Custodiol versus extracellular crystalloid cardioplegia in mitral valve replacement in patients with low ejection fraction

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Background
The use of cardioplegia solution is aimed to avoid myocardial muscle damage, leading to poor contraction and abnormal increased release of cardiac biomarkers enzymes during cardiac arrest. It remains the primary method for myocardial protection against ischemia–reperfusion injury during cardiac 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. Histidine–tryptophan–ketoglutarate solution is safe and used as a single dose that can last for up to 3 h. Comparison between custodiol cardioplegia and cold blood cardioplegia still remains a big debate till now.
Objective
To compare the clinical outcomes of custodiol solution with cold blood cardioplegia in mitral valve replacement (MVR) with cardiac ejection fraction less than 45%.
Patients and methods
This single? center randomized prospective study was carried out from January 2018 till June 2019 at Ain Shams University hospitals. Overall, 65 patients with poor left ventricular function undergoing mitral valve replacement were divided randomly according to type of myocardial protection into two groups: group A included 30 patients who received custodiol cardioplegia, and group B included 35 patients who received cold blood 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 inotropic support, length of mechanical ventilation, and ICU stay were statistically nonsignificant between the two groups. There was a statistically significant difference regarding the rhythm upon declamping [ventricular fibrillation (VF) in 17 (56.7%) cases in group A and nine (25.7%) cases in group B (P=0.016)], and also there was a significant difference in times of defibrillation cardioversion (DC) shock given after declamping (P=0.005). Overall mortality shows a statistically nonsignificant difference. There is a significant difference in postoperative echo assessment for both groups [ejection fraction in group A: 53.17±7.73 compared with 49.06±7.170 in group B (P=0.031)], and there is also a difference in hemoglobin postoperatively, with 10.35±0.843 in group A compared with 10.88±0.798 in group B (P=0.013).
Conclusion
Cardiac arrest using custodiol cardioplegia is a good choice in mitral valve replacement with the advantage of giving only one dose of cardioplegia without interruption of the operation, and also it gives good postoperative echo results than cold blood cardioplegia. Its disadvantages are lower hemoglobin levels postoperatively and hyponatremia during bypass in comparison with cold blood cardioplegia.

Keywords:
custodiol cardioplegia, low ejection fraction, mitral valve replacement

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Introduction

Inadequate myocardial protection in long ischemic periods followed by reperfusion is an issue of concern in cardiac surgery [1–3]. Cardioplegic solutions improve the tolerance to ischemia and reperfusion by preserving myocardial energy reserves, preventing osmotic and electrolyte imbalances, and buffering acidosis [4].

The cardioplegic solutions can be classified into two main groups. One is based on extracellular components with high potassium, magnesium, and bicarbonate

levels, whereas the other is based on intracellular electrolytes. Both have demonstrated beneficial effects as measured with the biochemical markers in biological models and in patients, although the latter option (intracellular composed solution) may appear more effective [5].

Custodiol is an intracellular crystalloid cardioplegic solution used by some centers for myocardial protection in complex cardiac surgery and for organ preservation in transplant surgery. Histidine–tryptophan–ketoglutarate (HTK), Bretschneider's, or custodiol is attractive for cardiac surgeons because it is administered as a single dose and is claimed to offer myocardial protection for a period of up to three hours [6,7], allowing performance of complex procedures without interruption. HTK was described by Bretschneider in the 1970s [8]. A high histidine content buffers the acidosis caused by the accumulation of anerobic metabolites during the long ischemic period, ketoglutarate improves ATP production during reperfusion, tryptophan stabilizes the cell membrane, and mannitol decreases cellular edema and acts as a free-radical scavenger [7].

There is concern about the adequacy of myocardial protection offered by only a single dose of cardioplegia. Similarly, concerns have been raised about hyponatremia that follows the rapid administration of the requisite high volume of this low-sodium cardioplegic solution [9,10].

Patients and methods

Ethical approval and consent was obtained. This single?center randomized prospective study was carried out from January 2018 till April 2019 at Ain Shams University hospitals. The study was subjected to inclusion criteria, such as patient undergoing isolated mitral valve replacement with ejection fraction (EF) less than or equal to 45 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 65 patients undergoing mitral valve replacement were divided randomly according to type of myocardial protection during revascularization into two groups: group A consisted of 30 patients who received custodiol, and group B consisted of 35 patients who received cold blood 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 off the 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 χ^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 when comparisons were performed for continuous variables in case of lack of normality in the distribution of the results.

Results

Baseline demographic and intraoperative data showed no significant difference between the two groups (Table 1). The need for inotropic support, length of mechanical ventilation, and ICU stay were statistically nonsignificant between the two groups. Postoperative arrhythmia was

Table 1 Baseline clinical and demographic characteristics of the study group (*N*=65)

Variables	Group A (*N*=30)	Group B (*N*=35)	*P* value
Age	43.23±14.185	40.06±5.836	0.259 (NS)
EF (%)	33.64±2.1	34.08±1.49	0.38 (NS)
LVEDD (ml)	6.1±0.67	5.92±0.62	0.32 (NS)
LVESD (ml)	4.93±0.62	4.79±0.59	0.399 (NS)
LAD (ml)	50.98±6.148	50.51±6.340	0.072 (NS)
Na (mmol/l)	137.90±2.023	138.12±1.291	0.312 (NS)
K (mmol/l)	4.00±0.563	4.17±0.234	0.121 (NS)
Hb (g/dl)	12.19±1.651	12.98±1.470	0.055 (NS)
Baseline CKMB (ng/ml)	2.38±0.905	2.40±0.991	0.245 (NS)

Values are represented as mean±SD. CKMB, creatine kinase MB; EDD, end diastolic diameter; EF, ejection fraction; ESD, end systolic diameter; Hb, hemoglobin; K, potassium; LAD, left atrial diameter; LVEDD, left ventricular end diastolic diameter, LVESD, left ventricular end systolic diameter; Na, sodium.

Table 2 Postoperative comparison between the two groups

	Group A	Group B	*P* value
ICU (days)	3.30±2.003	3.37±2.636	0.902 (NS)
Ventilation (h)	13.33±10.287	15.83±17.843	0.485 (NS)
Overall stay (days)	8.69±3.704	7.37±4.460	0.201 (NS)
Sodium (mmol/l) (postoperative)	8.69±3.704	139.11±3.479	0.066 (NS)
Potassium (mmol/l) (postoperative)	4.08±0.342	3.97±0.395	0.269 (NS)
CKMB (ng/ml) (2 h)	166.70±48.340	156.91±27.557	0.336 (NS)
CKMB (ng/ml) (8 h)	127.07±72.644	135.97±33.160	0.940 (NS)
CKMB (ng/ml) (24 h)	75.53±62.405	97.06±34.564	0.095 (NS)
Inotropes (h)	26.37±51.527	23.68±14.432	0.670 (NS)
EF (%)	53.17±7.733	49.06±7.170	0.031 (S)
EDD (ml)	50.90±4.248	55.540±4.925	0.000 (S)
ESD (ml)	33.80±3.737	40.04±4.468	0.000 (S)
LAD (ml)	45.70±7.975	44.83±5.628	0.021 (S)
Hb (g/dl)	10.35±0.843	10.88±0.798	0.013 (S)

Values are represented as mean±SD. CKMB, creatine kinase MB; EDD, end diastolic diameter; EF, ejection fraction; ESD, end systolic diameter; Hb, hemoglobin; LAD, left atrial diameter; S, significant.

Table 3 Intraoperative comparison between the two groups

Clinical outcome	Group A	Group B	*P* value
Bypass time (min)	112.23±18.721	92.17±17.713	0.000 (S)
Cross-clamp time (min)	68.97±16.712	61.06±17.603	0.068 (NS)
Ultrafiltration [*n* (%)]	11 (36.7)	8 (22.9)	0.222 (NS)
Ultrafiltration (ml)	810.34±806.379	214.29±388.922	0.001 (S)
Total colloid intake (ml)	1381.67±931.673	1118.57±850.613	0.242 (NS)
Number of doses of cardioplegia	1.04±0.192	2.73±1	<0.001 (S)
Serum sodium during bypass	127.03±5.786	133.77±3.326	<0.001
Serum potassium during bypass	4.60±0.839	4.10±0.818	0.018

Values are represented as mean±SD. S, significant.

significantly higher in custodiol group [17 (56.7%)] compared with cold blood group [nine (25.7%)] (P=0.016). There is a significant difference in postoperative EF between the two groups; in custodiol group, EF=53.17±7.73 compared with 49.06±7.170 in cold blood cardioplegia group (P=0.031) (Table 2), and there is also a difference in postoperative hemoglobin, with 10.35±0.843 in custodiol group compared with 10.88±0.798 in cold blood cardioplegia group (P=0.013). There was also a significant difference in number of doses of cardioplegia, which was less in custodiol group (1.04±0.192 times) than in cold blood cardioplegia (2.73±1 times) (P<0.001) (Table 3). There was a statistical difference in serum sodium during bypass, which was less in group A (127.03±5.786) than group B (133.77±3.326) (P≤0.001). Overall mortality shows a statistically nonsignificant difference (P=0.466). The amount of volume ultrafiltrated during cardiopulmonary bypass was 810.34±806.379 ml in custodiol group and 214.29±388.922 ml in cold blood cardioplegia (P=0.001), although the number of cases that required ultrafiltration in both groups was statistically insignificant, with 11 (36.7%) cases in custodiol group and eight (22.9%) cases in cold blood cardioplegia group (P=0.222).

Discussion

The cardioplegic solutions can be classified into two main groups. One is based on extracellular components with high potassium, magnesium, and bicarbonate levels, whereas the other is based on intracellular electrolytes. Both have demonstrated beneficial effects as measured with the biochemical markers in biological models and in patients, although the latter option (intracellular composed solution) may appear more effective [5].

In our institution, cold blood cardioplegia (extracellular crystalloid cardioplegia) has been used as the standard to protect the myocardium. However, cold blood cardioplegia must be administered every 30 min, and the surgical procedure has to be suspended during infusion. mitral valve replacement (MVR) requires a continuing quiet field; thus, it might be desirable to perform the procedure without interruption. A single high dose of HTK is apparently adequate to protect the myocardium for an extended period. However, if HTK provided less protection than cold blood cardioplegia, it would not be advisable. Thus, this study was designed to compare cold blood cardioplegia and HTK regarding myocardial protection in mitral valve operations.

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 [11].

Warm blood cardioplegia was first used to induce cardiac arrest in 1970s [12]. Intermittent antegrade perfusions of blood cardioplegia was introduced in 1980s and proved to provide optimum myocardial protection during heart surgery [13,14].

Our data show that there is a statistically significant difference regarding the rhythm upon declamping; ventricular fibrillation (VF) was more in custodiol group (P=0.016), with also significant difference in times of defibrillation cardioversion (DC) shock given after declamping (P=0.005), and also there is a statistical difference regarding postoperative echo findings, where EF in custodiol group was 53.17 ±7.73 compared with 49.06±7.170 in complete blood count (CBC) group (P=0.031). There was also electrolyte imbalance in the form of hyponatremia during cardiopulmonary bypass, low hemoglobin level postoperatively, and the amount of volume ultrafiltrated during cardiopulmonary bypass, which was 810.34±806.379 ml in custodiol group and 214.29±388.922 ml in CBC, although the number of cases that required ultrafiltration in both groups was statistically insignificant, with 11 (36.7%) cases in custodiol group and eight (22.9%) cases in CBC group (P=0.222).

A meta-analysis of 14 studies compared custodiol versus conventional blood cardioplegia for myocardial protection. Of the 14 studies, eight reported the incidence of ventricular arrhythmias during reperfusion. Overall, results showed that there was an increased incidence of ventricular fibrillation with custodiol, which did not reach statistical significance [15]. In a study done by Prathanee and colleagues, custodiol cardioplegia was compared with cold blood cardioplegia in 125 patients undergoing isolated coronary artery bypass grafting. 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 blood cardioplegia for myocardial protection in patients with coronary artery bypass grafting. They also noticed that there was an increased incidence of ventricular fibrillation during reperfusion period with custodiol group [16]. Sakata *et al.* [17] used the custodiol solution for valve surgery and found more spontaneous defibrillation and lower requirement of inotropic drugs compared with the use of cold blood cardioplegia. However, Fannelop *et al.* [18] in an experimental study found that cold blood cardioplegia provides better myocardial protection and preservation of left ventricular function than custodiol in the early hours after declamping. Braathen *et al.* [19] in a randomized study measured markers of myocardial injury and demonstrated that custodiol in elective mitral surgery protects the myocardium equally well compared with repetitive antegrade CBC.

In our study, data were collected from consecutive 65 patients with isolated mitral valve disease with EF less than 45% 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, ventilation hours, 30-day mortality, overall mortality, and overall hospital stay indicate that there was no significant difference between the two groups. This extends to the findings of Hoyer and colleagues, who had retrospectively viewed 471 consecutive patients who underwent valve surgeries. In the majority of patients (n=277, 58.8%), cardiac arrest was induced with custodiol cardioplegia, whereas in 194 (41.1%) patients cold blood cardioplegia according to Calafiore was administered. They reported that neither 30-day mortality nor overall 1-year survival were significantly different. Incidence of the cumulative end point (30-day mortality, MI, arrhythmia, low cardiac output syndrome, or need for permanent pacemaker implantation) was also comparable. They conclude that elective cardiac arrest with custodiol is equivalent to blood cardioplegia during valve surgeries, even when extended cardiac arrest is required [20].

The mortality rate in our patient groups was acceptable with no statistical significance. Overall, two patients died in custodiol group, where one patient died owing to low cardiac output (right ventricular failure) and the other patient died owing to chest problems (acute respiratory distress syndrome), and one patient died in in cold blood cardioplegia group owing to low cardiac output (right ventricular failure) (P=0.466).

Conclusion

Custodiol cardioplegia gives better results regarding postoperative EF than cold blood cardioplegia and also has the advantage of giving one dose of cardioplegia that can last for 3 h with no need to interrupt surgery. Disadvantages of custodiol cardioplegia is high incidence of postoperative arrhythmias, low hemoglobin levels, and low serum sodium level during bypass in comparison with cold blood cardioplegia.

Limitations

Limitations in this study include fewer number of cases, short follow?up period, and high cost of custodiol cardioplegia.

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Conflicts of interest

There are no conflicts of interest.

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