bretschneider's Histidine - Tryptophan - Ketoglutarate cardioplegic solution.

graph (Fig. 1, 2). The intercellular junctions (intercalated discs), intracellular and extracellular edema were analyzed separately in each biopsy specimen by grading this from 0 (unchanged) to 3 (severe alterations).

7) Statistical analysis

Statistical analysis was done with use of the SPSS statistical package program (SPSS, Inc., Chicago, Ill). We used descriptive statistics to characterize the groups. Mann-Whitney tests and chi square tests were used to compare the clinical characteristics and the patient groups. The significance level was set at $p < 0.05$.

RESULT

There was no operative mortality and spontaneous defibrillation was possible in all patients.

In the postoperative period, no differences were observed for the serial enzyme levels, the sinus rhythm recovery time, and the postoperative length of ICU stay between the two groups.

The semiquantitative score of mitochondrial morphology was 20.10 ± 4.74 in the group blood and 25.25 ± 5.85 in the group HTK ($p=0.03$)(Fig. 1, 2). Six of 11 patients (54.5%) in the group blood and 3 of 11 patients (27.3%) in the group HTK were graded 3 or more for the interstitial edema of the

myocardium.

DISCUSSION

In 1964 Bretschneider et al[9] performed successful heart surgery with inducing cardioplegia by infusing a high concentration potassium solution into the coronary artery and so inducing cardiac arrest. Then in 1975, a new solution was developed that contained low concentrations of sodium and potassium, but no calcium, and this was named HTK solution. The solution was developed after several trials that were based on the theory that the heart stimulation needed for myocardial contraction can be inhibited by equilibrating the nitrogen concentration in the cardioplegic solution and intracellular tissue of the heart[10].

HTK solution is prepared at a pH between 7.02~7.20 with an osmolality of 310 mosmol/L, and it should be kept at a low temperature between 8~15°C in the dark. The major components of this HTK solution are histidine, tryptophan, and α -ketoglutarate with mannitol, and there are minute amounts of crystalloid sodium and potassium. It contains lower concentrations of sodium, potassium and calcium than what is found in the cells so that it decreases the intracellular sodium concentration and the extracellular calcium, and so this inhibits the myocardial stimulation needed for myocardial contraction[11~13]. The solution has as strong a buffering capacity as that of extracellular hemoglobin with the addition of the histidine, and the buffering ability inhibits acidification that is due to ischemic changes in the myocardium. Tryptophan induces membrane stability that inhibits the introduction of histidine into cells and this improves the buffering capacity of histidine[12,14].

Sakata et al[15] compared blood and HTK cardioplegic solutions and they found that HTK cardioplegic solution afforded excellent myocardium protection. Blood cardioplegic solution and crystalloid cardioplegic solution have been compared for pediatric heart surgery, but no comparative study has been performed with HTK.

In addition, besides the cardioplegic solutions and the serologic markers, there are many other factors such as the myocardial temperature and the delivery methodology of the cardioplegic solution that could determine the effectiveness of

myocardial protection. Hence, it is impossible to assess the superiority of the myocardial protection between these cardioplegic solutions without controlling for these variables.

Therefore, we examined the cell ultrastructure using electron photomicrography and we performed morphometry that was not limited to clinical implications. We think that observing the ultrastructure of the myocardium is a good way to provide the objective evidence to evaluate the degree of myocardial damage due to ischemia or reperfusion and to presume the clinical effect of each cardioplegic solution.

The electron-microscopy findings of mitochondrial damages in the myocardium due to ischemia include normal cytoplasm and decreased granules in the case of mild damage, and there is granule loss, uniform cracking of the cristae and membrane destruction in severe damage. However, not much is known on the degree of irreversible cellular changes after reperfusion[16]. When reperfusion of the myocardium occurs and the myocardium is already severely damaged by ischemia, the ultrastructure of the heart would change drastically with myofibril and endoplasmic reticulum destruction, severe cellular edema, mitochondria damage and loss, and the calcium phosphate deposition. Vienten-Johansen et al[17] have reported that the ultrastructure of the myocardium did not change much when the left anterior coronary artery was ligated for one hour, but changed a lot after reperfusion.

Using electron microscopy to observe the degree of myocardium damage, Schaper et al[18] divided the degree of myocardium damage into 3 levels after open heart surgery. Flameng et al[8] divided the damage further into 5 steps. With using the classification proposed the latter authors, one investigator performed a blind trial in the current study.

We performed a prospective study by randomly selecting the patients. To gain more reliability, we used strict exclusion criteria, especially with trying to maintain the homogeneity of the patient groups by applying the same preoperative diagnosis, clinical conditions and operative technique, and these are the factors that could affect the postoperative myocardial preservation. Furthermore, we excluded those cases with incidental air bubbles that could have developed during the delivery of cardioplegic solution since we were observing the ultrastructure of the heart using electron photomicrography. Thus, a lesser number of patients was included in this study

compared with the actual prevalence of acyanotic heart disease. Nonetheless, we were able to increase the reliability of the results obtained in this study.

After performing a prospective study on the myocardium protective effect of HTK solution, Careaga et al[12] reported in their randomized study that the incidence of arrhythmias, inotropic support and the length-of-stay in ICU were effectively decreased with HTK solution compared with the conventional crystalloid cardioplegic solution. However, we did not find any difference between the two groups in the current study, perhaps because we limited inclusion to the study to the patients with acyanotic heart disease, i.e., ASD and VSD, according to preoperative diagnosis, to maintain the homogeneity of the subjects. So, we did not place much significance on any clinical results obtained by comparing the two groups at the planning stage of the study because the subjects had similar clinical conditions before their operations. In addition, unlike the study by Careaga et al, we compared HTK solution with a conventional cold blood cardioplegic solution. As we discussed earlier, there are many factors that affect the postoperative myocardial function besides the cardioplegic solutions. Especially, it was impossible to control for the myocardial temperature due to the different strategies for the delivery of cardioplegic solutions, i.e., the single dose and multidose technique. These reasons are why we think the postoperative echocardiographic evaluations are fruitless in this study.

As mentioned previously in the discussion section (and this widely known), the HTK solution has several advantages over the conventional crystalloid cardioplegic solutions. A single dose administration would reduce the aortic cross clamping time by reducing the burden of repeated administration of cardioplegic solution so that the surgeon could concentrate on a long, difficult and complex operation. Furthermore, the delivery catheter kit could be removed from the surgical field after delivering the solution, and this is an advantage during pediatric heart surgery with its especially narrow surgical field and also during minimal invasive procedures that have a crowded surgical field. However, the myocardial-cooling temperature is harder to maintain by administering the cardioplegic solution in a single dose rather than in multiple doses. Thus, we maintained a constant myocardial temperature by

evenly applying topical surface cooling.

However, the disadvantages of using HTK solution are left ventricle expansion and the hemodilution that occurs with the presence of a lot of HTK cardioplegic solution, and this solution is needed for sufficient protection of the myocardium. This problem, however, can be resolved by discarding the solution through the coronary sinus, and this is not burdensome since bicaval cannulation and opening of the right atrium are performed in most cases when correcting congenital cardiac anomalies. Researchers found that small changes occurred in the sodium and potassium concentrations even during adult heart surgery when the HTK cardioplegic solution was introduced into the bypass circuit. The serum sodium and potassium concentrations can be monitored and adjusted during cardiopulmonary bypass.

CONCLUSION

The ultrastructural integrity of myocardium was preserved better with HTK solution than with the conventional blood cardioplegic solution. These results can not support the superiority of the HTK solution over a conventional blood cardioplegic solution for myocardial protection during simple congenital heart surgery. But on this basis, our study could be a pilot study for the effects of HTK solution on myocardial preservation after complex congenital heart surgery.

ACKNOWLEDGEMENTS

This study was supported by the Dong-A University Research Fund in 2003.

The authors would like to thank Mr. Park for his excellent technical assistance.

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=국문 초록=

배경: 선천성 심장기형의 수술적 교정 시, Histidine-Tryptophan-Ketoglutarate (HTK) 심정지액과 혈성 심정지액의 심근 보호에 관한 비교를 위해 술 후 심근에 대한 전자현미경적 고찰을 시행하였다. **대상 및 방법:** 개심술을 계획하고 있는 선천성 심기형 환자 22명의 환자를 대상으로 하였고 이들은 무작위로 두 집단으로 나누어 전향적으로 연구를 진행하였다. 22명 중 11명(HTK 집단)은 개심술 시 HTK 심정지액을, 다른 11명(혈성 심정지액 집단)은 혈성 심정지액을 사용하였다. 술 중 재관류 30분 후 우심실에서 작은 조직을 채취하여 전자현미경적 관찰을 시행하였다. 전자현미경에 의한 심근 초미세구조에 대한 평가는 무작위 체계적 표본 추출법에 의한 반정량적 평가법을 사용하였다. 1명의 병리조직학자에 의해 사전정보의 제공 없이 시행되었다. **결과:** 미토콘드리아의 보존 형태에 대한 반정량적 평가는 혈성 심정지액 집단이 19.65 ± 4.75 그리고 HTK 집단이 25.25 ± 5.85 ($p=0.03$)였다. 혈성 심정지액 집단 중 6명의(54.5%) 환자에서 그리고 HTK 집단 중 3명(27.3%)에서 3도 이상의 사이질의 부종을 보였다. **결론:** 전자현미경적 초미세구조의 보존은 HTK 심정지액이 더 우수한 결과를 보였다. 그러나 임상적 그리고 수술 중의 다양한 요인을 고려한 술 중 심근 보호에 대한 우월성에 대한 비교는 지속적인 관찰과 연구를 요한다.

- 중심 단어 :**
1. 심근
 2. 심근 재관류
 3. 전자현미경
 4. 선천성 심기형