A comparative study between custodiol and warm blood cardioplegia in coronary artery bypass graft operation with poor left ventricular function

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A comparative study between custodiol and warm blood cardioplegia in coronary artery bypass graft operation with poor left ventricular function

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Abstract

Background
Cardioplegia is responsible for myocardial protection during open heart surgery. Cardioplegia was first presented as an agent for hypothermic hyperkalemic arrest. Blood was then introduced as a vehicle to convey potassium to the heart. Custodiol Histidine-Tryptophan-ketoglutarate (HTK) solution is safe and used as a single dose, which can last for up to 3 h. The comparison of the clinical outcomes of this particular solution with warm blood cardioplegia in coronary artery bypass graft (CABG) with poor left ventricular (LV) function has received little attention.

Objective
To compare the clinical outcomes of custodiol solution with warm blood cardioplegia in CABG with poor LV function.

Patients and methods
This single-center randomized prospective study was carried out from January 2017 till January 2018, at National Heart Institute of Egypt. Overall, 50 patients with poor LV function undergoing isolated CABG were divided randomly according to type of myocardial protection during revascularization into two groups: group A included 25 patients who received warm blood cardioplegia, and group B included 25 patients who received custodiol cardioplegia. Data from each group were collected and compared with each other.

Results
Baseline demographic and intraoperative data showed no significant difference between the two groups. The need for intra-aortic balloon pump was similar in both groups. The need for inotropic support, length of mechanical ventilation, and ICU stay was statistically nonsignificant between the two groups. Postoperative arrhythmia was significantly higher in custodiol group [nine (34.62%)] compared with warm blood group [two (8%)] \((P = 0.021)\). Overall mortality shows a statistically nonsignificant difference. Improvement in left ventricular ejection fraction after surgical revascularization was observed among both groups.

Conclusion
Both custodiol cardioplegia and warm blood cardioplegia offer a satisfactory method for myocardial protection in low ejection fraction ischemic heart disease, with increased incidence of postoperative arrhythmia in custodiol cardioplegia.

Keywords: Coronary artery bypass graft, custodiol, poor left ventricular function, warm blood cardioplegia

Introduction
Cardioplegia is responsible for myocardial protection during open heart surgery and provides static and bloodless field to facilitate surgical procedures. At first, cardioplegia was presented as an agent for hypothermic hyperkalemic arrest. Blood was then introduced as a vehicle to convey potassium to the heart [1,2].

Warm blood cardioplegia is known to be an excellent technique for myocardial protection, depending on the fact that blood, in comparison with crystalloid solution, can improve postoperative cardiac results, as it is more physiologic, that is,
conveying oxygen to the myocardium with less hemodilution. However, there is a continuous debate regarding best cardioplegic solution for myocardial protection during cardiac surgeries [3–8].

It was demonstrated that custodiol HTK solution can be safely used as a cardioplegic solution. It is given as a single dose. In addition, it can provide adequate myocardial protection for up to 3 h. Moreover, custodiol is preferable among cardiac surgeons as it ensures uninterrupted open heart procedures [3–5].

Comparing the clinical outcomes of this particular solution with warm blood cardioplegia in coronary artery bypass graft (CABG) with poor left ventricular (LV) function has received little attention. We therefore undertook this comparative study to investigate this aspect.

The aim of this study is to compare the clinical outcomes of custodiol solution with warm blood cardioplegia in patients with poor LV function undergoing isolated CABG.

**Patients and methods**

Ethical approval and consent was obtained. This single-center randomized prospective study was carried out from January 2017 till January 2018, at National Heart Institute of Egypt.

The study was subjected to inclusion criteria, such as patient undergoing isolated CABG with ejection fraction (EF) less than or equal to 35 and patient accepting to participate in the study, and exclusion criteria, such as combined open heart surgery, emergency cases, and patients refusing to participate in the study.

A total of 50 patients undergoing CABG were divided randomly according to type of myocardial protection during revascularization into two groups: group A consisted of 25 patients who received warm blood cardioplegia, and group B consisted of 25 patients who received custodiol cardioplegia. Data of each group were compared with each other.

These data included demographic data; preoperative data, including echo details, such as EF, left ventricular end diastolic volume, and left ventricular end systolic volume; intraoperative data such as cross-clamp time, post-cross-clamp arrhythmia, and operative mortality; and postoperative data such as weaning from ventilator, inotropic support, postoperative arrhythmias, ICU stay, and hospital stay.

**Statistical analysis**

Statistical Package for the Social Sciences for Windows (SPSS, version 24.0; SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis, and the results were considered statistically significant at \( P \) values of less than 0.05. The \( \chi^2 \) test was used to compare proportions between two groups. Continuous variables are presented as mean and SD. Independent two-tailed \( t \) test was used for comparing between normally distributed continuous variables and Mann–Whitney \( U \) test comparisons were performed for continuous variables in case of lack of normality in the distribution of the results.

**Study procedures**

Hemodynamic monitoring was performed by inserting an invasive arterial line in the radial and/or femoral artery, and a central venous pressure line was inserted in the internal jugular vein. Urine output was monitored via a urinary catheter. All patients underwent general anesthesia in the conventional way. Surgical approach was carried out through a median sternotomy. An arterial cannula was inserted in the ascending aorta/aortic arch to establish cardiopulmonary bypass. Venous drainage was achieved through a two-stage cannula inserted in the right atrium.

Cardiopulmonary bypass and aortic cross-clamping by giving 20 ml/kg of HTK cardioplegic solution (Custodiol; Koehler Chemie, Alsbach-Höhnlein, Germany) once over 9–11 min. Each liter contained 15 mmol/l sodium chloride, 10 mmol/l potassium chloride, 18 mmol/l histidine hydrochloride, 180 mmol/l histidine, 4 mmol/l magnesium chloride, 2 mmol/l tryptophan, 30 mmol/l mannitol, 0.015 mmol/l calcium chloride, and 1 mmol/l potassium hydrogen 2-ketoglutarate (osmolarity 310/kg, pH 7.02–7.20). The cardioplegic solution was administered at a temperature of 4–8°C in an antegrade fashion at an initial perfusion pressure of 80–100 mmHg. When the myocardium was at standstill, the perfusion pressure was maintained at 40–60 mmHg. The systemic temperature was drafted to 32.5–33°C.

In patients receiving blood cardioplegia, myocardial protection was achieved by intermittent infusion of normothermic hyperkalemic blood in the aortic root via cardioplegia cannula at a rate of 0.3 l/min and infusion of K⁺ at a dose of 15 ml (30 mEq) over 3 min. The subsequent doses are given every 15–20 min at the same rate with infusion of K⁺ at a dose of 5 ml (10 mEq) over 1 min. Just before cross-clamp removal, a hot shot (warm blood) dose was given in antegrade manner at a rate of 0.3 l/min over 3 min.

**Results**

A total of 53 surgical cases were included in the study. Of which 27 cases used custodial and 26 cases used warm blood cardioplegia. The demographics, preoperative investigations, and comorbidities are listed in Table 1. The mean age was 56.3 ± 7.47 years for custodial group and 54.81 ± 7.69 years for warm group. The number of diabetic patients was 17 (62.96%) in custodial group and 17 (65.38%) in warm group. Serum creatinine was 0.86 ± 0.22 in custodial group and 1.05 ± 0.32 in warm group. The average preoperative EF was 33.64 ± 2.1 and 34.08 ± 1.49, respectively.

The operative characteristics show a cross-clamp time of 66.85 ± 26.75 in custodial group and 63.81 ± 21.89 in warm blood group. The number of grafts was 2.96 ± 1.091 in custodial group and 2.65 ± 0.937 in warm blood group. There
was a slight increase in the use of IAPB with custodiol group, which does not reach a statistically significant level (Table 2). The use of inotropic support was nearly similar during the ICU period with a significant increase in postoperative arrhythmia in custodiol group, with a $P$ value of 0.021, as shown in Table 3.

The 30-day mortality was one (3.7%) in custodiol group and two (7.69%) in warm blood group, with no significant difference in morbidity between the two groups (Table 4).

**DISCUSSION**

The perfect cardioplegic solution for myocardial protection during cardiac surgery is still controversial. A meta-analysis of randomized trials comparing crystalloid cardioplegia and warm blood cardioplegia showed superiority of blood in protecting the myocardium. However, custodiol cardioplegia was not included in the crystalloid group [9].

Low EF has always been a challenge in cardiac surgery owing to high mortality and morbidity. Patients with advanced coronary artery disease and severe LV dysfunction represent a high-risk group referred for CAGB. High mortality and morbidity rates (2.7–33% and 30–67%, respectively) were reported in latest studies [10–12].

As there is no agreement for which is the perfect type of cardioplegia for these cases, surgeons are keen to select the most suitable type of cardioplegia on individual bases to maximize myocardial protection and to improve their results and decrease complications [13].

Custodiol represent an intracellular cardioplegic solution with low sodium concentration, which leads to cardiac arrest in diastole by inhibiting the rapid phase of the action potential. It contains histidine as a buffer, ketoglutarate to enhance ATP energy production during reperfusion, tryptophan to stabilize the cell membrane, and mannitol to diminish cellular edema and work as a free radical scavenger. The well-integrated components of this solution contribute to myocardial preservation and recovery of its function [6].

Warm blood cardioplegia was first used to induce cardiac arrest in 1970s [14]. Intermittent antegrade perfusions of warm blood cardioplegia was introduced in 1980s and proved to provide optimum myocardial protection during heart surgery [15,16].

A meta-analysis of 14 studies compared custodiol versus conventional blood cardioplegia for myocardial protection. Eight out of the 14 studies reported the incidence of ventricular arrhythmias during reperfusion. Overall, results showed that there was an increased incidence of ventricular fibrillation with custodiol that did not reach statistical significance [17].

In a study done by Prathanee and colleagues, custodiol cardioplegia was compared with blood cardioplegia in 125 patients undergoing isolated CAGB. Patients were divided into two groups: 60 patients received custodiol cardioplegia and 65 patients received blood cardioplegia. They concluded that custodiol cardioplegia was safe as tepid blood cardioplegia for myocardial protection in patients with CAGB. They also noticed that there was an increased incidence of ventricular fibrillation during reperfusion period with custodiol group [18].

Another study done by Boros compared custodiol cardioplegia versus 4: 1 blood cardioplegia in 229 adult patients undergoing cardiac surgeries. Results revealed no statistical difference in 30-day mortality or hospital stay. There was a statistically significant increased requirement for fresh frozen plasma during perioperative period with custodiol cardioplegia [19].

Some studies recommend the use of custodiol cardioplegia in adult patients. Myocardial protection offered by custodiol is more likely to be the same as warm blood cardioplegia.

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**Table 1: Baseline clinical and demographic characteristics of the study group (n=53)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Custodiol (n=27)</th>
<th>Warm blood (n=26)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56.3±7.47</td>
<td>54.81±7.69</td>
<td>0.48 (NS)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>20 (74)</td>
<td>21 (81)</td>
<td>0.56 (NS)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.44±9.65</td>
<td>80.88±10.93</td>
<td>0.38 (NS)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.33±7.33</td>
<td>168.08±9.05</td>
<td>0.33 (NS)</td>
</tr>
<tr>
<td>Smoker</td>
<td>14 (52)</td>
<td>12 (46.2)</td>
<td>0.68 (NS)</td>
</tr>
</tbody>
</table>

**Comorbidities**

- Hypertension: 16 (59.62%) vs 14 (53.85%) $P$=0.69 (NS)
- Diabetes: 17 (62.96%) vs 16 (61.54%) $P$=1.00 (NS)
- Atrial fibrillation: 1 (3.7%) vs 1 (3.85%) $P$=0.32 (NS)
- Stroke: 1 (3.7%) vs 1 (3.85%) $P$=0.32 (NS)
- COPD: 3 (11.1%) vs 2 (7.7%) $P$=0.08 (NS)
- Asthma: 1 (3.7%) vs 1 (3.85%) $P$=0.32 (NS)
- Renal impairment: 1 (3.7%) vs 1 (3.7%) $P$=0.32 (NS)
- Liver impairment: 1 (3.7%) vs 1 (3.7%) $P$=1.00 (NS)
- Others: 2 (7.4%) vs 4 (15.38%) $P$=0.61 (NS)

**Lab tests**

- HbA1C%: 6.49±0.94 vs 6.76±0.81 $P$=0.28 (NS)
- Urea: 43.5±9.74 vs 34.54±13.76 $P$=0.01 (S)
- Serum creatinine: 0.86±0.22 vs 1.05±0.32 $P$=0.02 (S)
- Echo findings
  - LVEDD: 6.1±0.67 vs 5.92±0.62 $P$=0.32 (NS)
  - LVESD: 4.93±0.62 vs 4.79±0.59 $P$=0.399 (NS)
  - % ejection fraction: 33.64±2.1 vs 34.08±1.49 $P$=0.38 (NS)

Data are presented as mean±SD and $n$ (%). COPD, chronic obstructive pulmonary disease; HbA1C, glycated hemoglobin; LVEDD, left ventricular end diastolic volume; LVESD, left ventricular end systolic volume; NS, nonsignificant; S, significant.

**Table 2: Operative characteristics of the study group (n=53)**

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Custodiol (n=27)</th>
<th>Warm blood (n=26)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bypass time (min)</td>
<td>113.59±31.93</td>
<td>106.54±37.69</td>
<td>0.465 (NS)</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>66.85±26.75</td>
<td>63.81±21.89</td>
<td>0.65 (NS)</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>2.96±1.091</td>
<td>2.65±0.937</td>
<td>0.27 (NS)</td>
</tr>
<tr>
<td>Intraoperative death</td>
<td>1 (3.7)</td>
<td>1 (3.85)</td>
<td>1.00 (NS)</td>
</tr>
<tr>
<td>IABP</td>
<td>3 (11.1)</td>
<td>1 (3.85)</td>
<td>0.37 (NS)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD and $n$ (%). IABP, intra-aortic balloon pump; NS, nonsignificant; S, significant.
Moreover, the single-dose administration provides a great advantage especially in long and complex cardiac procedures [20].

In our study, data were collected from consecutive 50 patients with isolated ischemic heart disease with EF less than or equal to 35% meeting the inclusion criteria. The baseline demographic and clinical variables are presented in Table 1.

Intraoperative data collected suggest that both groups shared the same operative conditions, which reflects the upper hand in myocardial protection referred to cardioplegic strategy.

The intraoperative mortality, the use of inotropic support, and insertion of intra-aortic balloon pump indicate that there was no significant difference between the two groups, except for a slight increase in intra-aortic balloon pump using custodiol cardioplegia.

We believe that the high percentage of patients without inotropic support in postoperative period indicates good myocardial protection with a nonsignificant difference between the two groups; this was also observed regarding mechanical ventilation duration and ICU length of stay.

The exception was in postoperative arrhythmia, which appeared clearly with custodiol group, as presented in Table 3. These arrhythmias were in the form of ventricular fibrillation during reperfusion period, AF, heart block with or without pacemaker support; S, significant.

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Custodiol (n=26)</th>
<th>Warm blood (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropic support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenaline</td>
<td>16 (61.54)</td>
<td>17 (68)</td>
<td>0.65 (NS)</td>
</tr>
<tr>
<td>Dose</td>
<td>52.63±53.18</td>
<td>70±71.89</td>
<td>0.32 (NS)</td>
</tr>
<tr>
<td>Dobutrex</td>
<td>1 (1.89)</td>
<td>2 (8)</td>
<td>0.53 (NS)</td>
</tr>
<tr>
<td>Dose</td>
<td>0.19±0.96</td>
<td>0.58±2.1</td>
<td>0.39 (NS)</td>
</tr>
<tr>
<td>Levophed</td>
<td>10 (18.9)</td>
<td>11 (44)</td>
<td>0.7 (NS)</td>
</tr>
<tr>
<td>Dose</td>
<td>29.63±46.5</td>
<td>33.85±51.39</td>
<td>0.76 (NS)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00 (NS)</td>
</tr>
<tr>
<td>Dose</td>
<td>0</td>
<td>0</td>
<td>1.00 (NS)</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>1 (1.89)</td>
<td>1 (4)</td>
<td>1.00 (NS)</td>
</tr>
<tr>
<td>Dose</td>
<td>2.59±13.4</td>
<td>0.77±3.92</td>
<td>0.51 (NS)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (h)</td>
<td>17±23.39</td>
<td>20.9±30.7</td>
<td>0.62 (NS)</td>
</tr>
<tr>
<td>ICU lengths of stay (h)</td>
<td>75.2±36.1</td>
<td>92.88±61.29</td>
<td>0.22 (NS)</td>
</tr>
<tr>
<td>Postoperative arrhythmia</td>
<td>9 (34.62)</td>
<td>2 (8)</td>
<td>0.021 (S)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD and n (%). NS, nonsignificant; postoperative arrhythmias, ventricular fibrillation during reperfusion period, AF, heart block with or without pacemaker support; S, significant.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Custodiol (n=26)</th>
<th>Warm blood (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00 (NS)</td>
</tr>
<tr>
<td>Stroke (delayed recovery)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00 (NS)</td>
</tr>
<tr>
<td>Left-sided pleural effusion</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>0.3 (NS)</td>
</tr>
<tr>
<td>Reopening</td>
<td>1 (3.7)</td>
<td>2 (7.69)</td>
<td>0.53 (NS)</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>0.3 (NS)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>1 (3.7)</td>
<td>2 (7.69)</td>
<td>0.53 (NS)</td>
</tr>
</tbody>
</table>

Data are presented as n (%). NS, nonsignificant.

Conclusion

We concluded that in the presence of complete revascularization and a skilled surgeon, both custodiol cardioplegia and warm blood cardioplegia offer satisfactory methods for myocardial protection in low EF ischemic heart disease.

As compared with warm blood cardioplegia, custodiol cardioplegia provides a long uninterrupted surgery (but does not affects total cross-clamp time) despite a higher chance for arrhythmia in the early postoperative period. In-hospital results were not affected by the use of either technique.

Limitations

Limitations in this study include few numbers of cases, short follow-up period, and high cost of custodiol cardioplegia.
The table below shows the post-ICU phase patient characteristics:

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Custodiol (n=26)</th>
<th>Warm blood (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay</td>
<td>4.19±2.17</td>
<td>4.31±2.45</td>
<td>0.85 (NS)</td>
</tr>
<tr>
<td>Echo findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD</td>
<td>6.02±0.67</td>
<td>5.89±0.56</td>
<td>0.45 (NS)</td>
</tr>
<tr>
<td>LVESD</td>
<td>4.46±0.61</td>
<td>5.84±6.67</td>
<td>0.31 (NS)</td>
</tr>
<tr>
<td>% EF</td>
<td>46.43±15.64</td>
<td>41.06±17.17</td>
<td>0.26 (NS)</td>
</tr>
<tr>
<td>% postoperative improvement in EF</td>
<td>45.43±15.64</td>
<td>40.06±17.17</td>
<td>0.26 (NS)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. EF, ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; NS, nonsignificant.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES