Custodial-HTK Solution for Myocardial Protection in CABG Patients

Sompop Prathanee MD*,
Chusak Kuptanond MD*, Worawit Intanoo MD*,
Chawalit Wongbhudha MD*, Chananya Karunasumaeta MD*

** Cardiovascular and Thoracic Unit, Department of Surgery, Queen Sirikit Heart Center of the Northeast, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

Background: *Many steps of myocardial preservation during open heart surgery are practical after the development of the heart-lung machine. A cardioplegia solution, infused after aortic cross clamping, is an important aspect. Two-thirds of cardioplegia solutions are an intracellular solution (such as HTK or Bretschneider solution) or extracellular solution (such as blood cardioplegia).*

Intracellular cardioplegia solution can provide protection for 3-4 hours after one-time infusion, which differs from extracellular cardioplegia solution requiring intermittent use every 20-30 minutes.

Material and Method: *Retrospective case-control study in CABG patients were reviewed in Cardiovascular and Thoracic Unit, Department of Surgery, Khon Kaen University during April 2011and September 2012.The study group was divided into groups A and B, for myocardial protection by blood cardioplegia and Custodiol-HTK (Histidine-Tryptophan-Ketoglutarate) solutions.*

Baseline data such as age, sex, NYHA, risk factors, associated disease, operation, CPB time, aortic cross clamp time, complication, defibrillation after surgery, ICU stay, length of stay and mortality rate were analyzed.

Results: *The study patients in groups A and B were 60 and 65 cases. Defibrillation after finishing CABG in groups A, B was 8.3% and 33.8%. Mortality rate in groups A, B were 1.7% and 4.6%. Other post operative complications were similar in both groups.*

Conclusion: *There was significantly more spontaneous ventricular fibrillation after release of cross clamping in HTK group. Clinical outcome of single doses of antegrade, cold Custodiol-HTK cardioplegia solution in CABG surgery protected the myocardium equally well as repetitive antegrade, cold blood cardioplegia.*

Keywords: *Myocardial protection in coronary artery bypass grafting (HTK versus cold blood cardioplegia)*

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Cardioplegia arrest remains the current gold standard for myocardial protection during open heart surgery. Blood cardioplegia is now the most common form of hyperkalemic cardioplegia[1,2]. The blood cardioplegia was mixed at a ratio of 1:4 (1 part of hyperkalemic crystalloid solution and 4 part of blood) inducing a rapid depolarized arrest. Nowadays, the patients are older, sicker and more severe and diffuse disease, requiring a more prolonged ischemic operative time. Therefore, myocardial protection during open heart surgery should be improved. Polarized cardiac arrest by Custodiol-HTK (Histidine-Tryptophan-Ketoglutarate) solution has some potential benefit and advantages. We can operate on the heart without interruption after single dose infusion[3-7].

The major aim of the study was to investigate all relevant clinical outcome variables in triple coronary artery disease patients. Comparison of two cardioplegia solution groups of patients was studied.

Correspondence to:
Prathanee S, Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Phone: +66-43-363252, Fax: +66-43-348393
E-mail: psom_pratha@hotmail.com

Material and Method

One hundred and twenty-five patients who underwent coronary artery bypass surgery (CABG) between April 2011 and September 2012 were enrolled in this study. All data were available at Srinagarind Hospital and Queen Sirikit Heart Center of the Northeast, Faculty of Medicine, Khon Kaen University. Inclusion criteria of the patients in this study were triple vessels coronary artery disease (TVD) who had performed CABG. Exclusion criteria were previous CABG, emergency surgery, LVEF less than 20% and

acute myocardial infarction within 30 days.

Patients characteristics such as age, gender, weight, height, left ventricular ejection fraction (LVEF), NYHA, peripheral arterial disease, DM, hypertension, carotid artery stenosis, renal disease, pre-operative heart rhythm, cardiogenic shock were obtained. Data on perioperative time including cardiopulmonary bypass time, aortic cross clamp time, defibrillation after aortic declamping, ICU stay, IABP use, major complication and mortality rate were collected.

One hundred twenty-five patients were separated into group A for blood cardioplegia infusion and group B for Custodiol-HTK crystalloid cardioplegia infusion.

Both groups received routine a CABG operation by median sternotomy two-stage atrial connulation, 28-32° C esophageal temperative, aortic cross clamp antegrade cardioplegia by intermittent cold blood cardioplegia in group A and single-shot 6-10° C Custodiol-HTK in group B.

After last distal coronary anastomosis, patients were weaned from cardiopulmonary bypass. An aortic side clamp was used for proximal anastomosis at ascending aorta as required.

Comparison of the two groups was done using Mann-Whitney U test for continuous variable and Chi-square test for ratio variables. The data were presented as mean □ standard deviations. A *p*-value of less than 0.05 was considered significant.

Results

The demographic data are listed in Table 1. Sixty patients were in group A and sixty-five patients were in group B.

The 30-day mortality rates were 1.7% in group A and 4.6% in group B.

Preoperative NYHA was 60% in NYHA 2-3 in both groups.

Diabetes mellitus and renal dysfunction was more common in group B with statistical significance. Pre-operative IABP used were 3.3%, 9.2% in group A, group B, respectively.

The operation data is shown in Table 2.

CABG alone was performed 96.7%, 87.7% in group A, group B. The number of distal coronary anastomosis ≥4 was 75%, 71.4% in group A, group B. Defibrillation after wean off cardiopulmonary bypass more commonly occurred in group B (8.3% vs. 33.8%) with statistical significance (*p*-value = 0.001).

No statistically significant differences were seen in postoperative variables (Table 3).

Table 1. Pre-operative variables

Variables	Blood (n = 60)	Crystalloid (n = 65)	*p*-value
Age (years)	61.83±7.98	62.28±7.56	0.750
Male (%)	68.30	73.80	0.496
Female (%)	31.70	26.20	0.496
NYHA I (%)	10.00	12.30	0.683
NYHA II (%)	31.70	41.50	0.253
NYHA III (%)	36.70	26.20	0.205
NYHA IV (%)	21.70	18.50	0.654
Number of previous MI (%)	75.00	63.10	0.151
Diabetic (%)	40.00	63.10	0.010
Cigarette smoking (%)	46.70	38.50	0.354
Hypertension (%)	60.00	72.30	0.238
Hyper-cholesterolemia (%)	28.30	47.70	0.045
Renal disease (%)	1.70	16.90	0.005
Pre-operative sinus rhythm (%)	6.70	1.50	0.109
Left main stem disease (%)	43.30	40.00	0.706
Good (%)	55.00	55.40	0.966
Fair (%)	35.00	33.80	0.892
Poor (%)	10.00	10.80	0.888
IV inotropes prior to anesthesia (%)	8.30	9.20	0.860
Cardiogenic shock (%)	8.30	16.90	0.151

Table 2. Intra-operative variables

Variables	Blood (n = 60)	Crystalloid (n = 65)	*p*-value
2 Vessel (%)	0	15.40	0.002
3 Vessel (%)	25.00	21.50	0.647
4 Vessel (%)	50.00	46.20	0.667
5 Vessel (%)	25.00	15.40	0.179
6 Vessel (%)	0	1.50	0.335
CPB time (min)	113.73±27.61	103.22±24.76	0.027
Ao cross clamp time (min)	77.55±20.16	71.22±14.72	0.046

There were no differences in the rate of re-operation, post operative stroke, renal failure needed dialysis, new heart failure, pulmonary complication, GI complication.

Discussion

Custodiol-HTK solution was described by Bretschneider in the 1970s. It is an intracellular,

Table 3. Post-operative variables

Variables	Blood (n = 60)	Crystalloid (n = 65)	*p*-value
Defibrillation (%)	8.30	33.80	0.001
Renal failure (%)	11.70	16.90	0.318
Pulmonary complication (%)	8.30	16.90	0.079
GI complication (%)	0	1.50	0.173
New heart failure (%)	11.70	4.60	0.113
Mortality rate (%)	1.67	4.62	0.349
ICU stay (day)	1.98±1.98	2.25±1.72	0.429
Post-operative hospital stay (day)	10.45±7.00	10.14±7.67	0.813

crystalloid cardioplegia due to low sodium and calcium content. The components of custodial are Histidine, acting as a buffer against acidosis during the long ischemic period; Ketoglutarate improves ATP production during reperfusion; Tryptophan functioning as a membrane stabilizer[8-12].

Primary outcome of this study was ventricular fibrillation (VF) after removal of aortic cross clamp, which occurred more frequently in Custodiol-HTK group, significantly (33.8% vs. 8.3%).

Meta-analysis by Edelman[13] reported six of the eight studies that a higher incidence of VF in Custodiol group (Custodiol 20.1% vs. 9.7%) reached statistical significance.

Another article reported by Braathen et al[14], comparing Custodiol-HTK and cold blood cardioplegia in mitral valve surgery, found a similar result in that 71% of patients receiving HTK resumed VF and 13% in the other group after release of cross clamping.

It was a different result in a small sample size reported by Sindhu et al[15], which concluded that VF were almost absent in Custodiol-HTK group in open heart operation of patients who needed prolonged the cross clamp period. The reason for an increased rate of VF after reperfusion with Custodiol-HTK cardioplegia is not clear. Despite this, Braathen et al showed that the increase in spontaneous VF did not influence the release of myocardial enzymes compared with blood cardioplegia.

Clinical outcome of mortality, low cardiac output syndrome and major complications compared in this study and all reviewed literature have similar results.

Conclusion

A single dose custodial-HTK cardioplegia is a good option because of no re-administration of cardioplegia, which can disturb the technical flow of the operation. It is convenient, simple and at least as safe as tepid blood cardioplegia for myocardial protection in CABG patients. No difference was identified in mortality rate and other clinical outcome except VF was significant and happened during reperfusion period.

What is already known on this topic ?

Custodial can be used in valvular heart disease surgery. Single use is the important advantage.

What did this study add ?

Custodial is also used in CABG patients with comparable outcome to blood cardioplegia.

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Potential conflicts of interest

None.

References

1. Braathen B, Jeppsson A, Schersten H, Hagen OM, Vengen O, Rexius H, et al. One single dose of histidine-tryptophan-ketoglutarate solution gives equally good myocardial protection in elective mitral valve surgery as repetitive cold blood cardioplegia: a prospective randomized study. J ThoracCardiovascSurg 2011; 141: 995-1001.
2. Chambers DJ, Fallouh HB. Cardioplegia and cardiac surgery: pharmacological arrest and cardio-protection during global ischemia and reperfusion. PharmacolTher 2010; 127: 41-52.
3. Fannelop T, Dahle GO, Salminen PR, Moen CA, Matre K, Mongstad A, et al. Multidose cold oxygenated blood is superior to a single dose of Bretschneider HTK-cardioplegia in the pig. Ann ThoracSurg 2009; 87: 1205-13.
4. Demmy TL, Molina JE, Ward HB, Gorton ME, Kouchoukos NT, Schmaltz RA, et al. Custodiol versus Plegisol: A phase 3 multicentre myocardial protection study. Int J Angiol 2008; 17: 149-53.
5. Bingyang J, Jinping L, Cun L. Optimal cardioplegia solution during cardiopulmonary bypass: Crystal

or blood, single or repeated dose. Indian J Extra CorporTechnol 2010; 20: 27.
6. Edelman JJ, Seco M, Dunne B, Matzelle SJ, Murphy M, Joshi P, et al. Custodiol for myocardial protection and preservation: a systematic review. Ann CardiothoracSurg 2013; 2: 717-28.
7. Gaudino M, Pragliola C, Anselmi A, Pieroni M, De Paulis S, Leone A, et al. Randomized trial of HTK versus warm blood cardioplegia for right ventricular protection in mitral surgery. ScandCardiovasc J 2013; 47: 359-67.
8. Garbade J, Davierwala P, Seeburger J, Pfannmueller B, Misfeld M, Borger MA, et al. Myocardial protection during minimally invasive mitral valve surgery: strategies and cardioplegic solutions. Ann CardiothoracSurg 2013; 2: 803-8.
9. Kokotsakis J, Anagnostakou V, Kratimenos T, Ashrafian H, Athanasiou T. Frozen Elephant Trunk: a technique which can be offered in complex pathology to fix the whole aorta in one setting. J CardiothoracSurg 2011; 6: 66.
10. Korun O, Ozkan M, Terzi A, Askin G, Sezgin A, Aslamaci S. The comparison of the effects of Bretschneider'shistidine-tryptophan-ketoglutarate and conventional crystalloid cardioplegia on pediatric myocardium at tissue level. Artif Organs 2013; 37: 76-81.
11. Marten K, Schmiedl A, Schnabel PA, Richter J. Structural protection of the myocardial capillary endothelium by different forms of cardiac arrest and subsequent global ischemia at 5 degrees C. ThoracCardiovascSurg 1999; 47: 205-12.
12. Ovrum E, Tangen G, Tollofsrud S, Oystese R, Ringdal MA, Istad R. Cold blood versus cold crystalloid cardioplegia: a prospective randomised study of 345 aortic valve patients. Eur J CardiothoracSurg 2010; 38: 745-9.
13. Patel N, DeLaney E, Turi G, Stapleton T. Custodiol HTK cardioplegia use in robotic mitral valve. J Extra CorporTechnol 2013; 45: 139-42.
14. Sindhu DR, Srivastava PK, Agrawal S, Saji R, Vaarghese T, Cherian KM. Clinical assessment of prolonged myocardial preservation using Histidine Tryptophan-alpha Ketoglutarate (HTK) solution. Indian J Extra CorporTechnol 2010; 20: 24-6.
15. Zhidkov IL, Belianko IE, Sitnichenko NV, Paliulina MV, Laptii AV. Effect of perfusion volume of the Custodiol solution on the efficiency of cardioplegia in experiment. AnesteziolReanimatol 2008; 42-7.

เปรียบเทียบการให้สารละลายเพื่อป้องกันกล้ามเนื้อหัวใจระหว่างผ่าตัดทางเบี่ยงเส้นเลือดหัวใจ

สมภพ พระธานี, ชูศักดิ์ คุปตานนท์, วรวิทย์ อินทนู, ชวลิต วงศ์พุทธะ, ชนัญญา การุณาสุเมตตา

ภูมิหลัง: *การผ่าตัดหัวใจชนิดเปิด เพื่อทำทางเบี่ยงหลอดเลือดหัวใจ วิธีป้องกันกล้ามเนื้อหัวใจที่สำคัญระหว่างผ่าตัดคือ การให้สารละลายเข้าทางหลอดเลือดโคโรนารี เพื่อให้หัวใจหยุดเต้นและกลับฟื้นใหม่เพื่อให้มีความเสียหายน้อยที่สุด สารละลายเดิมที่ใช้คือ เลือดร่วมกับสารละลายที่มีส่วนผสมของโพรแทสเซียม แต่ต้องให้สารละลายทุก 20-30 นาที จึงได้ศึกษาเปรียบเทียบสารละลายอีกชนิด ซึ่งมีส่วนผสมของโพรแทสเซียมต่ำ แต่ให้สารละลายเพียงครั้งเดียวระหว่างผ่าตัด*

วัตถุประสงค์: *เพื่อเปรียบเทียบผลสำเร็จหลังผ่าตัดในผู้ป่วยที่ให้สารละลายเพื่อป้องกันกล้ามเนื้อหัวใจระหว่างผ่าตัดทางเบี่ยงหลอดเลือดหัวใจ 2 ชนิด*

วัสดุและวิธีการ: *เป็นการศึกษาแบบพรรณนาย้อนหลัง เปรียบเทียบผู้ป่วยที่รับการผ่าตัดทางเบี่ยงหลอดเลือดหัวใจระหว่าง เดือนเมษายน พ.ศ. 2554 ถึงเดือนกันยายน พ.ศ. 2555 จำนวน 125 ราย กลุ่มเอให้ใช้สารละลายที่มีส่วนผสมของเลือด กลุ่มบีใช้สารละลายชนิดให้ครั้งเดียว*

ผลการศึกษา: *กลุ่มบีพบว่าต้องใช้เครื่องกระตุ้นไฟฟ้าหัวใจร้อยละ 33.8 มากกว่ากลุ่มเอร้อยละ 8.3 อัตราการตายกลุ่มบีร้อยละ 4.6 มากกว่ากลุ่มเอ ร้อยละ 1.7 ปัญหาแทรกซ้อนหลังผ่าตัดอื่นๆ ไม่แตกต่างกัน*

สรุป: *ผลการแทรกซ้อนการใช้สารละลายทั้งสองแบบไม่แตกต่างกัน แต่การใช้เครื่องกระตุ้นหัวใจหลังผ่าตัดในกลุ่มบีมากกว่าอย่างมีนัยสำคัญทางสถิติ*