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Comparing the Efficacy of Custodiol and Cold Blood Cardioplegia in Myocardial Preservation

Shady Arboud[1], El Sayed Fayad[2], Mohamed Amr[2], Hany Eldemiaty[2]

[1] Department of Cardiothoracic Surgery, Nasser Institute, Cairo, Egypt

[2] Department of Cardiothoracic Surgery, Suez Canal University, Egypt

Abstract

Background: Strategies for myocardial protection vary among surgeons, and data on the optimal cardioplegia solution are insufficient. The perfect cardioplegia solution for myocardial protection during cardiac surgery is still controversial. This study aimed to compare the efficacy of custodiol and cold blood cardioplegia in preserving the myocardium.

Methods: In this comparative prospective study, the patients were split into two groups of 60 patients each. Group A received Custodiol HTK solution, whereas Group B received cold blood cardioplegia. Preoperative laboratory investigations, operative data, postoperative ICU stays, and complications were compared between groups.

Results: The number of cardioplegia doses was significantly greater in Group B (1.05 ± 0.22, vs. 1.90 ± 0.82; p<0.001). There were no significant differences between the cardioplegia groups regarding hospital stay (p= 0.246), intensive care unit stay (p= 0.144), mortality (p= 0.769), low cardiac output (p>0.99), postoperative myocardial infarction (p= 0.432), intra-aortic balloon pump insertion (p= 0.224), reoperation (p>0.99), duration of mechanical ventilation (p= 0.389), pulmonary complications (p= 0.432), stroke (p>0.99), or the need for renal dialysis (p= 0.559).

Conclusions: Custodiol cardioplegia could be advantageous in cardiac surgeries when a longer duration is expected. However, this study did not report differences in postoperative outcomes between patients with custodiol or cold blood cardioplegia.

KEYWORDS

Cardiac surgery; Hypothermic hyperkalaemic arrest; Myocardial preservation; Cardiology

Introduction

Thoracic injury is a common cause of mortality and all cardiac surgeries performed using cardiopulmonary bypass must prioritize myocardial preservation. There are two basic categories in which to administer cardioplegia treatments. One is based on internal electrolytes, while the other is based on extracellular components with high quantities of potassium, magnesium, and bicarbonate. Both have shown positive results in biological models and patients, as evaluated by biochemical markers; nevertheless, the latter approach (intracellularly prepared solution) may seem more efficient [1].

Corresponding author: Shady Arboud shady3rboud@gmail.com

Bretschneider introduced the Custodiol (Custodiol HTK, Köhler Chemie GmbH, Bensheim, Germany) histidine-tryptophan-ketoglutarate (HTK) solution in the 1970s. It is a solution based on the intracellular level of electrolytes [2]. The buffering effects of histidine, tryptophan, ketoglutarate, and mannitol enhance high energy output during reperfusion via adenosine triphosphate, stabilize cell membranes, and maintain osmotic regulation of the cell membrane [3]. With verified clinical use in both adults and children, HTK has recently been employed as a multiorgan preservation solution and as a cardioplegia in cardiac surgery in various countries [4-7].

Previous studies have demonstrated that single-dose Custodiol is as safe as blood cardioplegia for myocardial protection during congenital heart surgery [8, 9]. To ascertain whether there is a greater benefit to single-dose Custodiol versus more repeated doses of blood cardioplegia for longer cross-clamp times, evaluation at longer cross-clamp times might be helpful [8]. Compared to cold blood cardioplegia, neonatal myocardium preservation with custodiol during the arterial switch operation showed optimum ventricular function recovery with reduced inotropic support [9].

Therefore, this study aimed to compare the efficacy of custodiol cardioplegia in preserving the myocardium to that of cold blood cardioplegia. The surgeries performed included coronary artery bypass grafting, valve replacement or repair, and ascending aortic replacement surgeries.

Patients and Methods

Design and patients

This prospective study was conducted at a tertiary referral center between March and November 2021. In this comparative prospective cohort study, patients were randomly split into two groups of 60 patients each: Group A received cold blood cardioplegia, whereas Group B received Custodiol HTK solution.

Adult patients who underwent elective on-pump cardiac surgery (coronary artery bypass grafting, valve replacement or repair, or ascending aortic replacement), were aged between 18 and 70 years, had an ejection fraction (EF) > 35%, had normal kidney function (creatinine clearance 107-139 ml/min for males, 87-107 ml/min for females), or had a normal preoperative bleeding profile (INR 0.8-1.2, BT 1-4 min, PT 9.2-11.9 sec) were included. We excluded patients with an EF < 35%, emergency cases, documented preoperative stroke (history of previous cerebrovascular accident confirmed by CT), altered kidney function (creatinine clearance less than 107 ml/min for males or 87 ml/min for females), a preoperative bleeding profile of >1.2 (INR >1.2, BT >4 min, PT >11.9 sec), pregnant women, or redo cases.

Patients were grouped into Group (A), which received Custodiol HTK solution, whereas those in Group (B) received cold-blood cardioplegia. Clinical follow-up data were collected in the ICU, after the first month postsurgery in an outpatient clinic, and through pre- and postoperative history questionnaires.

Outcomes

The study outcomes included hospital stay, intensive care unit stay, mortality, low cardiac output, postoperative myocardial infarction, intra-aortic balloon pump insertion, reoperation, duration of mechanical ventilation, pulmonary complications, incidence of stroke, and need for renal dialysis.

Study data

Preoperative data included demographic data (age, sex, weight, height, smoking), laboratory data (serum creatinine, hemoglobin, bilirubin, coagulation profile), medical history (diabetes mellitus, hypertension, hypothyroidism, bronchial asthma), surgical history and echocardiographic data [EF (poor<40% – fair 40-50%– good >50%). The operative data included the type of operation, cardiopulmonary bypass and cross-clamp time, minimal temperature, blood product transfusion, total balance during cardiopulmonary bypass (CPB), hemofiltration, duration of hemostasis, arrhythmias during CPB weaning, need for support during weaning from CPB, minimum and maximum PO2 during CPB, and number of cardioplegia doses. Postoperative data included ICU stay, duration of mechanical ventilation,

Table 1: Comparison of demographic data between patients who received Custodiol and those who received cold blood cardioplegia. The data are presented as the mean and SD or as numbers and percentages

	Custodiol (n= 60)	Cold blood cardioplegia (n= 60)	P value
Male	35 (58.3%)	45 (75.0%)	0.053
Age (years)	53.77 ± 11.31	55.52 ± 10.55	0.383
Body mass index (kg/m2)	30.29 ± 5.22	29.39 ± 5.38	0.355
Previous transcatheter intervention	7 (11.7%)	4 (6.7%)	0.343
Diabetes mellitus			
Insulin	7 (11.7%)	15 (25%)	
Oral therapy	6 (10%)	9 (15%)	0.055
Diet controlled	0	2 (3.3%)	
Hypertension	17 (28.3%)	24 (40%)	0.178
Dyslipidemia	5 (8.3%)	2 (3.3%)	0.243
Hypothyroidism	2 (3.3%)	1 (1.7%)	0.559
Peripheral vascular disease	1 (1.7%)	1 (1.7%)	>0.99
Atria arrhythmia	6 (10%)	1 (1.7%)	0.051

hospital stay, mortality within 30 days of operation, postoperative morbidities and complications within 30 days, postoperative reopening for any cause, postoperative transthoracic echocardiography, postoperative stroke (new postoperative motor or verbal deficit confirmed by CT brain findings), the need for renal dialysis, the need for IABP insertion, postoperative arrhythmias, one month postoperative follow-up and follow-up after one month of EF, ECG, creatinine, and hemoglobin.

Operative techniques

Cardiopulmonary bypass was started after systemic heparinization, and anticoagulation was carried out in addition to the solution needed to maintain an active clotting time longer than 480 seconds. All procedures were carried out with moderate systemic hypothermia, ascending aortic cannulation, and cardiopulmonary bypass with extracorporeal circulation utilizing a roller pump (32C–34C). Myocardial protection was achieved using one of two cardioplegia solutions: custodiol (1 liter) or blood cardioplegia. The following ingredients were present in one liter of cold blood cardioplegia solution mixed at a ratio of 4:1 (cardioplegia solution/blood). The temperature range for the delivery of the cardioplegia was 4°C to 8°C.

Statistical analysis

SPSS® Statistics version 25 was used for all the data manipulation and analysis (IBM Corporation, Armonk, NY, USA). The mean, standard deviation, and range were used to summarize continuous variables. The categorical variables are presented as frequencies and percentages (%). When more than 20% of the predicted values fell below 5, Fisher's exact test was used to assess the differences in frequency between groups. The Kolmogorov–Smirnov test was used to determine whether continuous variables were normally distributed. Given that the continuous variables were not normally distributed, Mann–Whitney and Kruskal–Wallis tests were utilized. A p value of 0.05 indicated statistical significance.

Results

Preoperative data

Moreover, there were no significant differences in patient sex (p= 0.053), age (p= 0.383), height (p= 0.160), weight (p= 0.779), or BMI (p= 0.355) between the two cardioplegia methods. Moreover, there were no significant differences between the two cardioplegia methods regarding previous transcatheter intervention (p= 0.343), diabetes mellitus (p= 0.055), dyslipidemia (p=0.243), hypertension (p= 0.178), hypothyroidism (p=0.559), peripheral vascular disease (p<0.99), or atrial arrhythmia (p= 0.051). (Table 1)

Table 2: Comparison of operative data between patients who received Custodiol and those who received cold blood cardioplegia. The data are presented as numbers and percentages.

	Custodiol (n= 60)	Cold blood cardioplegia (n= 60)	P value
Operations			<0.001
CABG	18 (30%)	44 (73.3%)	
MVR	5 (8.3%)	2 (3.3%)	
DVR	4 (6.7%)	3 (5%)	
AVR	1 (1.7%)	3 (5%)	
Bental	3 (5%)(	1 (1.7%)	
Supracoronary tube graft	5 (8.3%)	0	
Mitral valve repair	0	1 (1.7%)	
CABG and Mitral valve repair	0	2 (3.3%)	
CABG and AVR	1 (1.7%)	0	
CABG and Tricuspid repair	1 (1.7%)	0	
CABG and MVR	3 (5%)	0	
CABG and DVR	1 (1.7%)	1 (1.7%)	
CABG, MVR, and Tricuspid repair	2 (3.5%)	1 (1.7%)	
CABG, AVR, and Tricuspid repair	1 (1.7%)	0	
CABG, DVR, and Tricuspid repair	1 (1.7%)	0	
AVR and Supracoronary tube graft	2 (3.3%)	0	
AVR and ASD	1 (1.7%)	0	
DVR and Tricuspid repair	3 (5%)	0	
MVR and Tricuspid repair	5 (8.3%)	1 (1.7%)	
MVR, Tricuspid repair & ASD	1 (1.7%)	1 (1.7%)	
MVR and ASD	1 (1.7%)	0	
DVR and TVR	1 (1.7%)	0	
Incision			0.079
Antero-lateral right thoracotomy	3 (5%)	0	
Midline sternotomy	57 (95%)	60 (100%)	

CABG: coronary artery bypass grafting, MVR: mitral valve replacement, DVR: double valve replacement, AVR: aortic valve replacement, ASD: atrial septal defect, TVR: tricuspid valve repair or replacement

Operative and postoperative data

There was a highly significant difference between the two cardioplegia methods regarding operation type (p< 0.001). Moreover, there was no statistically significant difference between the two cardioplegia methods regarding incision type (p=0.079). The number of cardioplegia doses was significantly greater in Group B (1.05 ± 0.22 vs. 1.90 ± 0.82; p<0.001). (Table 2)

Moreover, there was no statistically significant difference between cardioplegia methods regarding any of the postoperative complications. Moreover, there was no statistically significant difference between the two cardioplegia methods regarding ICU stay (p= 0.144), hospital stay (p= 0.246), or mortality (p= 0.769). (Table 3)

Discussion

Myocardial protection aims to maintain ventricular function, improve optimal oxygen delivery, reduce metabolic ischemia, and reduce myocardial edema while creating a bloodless surgical field that makes cardiac surgery easier on an arrested, relaxed heart [10]. However, the optimal cardioplegia solution for patients undergoing adult cardiac surgery is still controversial. We did not find a statistically significant difference in age between the two groups. Gatti and colleagues [11] revealed that the mean age of individuals in the cold blood cardioplegia group in the overall series was 66.3± 9 years, and the mean age of individuals in the custodial group was 66.1± 10 years. The inclusion

Table 3: Comparison of postoperative data between patients who received Custodiol and those who received cold blood cardioplegia. The data are presented as the mean and standard deviation (SD), median (interquartile range), or number and percentage

	Custodiol (n= 60)	Cold blood cardioplegia (n= 60)	P value
Low cardiac output	3 (5%)	3 (5%)	>0.99
Acidosis	8 (13.3%)	6 (10%)	0.570
Postoperative MI	7 (11.7%)	10 (16.7%)	0.432
IABP	8 (13.3%)	4 (6.7%)	0.224
LVEF			
Poor	9 (15%)	5 (8.3%)	
Fair	16 (26.7%)	22 (36.7%)	0.341
Good	35 (58.3%)	33 (55%)	
Reoperation	7 (11.7%)	7 (11.7%)	>0.99
Mechanical ventilation (h)	21 (12- 35)	12 (12- 14)	0.389
Pulmonary complications	7 (11.7%)	10 (16.7%)	0.432
Stroke	6 (10%)	6 (10%)	>0.99
Infective complications	3 (5%)	6 (10%)	0.298
Renal dialysis	2 (3.3%)	1 (1.7%)	0.559
Arrhythmia			
Sinus rhythm	44 (73.3%)	46 (76.7%)	
Atrial fibrillation	12 (20%)	7 (11.7%)	0.475
VF	3 (5%)	4 (6.7%)	
SVT	1 (1.7%)	3 (5%)	
ICU stay	2.67 ± 1.49	2.26 ± 1.40	0.144
Hospital stay	9.40 ± 3.11	8.65 ± 3.54	0.246
Hospital mortality	7 (11.7%)	6 (10.0%)	0.769

MI: Myocardial infarction, IABP: Intra-aortic balloon pump, LVEF: Left ventricular ejection fraction, VF: ventricular fibrillation, SVT: supraventricular tachycardia

of isolated coronary procedures may have contributed to the greater mean age than that in our study. Our study showed no statistically significant difference between the two groups in terms of mean BMI. In Azzam and coworkers' [12] study, the mean BMI for the custodial group was 26.4± 1.3 kg/m2, while the mean BMI for the cold blood cardioplegia group was 22.3 ± 1.5 kg/m2. The lower BMI in our study could be explained by cachexia associated with stenotic valvular heart illnesses or by a lower body weight associated with a comparatively younger age in patients with rheumatic valvular heart diseases.

In our study, there was no statistically significant difference in the prevalence of diabetes mellitus between the two groups. In Azzam and colleagues' [12] study, the prevalence of diabetes mellitus was 6.4% in the custodial group and 8.3% in the cold blood cardioplegia group. The significantly lower incidence of diabetes in our study may be due to the tendency of type II diabetes to manifest at older ages [12]. We did not observe a statistically significant difference in the incidence of hypertension between the two groups. In the study by Scrascia et al. [13], the prevalence of hypertension in the custodial group was 72%, and the prevalence in the cold blood cardioplegia group was 60%. The greater incidence of hypertension in our study may be related to the greater mean age.

Regarding postoperative sequelae, the present study revealed that three patients (5%) in the custodiol group and the same number of patients in the cold blood cardioplegia group had low cardiac output (LCOP) throughout their ICU postoperative courses. In the study by Scrascia et al. [13], low cardiac output syndrome was more common in the custodial group (26%) than in the cold blood cardioplegia group (26%). A subsequent study and our study revealed similar incidences of low cardiac output syndrome in the custodial and cold blood cardioplegia groups;

however, a later study revealed a greater incidence of low cardiac output syndrome, which may be related to the use of more advanced surgical procedures, such as acute aortic dissection.

In this study, 7 (11.7%) patients in the custodial group required reoperation, and the same number of patients in the cold blood cardioplegia group underwent reoperation. In the study by Azzam and coworkers [12], the rate of reopening in the custodial group was 9.6%, and the rate of cold blood cardioplegia was 8.3%. These rates are marginally lower than those found in our study; this may be because aortic root replacement surgeries were performed as part of the study, and older age groups are more susceptible to medical bleeding. We did not observe a difference in the duration of mechanical ventilation between the two groups. In the study by Scrascia et al. [13], there was no statistically significant difference in the length of mechanical ventilation between the custodial and cold blood groups. The longer bypass time and greater mean age in our study could explain the prolonged ventilation duration.

We did not observe a difference in pulmonary complications between the groups. A study by Scrascia et al. [13] showed no statistically significant difference between the two groups regarding pulmonary complications. In this study, six patients (10.0%) in the Custodiol group experienced varying degrees of neurological symptoms consistent with stroke. In the study by Scrascia et al. [13], the difference in the incidence of stroke was not significant.

In our study, differences between the two groups regarding experiencing sternal wound infection were not statistically significant. In the study by Azzam et al. [12], the incidence of deep wound infections was 3.2% in the custodial group and 2% in the group with cold blood cardioplegia. The study only evaluated deep wound infections and excluded superficial mediastinitis or lower limb wound infections related to long saphenous vein harvesting, which could account for the significantly lower incidence of these infections in our study. In this study, 2 (3.3%) patients needed renal dialysis at least once in the ICU throughout their postoperative course. Among the patients with cold blood cardioplegia, just one (1.7%) patient underwent renal dialysis. Azzam et al. [12] reported that 4.1% of the patients in the cold blood cardioplegia group required renal dialysis, whereas 3.2% of the patients in the custodial group did.

In this study, the difference between the two groups was found to be nonsignificant regarding the mean length of hospital stay. In the study by Scrascia et al. [13], there was no significant difference in the mean length of hospital stay between the two groups; the mean hospital stay was 18± 25 days in the custodial group and 16±9 days in the cold blood cardioplegia group. The longer hospital stays in that study than in our study can be attributed to the older mean age, greater involvement of emergency aortic dissection cases, and greater mean CPB time. We did not observe a significant difference in hospital mortality between the two groups. In the study by Scrascia et al. [13], the mortality rate in the custodial group was 6%, whereas the mortality rate in the cold blood cardioplegia group was 14%. We find that these results are comparable to those from our study.

Limitations

This study is limited by its single-center experience, and the results should be generalized to other centers with caution. The study included various types of procedures. These heterogeneous cardiac procedures could have affected the outcomes.

Conclusion

Many factors affect the outcomes of on-pump cardiac surgery. Custodiol cardioplegia could be advantageous in cardiac surgeries when a longer duration is expected. However, this study did not report differences in postoperative outcomes between patients with custodiol or cold blood cardioplegia.

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Ethics Committee (REC) was obtained. All patient data involved were kept private. The patients had the option to decline to take part. All participants provided informed consent after being informed of the survey's objectives, potential advantages, and potential drawbacks. The patient's ability to leave the study at any time did not impact their ability to receive the necessary medical care. This information was solely used for the purposes of this study.

References

1. Sakata JI, Morishita K, Ito T, Koshino T, Kazui T, Abe T. Comparison of clinical outcome between histidine-triptophan-ketoglutalate solution and cold blood cardioplegic solution in mitral valve replacement. Journal of Cardiac Surgery. 1998;13(1):43-7.
2. Schaper J, Scheid HH, Schmidt U, Hehrlein F. Ultrastructural study comparing the efficacy of five different methods of intraoperative myocardial protection in the human heart. The Journal of Thoracic and Cardiovascular Surgery. 1986;92(1):47-55.
3. Camilleri L, Moins N, Mouchonière M, et al. Cultured neonatal rat cardiomyocytes and 99mTc-sestamibi to assess the direct effects of cardioplegia. Cardiovascular Surgery. 1998; 6(6):614-21.
4. Careaga G, Salazar D, Téllez S, Sánchez O, Borrayo G, Argüero R. Clinical impact of histidine-ketoglutarate-tryptophan (HTK) cardioplegic solution on the perioperative period in open heart surgery patients. Archives of medical research. 2001; 32(4):296-9.
5. Arslan A, Sezgin A, Gultekin B, et al. Low-dose histidine-tryptophan-ketoglutarate solution for myocardial protection. Transplantation proceedings. 2005; 37(7):3219-3222.
6. Angeli E. The crystalloid cardioplegia: advantages with a word of caution. Annales françaises d'anesthésie et de reanimation. 2011;30:S17-S19.
7. Viana FF, Shi WY, Hayward PA, Larobina ME, Liskaser F, Matalanis G. Custodiol versus blood cardioplegia in complex cardiac operations: an Australian experience. European Journal of Cardio-Thoracic Surgery. 2013;43(3):526-31.
8. Bibevski S, Mendoza L, Ruzmetov M, et al. Custodiol cardioplegia solution compared to cold blood cardioplegia in pediatric cardiac surgery: a single-institution experience. Perfusion. 2020;35(4):316-22.
9. Pérez-Andreu J, Fernández-Doblas J, Sao Avilés A, de la Torre García T, Roses Noguer F, Abella RF. Myocardial protection in the arterial switch operation: Custodiol versus cold blood cardioplegia. Interactive CardioVascular and Thoracic Surgery. 2020;30(1):136-43.
10. Garbade J, Davierwala P, Seeburger J, et al. Myocardial protection during minimally invasive mitral valve surgery: strategies and cardioplegic solutions. Annals of Cardiothoracic Surgery. 2013;2(6):803.
11. Gatti G, Taffarello P, Forti G, et al. Custodiol®-HTK Solution vs. Cold Blood Cardioplegia for Isolated Coronary Surgery Requiring Prolonged Cross-Clamp Time: A Propensity-Matched Analysis. Arq Bras Cardiol. 2020;115(2):241-50.
12. Azzam M, Omar A, Abass SM, Saleh HZ. Myocardial Protection Using Custodiol versus Cold Blood Cardioplegia in Patients Undergoing Triple Valve Surgery. The Egyptian Journal of Hospital Medicine. 2021; 85(1):3297-300.
13. Scrascia G, Guida P, Rotunno C, et al. Myocardial protection during aortic surgery: comparison between Bretschneider-HTK and cold blood cardioplegia. Perfusion. 2011; 26(5):427-33.