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## Custodiol (Histidine-Tryptophan-Ketoglutarate) versus Modified St. Thomas Cold Crystalloid Cardioplegia: Short-term Results

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## INTRODUCTION

The term "myocardial protection" refers to strategies used either to reduce or to prevent post-ischemic myocardial insult that occurs throughout, and after open-heart surgery.<sup>1</sup> A single dose method for myocardial protection is attractive in long operations, as the surgeon does not need to stop several times to re-administer cardioplegia.<sup>2</sup>

The mechanism of cold crystalloid cardioplegia is extracellular, it induces fast cardiac arrest through excessive potassium and magnesium concentrations, while the Histidine-Tryptophan-Ketoglutarate (HTK) cardioplegia is an intracellular type, it contains lower concentrations of sodium and calcium and induces cardiac arrest with the aid of deprivation of extracellular sodium for action potential.<sup>3</sup>

The major advantage of HTK cardioplegia is derived specially from histidine, which acts as a buffer, enhancing the efficiency of anaerobic glycolysis.

## ABSTRACT

**Background:** Myocardial protection refers to strategies used to avoid post-ischemic myocardial dysfunction. One dose approach for myocardial safety is attractive in long operations.

**Aim of work:** to assess differences among the custodial cardioplegia and the cold crystalloid cardioplegia according to myocardial protection in cases listed for Double Valve Replacement Surgery.

**Patient and Methods:** This prospective cohort trial included 50 cases had double valve replacement surgery between August 2017 and July 2019. Twenty-nine patients were males (58%), and the mean age was 57.66±8.81 years. The mean ejection fraction was 41.43±9.25 %.

**Results:** The mean CPB time in custodial group was 99.4±8.46 while in cold crystalloid cardioplegia group was 95.6±12.27 minutes. The mean DC shocks that was required in custodial group was 9(36%) while in cold crystalloid cardioplegia group was 17(68%) times. Mean days of ICU stay in custodial group were 1.28±0.46 while in cold crystalloid cardioplegia group were 1.72±0.61 days. The mean duration of mechanical ventilation in custodial group was 4.64±0.86 while in cold crystalloid cardioplegia group was 7.04±0.84 hours. Troponin elevation mean in the immediate post-operative: in custodial group was 8.46±2.21 while in the cold crystalloid group was 10.08±2.18.

**Conclusion:** This study showed that the evidence supporting the superiority of custodial over cold crystalloid cardioplegia are limited however, Custodial cardioplegia is appealing as it gives lengthy myocardial protection with a single-dose. The present work demonstrated that Histidine-Tryptophan-Ketoglutarate cardioplegia is related with less ICU stay, mechanical ventilation, postoperative hospitalization and troponin T release in low-risk patients who had double valve replacement.

**Keywords:** Cardioplegia; Custodiol; Myocardial protection; Valve replacement.

Kresh et al. discovered that a histidine protein-kind buffer solution was better than bicarbonate in stabilizing intracellular PH.<sup>4</sup>

The primary endpoint aimed to evaluate whether the custodial or the crystalloid cardioplegia is better in myocardial protection in patients Undergoing Double Valve Replacement Surgery. Secondary endpoint aimed to show the effect of both cardioplegic solutions on myocardium regarding cardiac enzymes, postoperative ICU stay and ejection fraction (EF).

## PATIENTS AND METHODS

Design and patients:

This study is prospective, comparative, non-randomized, non-blinded, multicenter (not single) and small volume sample cohort. The study was conducted from 08/2017 -07/2019 on 50 patients who had double valve replacement surgery (DVR) attending the National Heart Institute and Alazhar University Hospital. We included Patients with double valve disease who underwent Valve

replacement through conventional Median Sternotomy with cardio-pulmonary bypass time more than 80 minutes. We excluded cases with concomitant surgical procedure, emergency, re-operative surgery, cases with end-organ dysfunction and cases with ejection fraction less than 40%. The median follow-up duration was 6 months.

Ethical consideration:

The local Ethical Committee accredited the work, and all the cases signed consent previous to enrollment.

Method and information collection:

All cases had preoperative laboratory investigations, 12-lead ECG, trans-thoracic echocardiography, and cardiac catheterization.

All cases had surgical intervention under general anesthesia with endotracheal intubation. The surgical approach was through median sternotomy, then the pericardium is opened. All patients had aortic and venous cannulation. Antegrade cardioplegia was given in all patients. Left atrial unipolar radio frequency ablation was done in cases with permanent AF just after applying the cross clamp and administering cardioplegia. Ablation was done using (Medtronic Inc.) probe encircling the orifices of the pulmonary veins and postero lateral part of mitral annulus. After ablation, the mitral and the aortic valves were replaced and cases with tricuspid regurg under went tricuspid repair using segmental DeVega technique. The heparin action was reversed with protamine sulfate with ratio of one mg for every 100 IU heparin. After achieving medical and surgical hemostasis, the sternum was closed, and the patient got transported automatically ventilated to the intensive care unit (ICU). We studied the cardiopulmonary bypass time, and the ischemic time, and the need for mechanical support.

Postoperative analysis covered the duration of mechanical ventilation, arrhythmias, and length of ICU stay. Postoperative echocardiography was routinely ordered prior to discharge.

Statistical analysis:

Data had been collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative statistics had been demonstrated as mean, standard deviations and ranges when their distribution found. Also, qualitative variables had been demonstrated as number and percentages.

The comparison among the studied groups concerning the qualitative data was achieved by the Chi-square test. The comparison between the two independent groups with quantitative information and parametric distribution had been achieved by the usage of Independent t-test while two groups with paired data were compared by the usage of Paired t-test.

The confidence interval has been adjusted to 95% and the margin of error accepted has been adjusted to 5%. So, the p-value was considered non-significant

( $P > 0.05$ ); significant ( $P < 0.05$ ) and highly significant ( $P < 0.01$ ).

## RESULTS

Fifty patients were collected among them, 14 patients were males (56%) and 11 patients (44%) were females in Group A while in Group B 15 patients (60%) were males and 10 patients (40%) were females. 15 patients (60%) were diabetic in Group A, while 10 patients (40%) were diabetic in Group B. 15 patients (60%) were hypertensive in Group A, and 18 (72%) patients in Group B (Table 1). In Group A, 4 patients (16.0%) had permanent AF, while in Group B 3 patients (12%) had permanent AF. Maze procedure was done to both groups using left atrial unipolar radio frequency ablation. Patients were reviewed regularly at one, three, six and twelve months with ECG. The difference in freedom from AF was not statistically significant between the two groups with 75% (3/4) in Group A compared to 66% (2/3) in Group B.

		Custodial group	Cold crystalloid cardioplegia group	Test value*	P-value	Sig.
		No. = 25	No. = 25			
Diabetes	No	10 (40.0%)	15 (60.0%)	2.000	0.157	NS
	Yes	15 (60.0%)	10 (40.0%)			
Hypertension	No	10 (40.0%)	7 (28.0%)	0.802	0.370	NS
	Yes	15 (60.0%)	18 (72.0%)			

NS: Non significant

**Table 1:** Risk factors distribution of the study group shows that there was no statistically significant difference found between the two studied groups regarding risk factors with p-value  $> 0.05$ .

The mean cardiopulmonary bypass time was in custodial group was  $99.4 \pm 8.46$  while in cold crystalloid cardioplegia group was  $95.6 \pm 12.27$  minutes. (Table 2) .

		Custodial group	Cold crystalloid cardioplegia group	Test value	P-value	Sig.
		No. = 25	No. = 25			
Cardiopulmonary bypass time	Mean $\pm$ SD	$99.4 \pm 8.46$	$95.6 \pm 12.27$	1.275	0.209	NS
	Range	90 – 115	70 – 120			
Cross clamp time	Mean $\pm$ SD	$72.2 \pm 9.36$	$68 \pm 12.58$	1.339	0.187	NS
	Range	60 – 90	50 – 90			

NS: Non significant

**Table 2:** Cardiopulmonary bypass time and aortic cross-clamp time (minutes) presented as range and (mean and standard deviation):

The mean ICU stay in custodial group was  $1.28 \pm 0.46$  while in cold crystalloid cardioplegia group was  $1.72 \pm 0.61$ . The mean duration of mechanical

ventilation (MV) in custodioid group was  $4.64 \pm 0.86$  while in cold crystalloid cardioplegia group was  $7.04 \pm 0.84$ . The mean total hospital stay in custodioid group was  $6.48 \pm 0.59$  while in cold crystalloid cardioplegia group was  $7.96 \pm 1.27$  (Table 3).

		Custodioid group	Cold crystalloid cardioplegia group	Test value	P-value	Si g.
		No. = 25	No. = 25			
Need for inotropes	Yes	19 (76.0%)	19 (76.0%)	0.000	1.000	NS
ICU stay (days)	Mean $\pm$ SD	$1.28 \pm 0.46$	$1.72 \pm 0.61$	-2.872	0.006	HS
	Range	1 – 2	1 – 3			
Duration of MV (hrs)	Mean $\pm$ SD	$4.64 \pm 0.86$	$7.04 \pm 0.84$	-9.977	0.000	HS
	Range	3 – 6	6 – 9			
Total hospital stay	Mean $\pm$ SD	$6.48 \pm 0.59$	$7.96 \pm 1.27$	-5.277	0.000	HS
	Range	6 – 8	6 – 10			

HS: highly significant; ICU: Intensive care unit; MV: Mechanical ventilation; NS: not significant

**Table 3:** Comparison between the two studied groups regarding postoperative data showing that there was statistically significant difference between them regarding ICU stay total hospital stay and duration of mechanical ventilation.

Troponin: Venous blood samples were collected immediately postoperative, 12 hours and 24 hours postoperative. The troponin elevation mean in the immediate post-operative: in custodioid group was  $8.46 \pm 2.21$  while in the cold crystalloid group was  $10.08 \pm 2.18$ . While, in twelve hours post-operative: in custodioid group was  $21.62 \pm 5.24$ , while in the cold crystalloid group was  $24.86 \pm 5.33$  (Table 4). In twenty-four hours after CPB Troponin values decreased in both groups without statistically significant difference among them, with mean Troponin I in custodioid group was  $8.1 \pm 0.84$  in comparison to  $8.6 \pm 1.5$  in crystalloid group.

		Custodioid group	Cold crystalloid cardioplegia group	Test value	P-value	Si g.
		No. = 25	No. = 25			
Immediate postoperative	Mean $\pm$ SD	$8.46 \pm 2.21$	$10.08 \pm 2.18$	2.609	0.012	S
	Range	4.12 – 12.95	5.32 – 14.16			
12 hours postoperative	Mean $\pm$ SD	$21.62 \pm 5.24$	$24.86 \pm 5.33$	2.167	0.035	S
	Range	12.32 – 28.62	13.45 – 31.96			
Paired p-value		<0.001	<0.001			

S: significant

**Table 4:** Comparison between the two studied groups regarding troponin showing significant elevation in the troponin level in the cold crystalloid group in the immediate and 12 hours post operative in comparison to the custodioid group.

Echocardiography: A comparison of postoperative echo study revealed that the mean EF in Group A was  $50.4 \pm 4.29$  while in Group B was  $50.24 \pm 6.79$  (Table 5).

		Custodioid group	Cold crystalloid cardioplegia group	P-value	Si g.
		No. = 25	No. = 25		
EF (%)	Mean $\pm$ SD	$50.4 \pm 4.29$	$50.24 \pm 6.79$	0.921	NS
Pericardial effusion	No	19 (76.0%)	20 (80.0%)	0.733	NS
	Yes	6 (24.0%)	5 (20.0%)		

EF: Ejection fraction; NS: not significant

**Table (5):** Comparison between the two studied groups regarding Postoperative Echo

Reopening: there was no significant difference in the rate of re-exploration for bleeding between the two groups as 1 patients (4%) in the custodioid group was re-explored due to bleeding from sternal wire and 2 patients (8%) in the cold crystalloid group were re-explored due to bleeding from left atriotomy.

No valve complications were detected till the end of the study.

## DISCUSSION

Our trial was conducted on 50 cases, which were categorized into two groups, Group A (n=25) with custodioid cardioplegia, and Group B (n=25) with intermittent antegrade cold cardioplegia. Clinical and laboratory investigations were ordered to assess the two methods regarding myocardial protection in double valve replacement surgery.

In our study 27 cases (54%) are diabetics, which is comparable to different studies.<sup>5</sup> Hypertension was diagnosed in 66% of our cases, in agreement to different studies.<sup>5,6</sup>

Echocardiography was routinely ordered preoperatively to evaluate left ventricle function, valves, and pulmonary artery systolic pressure. The mean EF in our study is  $[41.43 \pm 9.25]$  %. In agreement to other studies.<sup>7,8</sup>

In our results, the cardiopulmonary bypass time in Group A is  $99.4 \pm 8.46$ , and in Group B is  $95.6 \pm 12.27$ . The mean cross clamp time in Group A is  $72.2 \pm 89.36$ , and in Group B was  $68 \pm 12.58$  showing no statistical difference compared to different studies.<sup>7,9</sup>

The mean ICU stay in our results in Group A is  $1.28 \pm 0.46$  and at the same time in Group B it is  $1.72 \pm 0.61$  with p-value 0.006. We found that the mean length of MV in custodioid group is  $4.64 \pm 0.86$  and in crystalloid cardioplegia group it is  $7.04 \pm 0.84$  with p-value 0.000 showing a remarkable statistical difference between the two groups suggesting the superiority of HTK solution over the crystalloid cardioplegia which was similar to different studies.<sup>10,11</sup> (Table 3)

The mean elevation of troponin-T in 12 hours post-operative in group A is  $21.62 \pm 5.24$  in our results, whilst in Group B is  $24.86 \pm 5.33$  with p-value 0.035 Showing a remarkable statistical difference suggesting higher myocardial safety with HTK cardioplegia, which come in agreement with different studies.<sup>6,12</sup> (Table 4)

Postoperative echocardiography revealed that the mean EF in Group A became  $50.4 \pm 4.29$  while in Group B became  $50.24 \pm 6.79$ . 6 patients (24%) in Group A had pericardial effusion and 5 patients (20%) had pericardial effusion in Group B with no statistical difference, which is comparable to different studies.<sup>13</sup> (Table 5)

#### Study limitations:

The main limitation of the study is the restricted number of patients and short period of study. We suggest the conduction of a multi-center study for a better evaluation of the effect of HTK VS cold crystalloid cardioplegia in myocardial protection.

### CONCLUSION

The results suggest that Custodiol provides myocardial protection that is equivalent to that of cold crystalloid cardioplegia however; Custodiol cardioplegia is attractive for its potential to give long myocardial protection and motionless operative field after single-dose application. The present study demonstrated that HTK cardioplegia is associated with less ICU stay, mechanical ventilation, postoperative hospitalization, and troponin T release in low-risk patients undergoing double valve replacement.

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