Available online at www.sciencedirect.com

ScienceDirect

Journal of the Egyptian Society of Cardio-Thoracic Surgery 24 (2016) 38–42
http://www.journals.elsevier.com/journal-of-the-egyptian-society-of-cardio-thoracic-surgery/

Original article

# Custodiol versus blood cardioplegia in pediatric cardiac surgery, two-center study

Ebtehal A. Qulisy [a], Anas Fakiha [a], Ragab S. Debis [a], Ahmed A. Jamjoom [b], Ahmed A. Elassal [a,c], Osman O. Al-Radi [a,b,*]

[a] *Abdullah Bakhsh Children's Heart Center, Department of Surgery, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia*
[b] *Division of Cardiovascular Surgery, The Cardiovascular Department, King Faisal Specialist Hospital, Jeddah, Saudi Arabia*
[c] *Cardiothoracic Surgery Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt*

Received 2 April 2016; revised 27 April 2016; accepted 4 May 2016
Available online 16 June 2016

## Abstract

*Background:* Cold blood cardioplegia is widely used as a method of myocardial protection in pediatric cardiac surgery. Operative interruption to administer cardioplegia and need for repeated administration and occasional direct coronary ostial cannulation are considered a drawbacks of this technique. Custodiol, a crystalloid solution, has been used in children as an alternative cardioplegia solution with the potential advantage of single dose administration with equivalent myocardial protection. We sought to compare the outcomes of cold blood cardioplegia versus Custodiol cardioplegia in pediatric cardiac surgery.

*Methods:* A retrospective cohort study was performed between November 1st, 2013 and June 30th, 2014. All children who underwent heart surgery at two institutions with the use of cardiopulmonary bypass and cardioplegia were included. Patients were identified from a prospective database and additional data were collected from operative report and electronic and paper charts. Continuous data were represented as median and interquartile range, and tested with Wilcoxon rank-sum test. Categorical data were represented as proportions, and tested with Pearson test. A composite endpoint of all cause death, Low Cardiac Output Syndrome (LCOS), Acute Kidney Injury (AKI), and significant arrhythmia was analyzed with a multiple logistic regression model adjusted for complexity using the Risk Adjustment of Congenital Heart Surgery -1 (RACHS-1) categories. A p-value of less than 0.05 was considered to be significant.

*Results:* Blood cardioplegia was administered in 88 (57.1%) patients, and Custodiol cardioplegia was administered in 66 (42.9%) patients according to surgeon's preference. In the risk adjusted comparison of the composite outcome of all-cause death, LCOS, AKI and significant arrhythmia, Custodiol cardioplegia was found to be an independent predictor of an adverse outcome, OR 3.17 (95% CI 1.41–7.14, P-value = 0.0054).

*Conclusions:* Custodial cardioplegia is associated with less optimal myocardial protection and higher adverse outcomes compared to cold blood cardioplegia in children undergoing cardiac surgery. A randomized comparison is warranted.



*Abbreviations:* AKI, Acute Kidney Injury; HTK, Histidine-Tryptophan-Ketoglutarate; LCOS, Low Cardiac Output Syndrome; MV, Mechanical Ventilation; RACHS-1, Risk Adjustment in Congenital Cardiac Surgery – Version 1.

* Corresponding author. Department of Surgery, King Abdulaziz University Hospital, P.O. Box 80215, Building 10 Room 1027, Jeddah 21589, Saudi Arabia.
*E-mail address:* oradi@kau.edu.sa (O.O. Al-Radi).

Peer review under responsibility of The Egyptian Society of Cardio-thoracic Surgery.

http://dx.doi.org/10.1016/j.jescts.2016.05.001

***Ultra-mini abstract**: In a retrospective multicenter study, 88 children received blood cardioplegia, and 66 received Custodiol cardioplegia. In a risk adjusted comparison of the composite outcome of all-cause death, morbidity and significant arrhythmia, Custodiol cardioplegia was found to be an independent predictor of an adverse outcome, OR 3.17 (95% CI 1.41–7.14, P-value = 0.0054).*

*Keywords:* Cardiopulmonary bypass; Congenital heart disease; Custodiol; Cardioplegia; Pediatric; Cardiac surgery

## 1. Introduction

Cardioplegia, a solution used to stop the heart, is an essential tool for cardiac surgery. In conjunction with cardiopulmonary bypass it provides a motionless bloodless protected heart for the surgeon to repair any intra-cardiac or extra-cardiac defect. This is achieved by arresting the heart and minimizing myocardial metabolism during the ischemic time. After placing the patient on cardiopulmonary bypass, the cardioplegia solution is infused in the clamped proximal ascending aorta exclusively supplying the coronary arteries perfusing the myocardium. The ideal cardioplegia solution should provide excellent myocardial protection, cause minimal systemic electrolyte imbalance, and be effective for prolonged periods of time to minimize repeated administration. In a survey of congenital heart surgeons, Kotani et al. identified that there is no agreement between surgeons about the ideal cardioplegia solution [1]. The main types of cardioplegia used are blood based cardioplegia and crystalloid based cardioplegia. Recently, there has been growing interest in the use of a more simplified solution that offers simplified perfusion technique, prolonged ischemic tolerance and minimized disruption during surgery. The Histidine-Tryptophan-Ketoglutarate solution, known as HTK Custodiol (Essential Pharmaceuticals, LLC, Newton, PA, and MACURE PHARMA ApS, Copenhagen, Denmark) has emerged as an option [2]. The goal of this study was to compare the safety and efficacy of Custodiol cardioplegia versus blood cardioplegia.

## 2. Methods

A multi-centered, retrospective review was conducted at two institutions. The participating institutions were Abdullah Bakhsh Children's Heart Center, King Abdulaziz University, Jeddah, Saudi Arabia and the division of cardiovascular surgery, King Faisal Specialist Hospital, Jeddah, Saudi Arabia. The study protocol was approved by the research ethics boards at both institutions. All children (1 day–18 years of age) who underwent congenital heart surgery with the use of cardiopulmonary bypass and cardioplegia between November 2013 and June 2014 at one of the two participating institutions were included. Patients were divided into two groups on the basis of the cardioplegia solution used. In the Blood group, cardioplegia was given in the standard ratio of (4:1) four parts of blood from the cardiopulmonary bypass circuit, and one part potassium-rich crystalloid (K = 60 ml eq/L) named Plegisol (Hospira, Inc, Lake Forest, IL). The initial dose was 30 ml/kg body weight, and subsequent doses were 20 ml/kg given every 20 min. Temperature was reduced to 10–15 °C, while maintaining a perfusion pressure of 100–125 mmHg. In contrast, the Custodiol group was given Custodiol solution at 4–8 °C perfused for 5 min. The dose was 40 ml/kg body weight, with a minimum of 5 min of perfusion time.

All available electronic and paper patient charts as well as the perfusion record, the anesthetic chart, the intensive care record and the operative reports were examined. All cause death was defined as death during the index admission from any cause and regardless of length of stay. Low Cardiac Output Syndrome (LCOS) was defined as the use of more than 0.7 mic/kg/min of Milrinone and/or more than 0.05 mic/kg/min of Epinephrine for more than 5 days. The length of Mechanical Ventilation (MV) was defined as time of mechanical ventilation using endotracheal intubation in hours, re-intubation episodes and subsequent ventilation time was added. Acute Kidney Injury (AKI) was defined as postoperative increase in serum creatinine of more than double the preoperative baseline at any point up to hospital discharge. Significant arrhythmia was defined as any sustained cardiac arrhythmia requiring pharmacologic intervention or cooling of body temperature. Length of ICU stay in days and length hospital stay in days were also reported.

### 2.1. Statistical analysis

Variable distribution was checked for normality. Continuous data were represented as median and interquartile range, while categorical data were represented as frequencies and proportions. Differences between two groups were analyzed using non

parametric tests; Wilcoxon rank-sum test for continuous data and Pearson Chi-Square test for categorical data. To facilitate a risk adjusted comparison between the two groups a composite outcome was created. This composite outcome was defined as any of the following; death from any cause during the index admission, LCOS, AKI, mechanical ventilation longer that 48 h, or significant arrhythmia. A multiple logistic regression model including age, weight, Risk Adjustment in Congenital Heart Surgery (RACHS-1) categories2, and type of cardioplegia was used. A P-value of less than 0.05 was considered to be significant.

## 3. Results

A total of 154 patients were included in the analysis, this excludes two patients who met inclusion criteria but had significant missing variables. Blood cardioplegia was administered in 88 (57.1%) patients, and Custodiol cardioplegia was administered in 66 (42.9%) patients. Demographics and perioperative characteristics of the Blood and Custodiol groups are summarized in Table 1. The RACHS-1 categories are also reported. The unadjusted outcomes and test of significant differences are reported in Table 2. Patients receiving Custodiol vs. Blood had longer MV times, median 47 vs. 72 min (p-value = 0.005). A trend was also noted for more prevalent LCOS in the Custodiol vs. Blood groups, 33% vs. 23% (p-value = 0.14). The composite outcome was significantly more prevalent in the Custodiol vs. Blood groups, 68% vs. 49% (p-value = 0.021). In the risk adjusted comparison using multivariable logistic regression with the composite outcome of all-cause death, the cause of death was not necessarily related to cardioplegia but mostly to complex surgery & low cardiac output state, LCOS, AKI and significant arrhythmia and adjusting for body weight and RACHS-1 risk category, Custodiol cardioplegia was found to be an independent predictor of an adverse outcome, OR 3.17 (95% CI 1.41–7.14, P-value = 0.0054), Table 3.

## 4. Discussion

Myocardial protection is crucial during the repair of congenital heart diseases, and plays a key role in achieving successful results in heart surgery [3,4]. The aim of myocardial protection is to preserve cardiac function, enhance ideal oxygen delivery, and minimize both metabolic ischemia and myocardial edema, while generating a bloodless surgical field which facilitates cardiac repair in an arrested relaxed heart. Strategies for myocardial protection vary among surgeons with insufficient data regarding the optimal cardioplegic solution [1,3,4]. Custodiol cardioplegia has been used in hundreds of cases worldwide; it has been more recently used in children including neonates. Some studies in adults have shown that it may be equivalent to conventional blood cardioplegia [5,6]. A survey conducted among congenital heart surgeons demonstrated that blood-base cardioplegia was used by almost 90% [1]. Custodiol cardioplegia is believed to be convenient, simple to delivered, and less time consuming [5,7]. On the other hand, blood cardioplegia must be re-administered every twenty minutes to maintain its protective properties [8,9]. The current study shows that children including neonates who receive Custodiol cardioplegia for myocardial protection may have

Table 1
Preoperative patients' characteristics.

| | Blood n = 88 | Custodiol n = 66 |
|---|---|---|
| Male gender | 47% (41) | 56% (37) |
| Age days | 305.50 (98.25,1264.75) | 291.50 (145.25, 757.25) |
| Weight kg | 6.000 (4.250, 12.000) | 6.650 (4.925, 9.775) |
| Preoperative Creatinine mmol/L | 28.00 (23.00, 34.50) | 26.00 (18.00, 30.00) |
| RACHS-1 category | | |
| Category 1 | 8% (7) | 0% (0) |
| Category 2 | 41% (35) | 45% (30) |
| Category 3 | 35% (30) | 33% (22) |
| Category 4 | 3% (3) | 6% (4) |
| Category 5/6 | 10% (9) | 5% (3) |
| Uncategorized | 2% (2) | 11% (7) |
| CPB time min | 77 (50, 93) | 98 (70,136) |
| Cross clamp time min | 49 (32, 69) | 65 (48, 91) |
| Total operative time min | 168 (131, 202) | 195 (159, 247) |

Data are presented as Median and Interquartile Range (IQR) and Percentile (Frequencies).
CPB: Cardiopulmonary Bypass.

Table 2
Unadjusted outcomes.

| Outcome | Blood n = 88 | Custodiol n = 66 | Test P-value |
|---|---|---|---|
| All cause death | 5% (4) | 9% (6) | 0.24[a] |
| LCOS | 23% (20) | 33% (22) | 0.14[a] |
| MV time hours | 47 (12,96) | 72 (24,168) | 0.005[b]* |
| Acute kidney injury (AKI) | 15% (13) | 26% (17) | 0.086[a] |
| Significant arrhythmia | 17% (15) | 20% (13) | 0.67[a] |
| ICU length of stay days | 5 (3, 8) | 7 (3, 10) | 0.24[b] |
| Hospital length of stay days | 17 (10, 27) | 18 (11, 28) | 0.6[b] |
| Composite: Death, LCOS, AKI, prolonged MV, or significant arrhythmia | 49% (43) | 68% (43) | 0.021[a]* |

LCOS: Low Cardiac Output Syndrome, MV: Mechanical ventilation, ICU: Intensive Care Unit, Prolonged MV: MV longer than 48 h. *: P-value < 0.05.
[a] Categorical variables were tested with Pearson Chi square test.
[b] Continuous variables were tested with the non-parametric Wilcoxon rank sum test.

Table 3
Risk adjusted composite outcome logistic regression model.

| Variable | β | Odds ratio (CI) | P-value |
|---|---|---|---|
| Cardioplegia: Custodiol vs. Blood | 1.15 | 3.17 (1.41–7.15) | 0.0054 |
| RACHS-1 | | | 0.045 |
| Category 1 vs. category 2 | 1.42 | 4.12 (0.79–21.41) | |
| Category 3 vs. category 2 | 1.22 | 3.39 (1.51–7.63) | |
| Category 4 vs. category 2 | 9.87 | >100 | |
| Category 5/6 vs. category 2 | 10.12 | >100 | |

RACHS-1: Risk Adjustment in Congenital Heart Surgery – version 1. CI: 95% confidence interval.

more adverse outcomes. This effect may be mainly due to longer MV time and more prevalent LCOS. Although all-cause death was higher with Custodiol versus Blood cardioplegia, this did not reach statistical significance in this study.

In adults, a meta-analysis of fourteen studies compared Custodiol versus conventional blood cardioplegia for myocardial protection. Eight out of the fourteen 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. However, a prospective randomized study in patient having mitral valve surgery reported a significantly more spontaneous ventricular fibrillation in the operating room and postoperative arrhythmias were higher with Custodiol [3]. Gaudino et al., reported lower right ventricular ejection fraction, lower cardiac indices and longer duration on inotropes in patients who had Custodiol cardioplegia with poor preoperative right ventricular function [10]. Finally, a randomized clinical trial comparing single-dose Custodiol versus multiple dose blood cardioplegia in 80 consecutive patients operated on for mitral repair, using Troponin-T and Creatinine Kinase MB as a markers of myocardial ischemia concluded that Custodiol provides insufficient protection [10,11].

On the other hand, in two studies conducted among adults who underwent repair of the thoracic aorta demonstrated that the incidence of inotropic use and LCOS was similar for patient receiving Custodiol and blood cardioplegia [9,12]. Some studies recommend the use of custodial in adult cardiac surgery. Custodiol seems to offer myocardial protection that is equivalent to that of conventional blood cardioplegia. Moreover, a single dose cardioplegia strategy for myocardial protection has significant advantages for the performance of heart surgery particularly complex cardiac operations [13].

The present study is limited by the retrospective nature of the analysis and the small number of patients. The non-randomized nature of such study also limits its validity; however, we attempted to reduce this problem by adjusting for the complexity of cases by including RACHS-1 as a variable in the adjusted analysis. A prospective randomized trial may be warranted to confirm or dismiss our findings.

## 5. Conclusion

In children undergoing cardiac surgery, Custodiol cardioplegia may be associated with less effective myocardial protection and higher adverse outcomes compared to blood cardioplegia.

## Conflicts of interest

No conflicts of interest for any of the authors exist.

## Funding

No funding was provided for this study.

## References

[1] Kotani Y, Tweddell J, Gruber P, Pizarro C, Austin EH, Woods RK, et al. Current cardioplegia practice in pediatric cardiac surgery: a North American multiinstitutional survey. Ann Thorac Surg 2013;96(3):923–9.
[2] Jenkins KJ. Risk adjustment for congenital heart surgery: the RACHS-1 method. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2004;7:180–4.
[3] Garbade J, Davierwala P, Seeburger J, Pfannmueller B, Misfeld M, Borger MA, et al. Myocardial protection during minimally invasive mitral valve surgery: strategies and cardioplegic solutions. Ann Cardiothorac Surg 2013;6:803.
[4] Åmark K, Berggren H, Björk K. Blood cardioplegia provides superior protection in infant cardiac surgery. Ann Thorac Surg 2005;80(3):989–94.
[5] Demmy TL, Molina JE, Ward HB, Gorton ME, Kouchoukos NT, Schmaltz RA, et al. Custodiol versus plegisol: a phase 3 multicentre myocardial protection study. Int J Angiol Off Publ Int Coll Angiol, Inc 2008;17(3):149.
[6] 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 Cardiac Surg 1998;13(1):43–7.
[7] Bojan M, Peperstraete H, Lilot M, Tourneur L, Vouhé P, Pouard P. Cold histidine-tryptophan-ketoglutarate solution and repeated oxygenated warm blood cardioplegia in neonates with arterial switch operation. Ann Thorac Surg 2013;95(4):1390–6.
[8] 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.
[9] Edelman JJ, Seco M, Dunne B, Matzelle SJ, Murphy M, Joshi P, et al. Custodiol for myocardial protection and preservation: a systematic review. Ann Cardiothorac Surg 2013;2(6):717.
[10] Gaudino M, Pragliola C, Anselmi A, Pieroni M, De Paulis S, Leone A, et al. Randomized trial of HTK versus warm blood cardioplegia for right ventricular protection in mitral surgery. Scand Cardiovasc J 2013;47(6):359–67.
[11] Scrascia G, Guida P, Rotunno C, De Palo M, Mastro F, Pignatelli A, et al. Myocardial protection during aortic surgery: comparison between Bretschneider-HTK and cold blood cardioplegia. Perfusion 2011;26(5):427–33.
[12] Braathen B, Jeppsson A, Scherstén H, Hagen OM, Vengen Ø, Rexius 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: a prospective randomized study. J Thorac Cardiovasc Surg 2011;141(4):995–1001.
[13] Refaie M, Sharah M, Raslan S, et al. Is custodiol an equivalent alternative for conventional blood cardioplegia in cardiac surgery? J Egypt Soc Cardiothorac Surg 2015;23(2):19–23.