Custodiol over cold blood cardioplegia in minimal invasive cardiac valve surgery

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Background
Custodiol has been used as a multi-organ preservation solution and as cardioplegia in cardiac surgery in several nations, but not elsewhere in the globe. Long procedures can be completed without interruption with just one dosage, which offers myocardial protection for up to three hours.
Objective
This study compared the effects of Custodiol and Cold Blood Cardioplegia on the protection of the myocardium during minimally invasive cardiac valve surgery.
Patients and methods
On 82 patients receiving Custodiol and Cold Blood Cardioplegia during Minimally Invasive Cardiac Valve Surgery, a prospective research was done. The investigation took place between January 2021 and March 2022. There were two groups of patients. There were 41 patients in Group (A) who received Custodiol cardioplegia, and there were 41 patients in Group (B) who received cold blood cardioplegia. The study's secondary endpoint was the measurement of Left ventricular ejection fraction in serial echocardiograms, whereas the study's primary result was the detection of increased cardiac enzymes in serial measurements, signifying myocardial damage.
Results
Our data's statistical analysis revealed that none of the outcomes under investigation exhibited a statistically significant difference between groups.
Conclusion
As determined by CK-MB and EF, a single-dose of antegrade cold custodiol cardioplegia during minimally invasive cardiac surgery is just as effective at preserving the myocardial as repeated antegrade cold blood cardioplegia.

Keywords:
cardioplegia, custodiol, minimal invasive cardiac valve surgery, valve surgery

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Introduction

Myocardial protective methods are used during cardiac valve operations to reduce ischemia-reperfusion myocardial damage that may result in myocardial infarction, arrhythmias, ventricular dysfunction, and low cardiac output syndrome, among other complications [1]. Although there are several ways to preserve the myocardium during cardiac surgery, cardiopulmonary bypass, hypothermia, and cardioplegic arrest continue to be the major safeguards during open heart surgery [2,3].

Particularly in complex cardiac surgery involving an extended cross-clamp period, the best approach for myocardial preservation during ischemia diastolic cardiac arrest is still up for discussion. The complete sternotomy, which involves not just a single valve but also several valves and other difficult cardiac surgery, is beginning to lose ground to minimally invasive cardiac surgery (MICS) [3,4]. MICS uses smaller, less invasive incisions than a complete sternotomy in order to lessen surgical stress, prevent heart manipulation, and hasten recuperation. When compared to the standard median complete sternotomy, clinical results of MICS have been observed to be satisfactory [5,6]. In this study, we focused on the minimal invasive valve surgery (Mini-VS) as the valve lesions are more common nowadays as the rheumatic heart disease has been long considered the main aetiology of primary valve lesions [7].

A key tool for cardiac surgery is cardioplegia. In addition to cardiopulmonary bypass, both provide the surgeon a protected static heart during valve surgery. The best cardioplegic treatment is not universally agreed upon among surgeons [8]. Since it

improves perfusion to donors' kidney, liver, and pancreas, as well as cardioplegia in cardiac surgery in certain countries but not all, custodiol has been employed as a multi-organ preservation solution [9]. Custodial is a popular choice among surgeons, especially when doing lengthy operations. It may be delivered in a single dosage and is said to enable myocardial protection for up to three hours, allowing uninterrupted extended operations [10].

In order to preserve the myocardium during minimally invasive cardiac valve surgery, this study compared Custodiol with Cold Blood Cardioplegia.

Patients and methods

This prospective none randomized study was conducted on (82) patients with Minimal Invasive cardiac valve surgery receiving Custodiol and Cold Blood Cardioplegia. This study was conducted at El-Galaa military medical complex and cardiothoracic surgery academy—Faculty of Medicine—Ain Shams University between (January 2021) to (March 2022).

Ethical consideration

This study was approved by the ethical committee of Ain Shams University with No. (FWA00017585)

Study groups

All patients with valve lesions undergoing elective MICS intervention are candidates for the study. An agreed number of 82 consecutive patients were enrolled from El-Galaa military medical complex registry. Patients were included in this study according the following inclusion criteria: (a) Patients with informed consent; (b) Age: 18–65; (c) Both gender; (d) Elective procedure; (e) De novo patients.

Patients were split into two groups based on the type of intraoperative cardioplegia solution utilised. There were 41 patients in Group (A) who received Custodiol cardioplegia, and there were 41 patients in Group (B) who received cold blood cardioplegia.

Systemic temperature was decreased to 28° in Group A (Custodiol). An antegrade administration of the HTK solutions was performed at 4°C with an initial perfusion pressure of 80–100 mm Hg. The perfusion pressure was kept constant at between 40 and 60 mm Hg while the myocardium was at rest. In each case, a single dosage of 25 ml/kg is administered over 5-7 min If there is significant aortic regurge, one-third is administered straight into the coronary ostia based on coronary dominance after the other two-thirds are administered into the aortic root until the myocardium is at rest.

In group B (cold blood cardioplegia), the cardioplegia solution was fed through the aortic root to maintain the hematocrit between 21 and 25% and lower the systemic temperature to 28–30°C. An antegrade route was used to provide blood cardioplegia. Every 20 min, blood-induction cardioplegic solution and blood-maintenance cardioplegia were repeated. If there is significant aortic regurge, one-third is administered straight into the coronary ostia based on coronary dominance after the other two-thirds are administered into the aortic root until the myocardium is at rest. One litre of Cold Blood cardioplegia was administered at a rate of 150–180 ml/min, with successive doses of 500 ml each.

Outcomes of interest

Myocardial damage in the form of increased cardiac enzymes served as the study's primary endpoint, while left ventricular ejection fraction served as its secondary result.

Statistical analysis

Statistical package for social sciences version 24 software for Windows was used to analyse the data. Frequency and percentage descriptions were used to describe categorical data. If numerical data were regularly distributed, they were described in terms of means and standard deviations. To examine the normality of the distribution of numerical data, the Kolmogorov-Semornov test was utilised. To investigate the relationship between categorical variables, the X^2 test was applied. In cases when the assumptions were broken, the fissure exact test was used. A parametric numerical variable difference between two groups was tested using an independent sample t-test. Repeated actions the connection between more than two paired numerical variables was examined using ANOVA. A P value of 0.05 or less was regarded as statistically significant.

Results

Sample size

According to reviewing previous studies results (Palo & Paparella, 2016) and (Torun, 2016), and by using confidence interval 95%, power 80% and standard deviation of CK-MB in the general population (4.54), means of CK-MB at 48 h among custodiol and cold blood [9,11] respectively and 10% response rate. The required sample size will be 41 patients in each group.

Eighty-two patients with valve lesions undergoing minimally invasive cardiac surgery (MICS) were recruited to participate in the study. All patients were divided into 2 groups; 41 patients underwent Cold blood cardioplegia while the other 41 patients underwent cold crystalloid cardioplegia.

Table 1 outlines the comparison between both groups concerning their sociodemographic characteristics and found that Patients who received cold blood were significantly older than those received cold crystalloid. On the other hand, we found that there was a male predominance in both groups. Similarly, there was no significant difference between both groups concerning their mean weights, heights, weights and heights.

Table 2 outlines the comparison between both groups concerning their preoperative lab results and found that their preoperative hemoglobin levels were slightly higher among patients within the Cold crystalloid group when compared to the other group. Similarly, there was a significant increase in serum levels of INR among patients within the cold crystalloid group when compared to others.

On the other hand, serum creatinine levels were slightly higher among patients within the Cold blood group when compared to others. We also found that patients within the Cold crystalloid group had significantly elevated serum levels of Ck-mb when compared to others. Similarly, we found that significant increase in their Ejection fraction among patients within cold crystalloid group when compared to others. Regarding comorbidities, no significant difference between two groups regarding asthma, DM, HTN and smoking.

Table 3 outlines the comparison between both groups concerning their postoperative lab results. Regarding their 8 h postoperative results, hemoglobin levels were slightly higher among patients within the Cold crystalloid group when compared to the other group. There was a slight increase in serum levels of CK-mb among patients within the cold blood group when compared to others.

On the other hand, regarding their 24 h postoperative results, CK-mb serum levels were slightly higher among patients within the Cold crystalloid group when compared to others. After 48 h, we found that patients within the Cold crystalloid group had slightly lower serum levels of Ck-mb when compared to others.

Regarding postoperative INR serum levels, we found that it was significantly lower among patients within the cold blood group when compared to the other group. Regarding Ejection fraction, after 24 h, there was a slight increase in postoperative EF among those with the Cold crystalloid group when compared to the

Table 1 Difference between study groups concerning Sociodemographic characteristics

Variable	Cold crystalloid (n = 41)	Cold blood (n = 41)	P value
Age (years)	52.05±10.41	58.1±5.15	0.001
Gender			
Male	28 (68.3)	21 (51.2)	0.176*
Female	13 (31.7)	20 (48.8)	
Weight (Kg)	83.77±14.32	83.17±4.99	0.802
Height (Cm)	168.27±21.72	173.78±5.62	0.123

Independent sample t test. * Chi square test.

Table 2 Difference between study groups concerning preoperative parameters

Variable	Cold crystalloid (n = 41)	Cold blood (n = 41)	*P value*
Hemoglobin	13.34±1.29	12..81±0.94	*0.036*
INR	1.12±0.12	1.06±0.07	0.004
Creatinine	1.14±0.21	1.16±0.09	0.618
CK-mb	14.54±4.11	9.68±1.13	<0.001
Ejection fraction (EF)	59.71±6.92	53.68±3.53	<0.001
Comorbidities (N, %)			
Asthma	5 (12.2%)	3 (7.3%)	
DM	13 (31.7%)	7 (17.1%)	
HTN	18 (43.9%)	13 (31.7%)	0.0743
Smoking	0	2 (4.9%)	
No	11 (26.8%)	14 (34.1%)	

Independent sample t test.

Table 3 Difference between study groups concerning postoperative parameters

Variable	Cold crystalloid (n = 41)	Cold blood (n = 41)	P value
8 h Hemoglobin	11.22±0.87	10.92±0.71	0.086
8 h CK-mb	57.34±35.49	58.68±14.39	0.823
24 h CK-mb	43.17±36.17	40.32±10.02	0.629
48 h CK-mb	26.83±17.72	29.88±8.24	0.322
Post INR	1.27±0.19	1.49±0.08	0.002
24 h post EF	50.59±7.57	48.24±3.58	0.079
48 h post EF	55.56±6.88	51.2±3.36	0.001

Independent sample *t* test.

other group. Similarly, there was a significant increase in postoperative EF after 48 hours postoperative among those within the Cold crystalloid group when compared to others.

Discussion

Our study included 82 patients with valve lesions underwent MICS. All 82 patients were categorized into two groups: Cold crystalloid group ($n=41$): Patients who underwent cold crystalloid cardioplegia. Cold blood group ($n=41$): Patients who underwent Cold blood cardioplegia.

Regarding 8 h postoperative CK-mb, there was a slight increase in serum levels of CK-mb among patients within the cold blood group when compared to others. On the other hand, 24 h postoperative CK-mb serum levels were slightly higher among patients within the Cold crystalloid group when compared to others. After 48 h, patients within the Cold crystalloid group had insignificantly lower serum levels of Ck-mb when compared to others.

Similar to our finding, a study done 50 patients having mitral valve replacement procedures (MVR) were randomly split into two equal groups and given either cold crystalloid cardioplegia (CCC group, $n=25$) or custodiol (HTK group, $n=25$). They found no statistically significant difference between the custodiol group and the cold crystalloid group for CK-MB and troponin I level following surgery. The research that compared HES with St. Thomas cardioplegia during coronary artery bypass surgery to assess myocardial protection of both groups revealed no significant difference in the levels of CK-MB following surgery, supporting our conclusion. Six hours following surgery, all enzyme levels peaked.

Similar to this, a research comparing three groups—custodiol, St. Thomas cardioplegia, and blood cardioplegia solution—during paediatric cardiac surgery and evaluating the three groups' protective effects on the myocardium discovered that CK-MB [11]. Additionally, a research by who found no evidence to support a difference in CK-MB levels between custodiol and crystalloid cardioplegia [12].

The greatest levels were recorded 6 hours after surgery, which goes against our finding that creatine kinase-MB isoenzyme levels were considerably greater in group HTK compared with cold blood cardioplegia [13].

Regarding postoperative Ejection fraction, after 24 h, there was a slight increase in postoperative EF among those with the Cold crystalloid group when compared to the other group. Similarly, there was a significant increase in postoperative EF after 48 hours postoperative among those within the Cold crystalloid group when compared to others.

Elnahas *et al.* discovered that the conventional group's early postoperative echo revealed significantly worse LV function, proving that a single-dose of HTK solution offers better myocardial protection than repeated doses of cold-blood cardioplegia, particularly when there is a prolonged ischemic period. At discharge, however, there was no discernible distinction between the survivors of the two groups [14].

While, Rezk *et al.* revealed that comparing groups, postoperative echocardiographic measurements of LV function and size were comparable [15]. Additionally, 110 patients were randomly allocated to 1 of 2 groups in a research by Vivacqua *et al.* Cold-blood cardioplegia was repeatedly administered to group 1 (55 patients), and Custodiol histidine-tryptophan-ketoglutarate was administered to group 2 (55 patients). According to this investigation, there was no time-dependent change in LVEF between the Custodiol and regular cardioplegia groups [16]. **Saitoh *et al.*** demonstrated that the myocardial and coronary artery endothelium are protected by the preservation of Custodiol solution [17]. Human endothelium cell cultures were kept in different cardioplegic solutions and temperatures by Von Oppell and his colleagues. Custodiol, which was supported by other investigations, is the greatest option currently available for maintaining hypothermic endothelium cells, according to their findings [18].

The similarities and the differences between our study and the previously mentioned studies are due to various factors: different study populations, different

adjustments for comorbidities, cardiac intervention, techniques and methods to measure outcomes, all of which have been proposed to explain this heterogeneity.

Study limitation

The single-center observational approach and the relatively small sample size are the study's main weaknesses. Furthermore, no information on more accurate technologies to evaluate left ventricular function, such as speckle-tracking strain imaging based on echocardiography, is presented. Last but not least, the lack of additional outcomes such as the amount of cardioplegia administered, the restoration of heart rhythm following the removal of the aortic cross-clamp, and postoperative wall motion problems

Conclusion

As a result, patients having minimally invasive valve surgery have a safe choice for myocardial protection in single-dose Custodiol cardioplegia. As determined by CK-MB and EF, a single-dose of antegrade cold custodiol cardioplegia during minimally invasive cardiac surgery is just as effective at preserving the myocardial as repeated antegrade cold blood cardioplegia.

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Conflicts of interest

There are no conflicts of interest.

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