The Egyptian Cardiothoracic Surgeon

In Press

Original Article

Comparative Study Between Custodiol® versus Cold Blood Cardioplegia for Myocardial Protection in Double Valve Replacement Surgery

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Abstract

Background: Several cardioplegic solutions are available for myocardial preservation. The superiority of intracellular over extracellular cardioplegia is still debated. Our study aimed to compare the results of Custodiol® and blood Cardioplegia for myocardial protection in double valve replacement surgery.

Methods: This is a prospective study that included 301 patients. We grouped the patient into; Group A (n= 135) had Custodiol® cardioplegia, and Group B (n= 166) had cold blood cardioplegia. We included patients who had double valve surgery and excluded redo, emergency procedures, and patients who had concomitant coronary artery bypass grafting.

Results: Patients in Group A were significantly younger (43 ±9 vs. 47 ±10, P<0.001). There were 72 females (53.3%) in Group A and 71 (43.4%) in Group B (P= 0.09). The total bypass time was higher in group B (217± 40 vs. 179± 35 min, P< 0.001). The cross-clamp time was comparable between groups (90± 31 vs. 85± 29 min, P= 0.15). The duration of mechanical ventilation (7 ± 1 vs. 12 ± 2 h, P< 0.001), ICU stay (3± 0.7 vs. 4± 0.9, P< 0.001) and hospital stay (8± 1 vs. 13± 3, P< 0.001) were shorter in Group A. Postoperative wound seroma (5 (26.6%) vs. 60 (36.1%), P< 0.001) and mortality (2 (1.5%) vs. 11 (6.6%), p= 0.042) were lower in Group A.

Conclusion: Custodiol cardioplegia could be safe during double valve surgery. A larger randomized trial is required to confirm our findings.

KEYWORDS

Double valve replacement; Cold Blood Cardioplegia; Custodiol®

Introduction

Rheumatic heart disease is still the most frequent etiology of double valve lesions in developing countries, and double valve surgery accounted for 10.9% of valve surgeries [1]. In double valve surgery, myocardial protection has crucial importance to improve the outcomes in those patients [2].

The ideal cardioplegic solution should provide excellent myocardial protection, cause minimal systemic electrolyte imbalance, and be effective for prolonged periods to minimize repeated administration [3]. The cardioplegic solutions could have intracellular or extracellular formulations [4]. Extracellular cardioplegia, such as blood cardioplegia, requires frequent infusion every 20 minutes to achieve proper myocardial protection [5]. Recently, Custodiol® has been used as a multi-organ preservation solution. It increases perfusion to donors' kidneys, liver and pancreas; additionally, it can be used as a cardioplegic

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solution during cardiac surgery [6]. The single-dose Custodiol® prevents long-term ischemia and provides good solid-organ preservation [7].

The superiority of Custodial over cold blood cardioplegia is still the subject of several ongoing research. The aim of this study was to compare the results of Custodiol® and cold blood cardioplegia for myocardial protection in double valve surgery.

Patients and methods:

Design and patients:

We conducted a prospective study on 301 patients who underwent double valve surgery. We classified the patients into two groups according to the cardioplegic solution used. Group A included 135 patients who received Custodiol®, and Group B included 166 patients who received cold blood cardioplegia. Cardioplegia was selected based on surgeons' preferences and patients' ages. We included those who had double valve surgery with an ejection fraction of more than 50%. Patients who had re-operative surgery, emergency operation, and those who had concomitant coronary artery bypass grafting were excluded.

Technique

In Group A, a single dose of HTK solutions at 4°C (20-25ml/kg) was given over 5–8 min, and the systemic temperature was lowered to 30°. We infused the cardioplegia in antegrade fashion with an initial perfusion pressure of 80–100 mmHg. After cardiac arrest, the perfusion pressure was maintained at 40–60 mmHg.

In Group B, we infused cold blood cardioplegia through aortic root. The systemic temperature was reduced to 28-30 °C, and the hematocrit was kept between 21-25%. Blood cardioplegia was mixed at 1:4 (Blood- cardioplegic solution) and repeated every 20 minutes. The infusion rate was 150-180 ml/min for an initial dose of 1 liter and subsequent doses of 500 ml each until the mechanical mitral valve and aortic valve were replaced.

Endpoints

The study outcomes were postoperative ventilation, ICU, and hospital stay time. Echocardiographic follow-up was performed within three and six months postoperatively.

Ethical considerations

An approval from the Research Ethics Committee in the Benha Faculty of Medicine was obtained. Informed written consent was obtained from all participants before enrollment.

Statistical analysis

The collected data were summarized in terms of mean ± standard deviation (SD) for quantitative data and frequency and percentage for qualitative data. Comparisons between proportions were carried out using the Chi-square test ($\chi 2$) or Fisher exact test. Student t-test was used for comparing two means. The statistical analysis was conducted using the SPSS v21 (IBM Corp- Armonk- NY- USA).

Table 1: Preoperative and operative data. Data were presented as mean and SD or numbers and percentages

	Group A (n= 135)	Group B (n= 166)	P-value
Age (years)	43 ±9	47 ±10	<0.001
Females	72 (53.3%)	71 (43.4%)	0.09
Tricuspid regurgitation			
No	14 (10.4%)	22 (13.3%)	0.049
Mild	45 (33.3%)	77 (46.4%)	
Moderate	22 (16.3%)	17 (10.2%)	
Severe	54 (40%)	50 (30.1%)	
Mitral stenosis	135 (100%)	155 (93.4%)	0.001
Mitral regurgitation	135 (100%)	166 (100%)	
Aortic stenosis	54 (40%)	94 (56.6%)	0.004
Aortic regurgitation	135 (100%)	166 (100%)	
Cardiopulmonary bypass time (min)	179± 35	217± 40	<0.001
Cross-clamp time (min)	85± 29	90± 31	0.15

Table 2: Post-bypass and postoperative data. Data were presented as mean and SD or numbers and percentages

	Group A (n= 135)	Group B (n= 166)	P-value
Post bypass Atrial fibrillation	90 (66.6%)	94 (56.7%)	0.003
Post bypass ventricular tachycardia	22 (16.3%)	55 (33.3%)	0.001
Post bypass DC shock	112 (83%)	166 (100%)	<0.001
Rhythm after DC shock			
Sinus	67 (49.6%)	44 (26.7%)	<0.001
Nodal	9 (6.7%)	39 (23.4%)	
Atrial fibrillation	36 (26.7%)	77 (46.6%)	
Ventricular tachycardia	0	6 (3.6%)	
Mechanical ventilation (h)	7 ± 1	12 ± 2	<0.001
Intensive care stay (days)	3 ± 0.7	4 ± 0.09	<0.001
Hospital stay (days)	8 ± 1	13 ± 3	<0.001
Postoperative atrial fibrillation	36 (26.6%)	17 (10.2%)	<0.001
Wound seroma	5 (3.7%)	60 (36.1%)	<0.001
Operative mortality	2 (1.5%)	11 (6.6%)	0.042

A P-value of less than 0.05 was considered statistically significant

Results:

Preoperative and operative data:

Patients in Group A were significantly younger. There were 72 females (53.3%) in Group A and 71 (43.4%) in Group B (P= 0.09). Mitral and aortic regurgitation were the dominant lesions in both groups, while mitral stenosis was more in Group A and aortic stenosis was more in Group B. The total bypass time was higher in group B (217± 40 vs. 179± 35 min, P< 0.001). The cross-clamp time was longer in Group B but did not reach a significant level (90± 31 vs. 85± 29 min, P= 0.15). (Table 1)

Postoperative outcomes

Post-bypass ventricular tachycardia and atrial fibrillation were more common in Group B. (Table 1). After weaning from bypass, potassium was significantly higher in Group B (5.8± 0.8 vs. 3.7± 0.4, P<0.001). PH was lower in Group B (7.3± 0.04 vs. 7.37± 0.06; p <0.001). Sodium Bicarbonate levels were lower in Group B (19± 4 vs. 25± 5; p <0.001).

Postoperative mechanical ventilation, ICU, and hospital stay were significantly longer in Group B (Table 2). Group B had a higher postoperative wound infection and mortality (Table 2).

Table 3: Postoperative echocardiographic data. Data were presented as mean and standard deviation

	Group A (n= 135)	Group B (n= 166)	P-value
Ejection fraction (%)			
Postoperative	58.7± 5.6	58.1± 7	0.71
3 months	58.4± 5.3	57.8± 6.8	0.70
6 months	57.5± 5.8	57.1± 6.1	0.78
Left atrial diameter (cm)			
Postoperative	4.5± 0.3	4.8± 0.6	0.006
3 months	4.3± 0.3	4.6± 0.6	0.004
6 months	4.2± 0.3	4.6± 0.5	0.002
LVESD (cm)			
Postoperative	3.1± 0.4	2.8± 0.3	0.024
3 months	3.1± 0.5	2.8± 0.3	0.006
6 months	3± 0.4	2.7± 0.3	0.003

LVESD: left ventricular end-systolic diameter

Echocardiographic data

There were no differences in the ejection fraction between groups in the postoperative period and during the 3- and 6-months follow-up. The left atrial diameter was significantly higher in Group B and left ventricular end-systolic diameter were lower in Group B. (Table 3)

Discussion

This study was performed on 301 patients to compare Custodiol® versus intermittent cold blood cardioplegia. Custodiol cardioplegia was associated with lower post-bypass arrhythmia, shorter mechanical ventilation, ICU, and hospital stay. Blood cardioplegia has been used to protect the myocardium. Although, every 15–20 min the surgical procedure is suspended for repeated doses. For the long and technically complex case, such as double valve replacement, an uninterrupted surgery is desirable, making Custodiol® an attractive option. However, there is no agreement between surgeons about the ideal cardioplegic solutions [8]. In this study, surgeons' preferences and beliefs affected the administration of cardioplegia in both groups. Some surgeons believe that blood cardioplegia offers better myocardial protection in old age and hypertrophied left ventricle, hence the difference in age and valve lesion distribution between groups.

In our study, on coming off bypass, the arrhythmias were more common in the cold blood cardioplegia group. Del Nido and associates believe that postoperative conduction disturbances are associated with inadequate intraoperative myocardial protection, and hearts with good myocardial protection usually spontaneously defibrillate [9]. Sakata and coworkers evaluated the effect of HTK solution for complex cardiac surgery. They found more spontaneous defibrillation and lower requirement of inotropic drugs compared with cold blood cardioplegia [10].

In our study, about half of cases in Custodiol group returned to sinus rhythm (50%) after the use of DC, while (26.7%) of cases in the cold blood cardioplegia group. In a randomized study, markers of myocardial injury were measured and demonstrated that Custodiol in elective double valve surgery protects the myocardium equally well compared to repetitive antegrade cold blood cardioplegia. Braathen and associates found that spontaneous ventricular fibrillation after the cross-clamp removal in patients receiving HTK was significantly increased. After cross-clamp removal, this increase in fibrillation has been linked to oxidative stress and alteration of electrolyte concentration across the cell membranes. Conduction disturbances were associated with inadequate intraoperative myocardial protection caused by heterogeneous reperfusion and low ATP levels. Despite this, spontaneous ventricular fibrillation did not influence the release of myocardial enzymes compared to blood cardioplegia [11]. Our study reported VF as the first rhythm after reperfusion with cold blood cardioplegia, which was similar to Liu and coworkers. The reason for this is not clear. Some authors have suggested that VF after reperfusion may be an indication of inadequate myocardial protection [12].

There were statistically significant differences between both studied groups regarding ventilation time, hospital stay, and length of ICU stay. Li and associates found a shorter ICU stay with less mortality with Custodiol cardioplegia than cold blood cardioplegia because of low inotropic supports and postoperative complications in their cases with complex cardiac surgeries [13]. However, Kuslu and colleagues found both groups had the same results regarding the duration of mechanical ventilation and length of ICU stay; however, they studied pediatric patients with congenital heart diseases [14].

In this study, there was a significant statistical difference in arterial blood gases between both groups. Acidosis and hyperkalemia were common in the cold blood cardioplegia group. Other studies showed decreased serum sodium, but there was no significant change in osmolality, suggesting isotonic hyponatremia. Research suggested the use of hemofilter on the cardiopulmonary bypass circuit to treat hyponatremia after Custodiol® administration [14].

In our study, postoperative complications such as wound turbid seroma were reported with the cold blood cardioplegia group. Sansone and colleagues reported lower mortality in patients undergoing complex cardiac surgery using Custodiol® compared with those patients using cold blood cardioplegia, which was similar to our study [15, 16].

In this study, postoperative echocardiographic data, including LV function and LV dimensions, were comparable between groups. Saitoh and coworkers proved that the preservation of Custodiol solution protects the myocardium and the coronary artery endothelium [17]. Von Oppell and coworkers stored cultures of human endothelium cells in different cardioplegic solutions and temperatures. According to their findings, the best available solution for hypothermic endothelium cell preservation is Custodiol, which was compatible with other studies [18].

Limitations of the study:

The study is not a randomized trial, and surgeons' selection biased patients' distribution between groups. Several factors could have affected the outcomes other than the cardioplegic solutions. Moreover, the study is limited by being a single-center experience. However, the study showed the safety and feasibility of using Custodiol cardioplegia in double valve surgery.

Conclusion

A single dose cardioplegia strategy for myocardial protection (Custodiol®) could be beneficial for complex cardiac surgery performance. A larger randomized trial is recommended to confirm our finding.

Conflict of interest: Authors declare no conflict of interest.

References

1. Rafaie M, Sharah M, Raslan S, Ezzat N. Is custodial an equivalent alternative for conventional blood cardioplegia in cardiac surgery? J Egypt Soc Cardiothorac Surg 2015; 23(2):19–23.
2. Braathen B, Jeppsson A, Scherstén 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. J Thorac Cardiovasc Surg 2011; 141:995–01.
3. Kotani Y, Tweddell J, Gruber P, et al. Current cardioplegia practice in pediatric cardiac surgery: a North American multi institutional survey. Ann Thorac Surg 2013;96(3):923-9
4. Viana FF, Shi WY, Hayward PA, Larobina ME, Liskaser F, Matalanis G. Custodiol versus blood cardioplegia in complex cardiac operations: an Australian experience. Eur J Cardiothorac Surg 2013; 43(3):526-31.
5. 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.
6. Garbade J, Davierwala P, Seeburger J, et al. Myocardial protection during minimally invasive mitral valve surgery: strategies and cardioplegic solutions. Ann Cardiothorac Surg 2013; 6:803.
7. Joseph N, Madi D, Kumar GS, Nelliyanil M, Saralaya V, Rai S. Clinical spectrum of rheumatic Fever and rheumatic heart disease: a 10 year experience in an urban area of South India. N Am J Med Sci. 2013 Nov. 5(11):647-52.
8. Kotani Y, Tweddell J, Gruber P, et al. Current cardioplegia practice in pediatric cardiac surgery: a North American multi institutional survey. Ann Thorac Surg, 2013; 96(3): 923-9
9. Del Nido P, Wilson G, Mickle D, et al. The role of cardioplegic solution buffering in myocardial protection. A biochemical and histopathological assessment. J Thorac Cardiovasc Surg, 1985; 89: 689-99.
10. Sakata J, 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. J Card Surg, 1998; 13: 43-7.
11. Braathen B, Vengen OA, Tonnessen T, et al. Myocardial cooling with ice-slush provides no cardioprotective effects in aortic valve replacement. Scand Cardiovasc J. 2006; 40: 368-373.

12. Liu J, Feng Z, Zhao J, Li B, Long C. The myocardial protection of HTK cardioplegic solution on the long-term ischemic period in pediatric heart surgery. ASAIO J 2008; 54:470-3.
13. Li XW, Lin YZ, Huang JB, et al. Histidine-tryptophan-ketoglutarate solution decreases mortality and morbidity in high-risk patients with severe pulmonary arterial hypertension associated with complex congenital heart disease: an 11-year experience from a single institution. Braz J Med Biol Res, 2016, 49: 5208.
14. Kuslu S, Zeyneloglu P, Pirat A, Camkiran A, Ozkan M, Arslan G. Comparison of the effects of histidine-tryptophan-ketoglutarate solution and crystalloid cardioplegia on myocardial protection during pediatric cardiac surgery. Critical Care, 2014; 18: 178
15. Fannelop T, Dahle GO, Salminen PR, et al. Multidose cold oxygenated blood is superior to a single dose of Bretschneider HTK-cardioplegia in the pig. Ann Thorac Surg 2009; 87:1205-13.
16. Sansone F, Punta G, Parisi F, et al. Right minithoracotomy versus full sternotomy for the aortic valve replacement: preliminary results. Heart Lung Circ 2012; 21:169-73.
17. Saitoh Y, Hashimoto M, Ku K, et al. Heart preservation in HTK solution: role of coronary vasculature in recovery of cardiac function. Ann Thorac Surg. 2000; 69:107-12
18. Von Oppell U, Pfeiffer S, Preiss P, Dunne T, Zilla P, Reichart B. Endothelial cell toxicity of solid-organ preservation solutions. Ann Thorac Surg, 1990; 50: 902-10.