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ORIGINAL ARTICLE

Comparison Between Custodiol and Blood-enriched Cardioplegia on Myocardial Protection During Double Valve Replacement Surgeries

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Abstract

Background: **Cardioplegia is necessary during heart surgery to lessen the myocardium's metabolic needs and avoid osmotic, electrolytic, and pH imbalances.**

Methodology: **This prospective nonrandomized controlled clinical trial was conducted at the Cardiothoracic Surgery Department, Faculty of Medicine, Al-Azhar University from October 2019 to December 2022. During this study, 60 patients were assessed for eligibility and divided into two equal groups, group A included patients who were given a single dose of antegrade custodial cardioplegia with moderate hypothermia 30 °C, to be repeated after 3 h and group B included patients who were given intermittent antegrade cold blood cardioplegia with moderate hypothermia to be repeated every 20−25 min. All patients were evaluated preoperatively, intraoperatively, and postoperatively and particular attention was paid to all surgical problems and postoperative complications related to the technique of myocardial protection.**

Results: **Cardiopulmonary bypass time and return of spontaneous rhythm after defibrillator device shock were statistically significantly lower (145.86 ± 28.56) versus (165.24 ± 27.54) min and 10 (33.3%) versus 18 (60.0%), respectively among group A compared with group B.**

Conclusion: **In the surgical repair or replacement of double valve lesions, cold histidine-tryptophan-ketoglutarate solution demonstrated greater myocardial preservation than hypothermic hyperkalemic blood cardioplegia.**

Keywords: Blood-enriched cardioplegia, Custodiol, Double valve surgery, Myocardial protection

1. Introduction

Methods and procedures utilized during and after cardiac surgery to reduce or avoid post-ischemic myocardial dysfunction are referred to as myocardial protection.[1]

A variety of treatments and measures have been developed during the last 50 years to protect the heart during surgery. When hypothermia was originally described as a type of anesthetic method that could be used to broaden the scope of surgery in 1950, the concept of protecting the heart from perioperative harm was born.[2]

Melrose *et al*. published five years later on the injection of potassium citrate into the root of the aorta at both normal and low body temperatures.[3]

Numerous surgeons instantly switched from potassium-induced cardiac arrest to intermittent aortic obstruction-induced normothermic cardiac ischemia. Clinical evidence, on the other hand, linked it to metabolic acidosis, decreased cardiac output, and an increased risk of stroke.[4]

In response to this problem, another type of cardioplagia, potassium-enriched blood cardioplagia, was developed. Because of its ability to oxygenate and buffer, blood was thought to be a superior

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delivery medium.[5] Blood cardioplagia has essentially supplanted previous procedures for stopping the heart during open heart surgery since its initial description. This shift from crystalloid-type to blood cardioplagia occurred as a result of experimental and clinical research that shown blood cardioplagia to be more protective of the arrested myocardium.[6] However, experimental data suggests that blood may not provide significant protection for the myocardial at low temperatures. Hypothermia promoted sludging and red cell rouleau development.[7]

In the 1970s, Bretschneider described histidine-tryptophan-ketoglutarate (HTK), a well-known intracellular crystalloid cardiologic solution. It is used to preserve organs after organ transplant surgery. It is appealing to cardiac surgeons since it is administered as a single dose and is supposed to preserve the myocardium for up to 3 h, allowing intricate procedures to be performed without interruption. It is sometimes referred to as HTK cardioplegia or Bretschneider's cardioplegia.[8]

There are different methods for administering the solutions, as well as a range of solutions and temperatures. There are several types of antegrade and retrograde infusions, including simultaneous antegrade and retrograde infusions, intermittent antegrade and retrograde infusions, continuous antegrade and retrograde infusions, and intermittent retrograde infusions. Furthermore, there is continuous dispute about the optimal manner to provide cardiologic treatment.[9]

The safety and efficacy of custodial cardioplegia during double valve replacement surgery will be compared in this study to those of intermittent antegrade cold blood cardioplegia.

2. Patients and methods

From October 2019 to December 2022, 60 patients were included in this prospective nonrandomized controlled clinical trial at Al Azhar University's Department of Cardiothoracic Surgery, Faculty of Medicine. Patients with double valve lesions, patients with or without tricuspid valve disease, and patients undergoing repair or replacement surgical methods were all included in the study. While individuals with single valve disease and congenital heart disease require surgical repair, patients with cardiac tumors, extensive liver illness, and renal dialysis were excluded from the study.

2.1. Ethical considerations

Participants provided informed written consent after being fully informed of the purpose and nature of the current study. Patients can opt out of the project at any time without affecting their medical care. The Ethical Research Committee of Al-Azhar University's Cardiothoracic Surgery Department and Faculty of Medicine approved the study plan. The confidentiality of data was preserved.

2.2. Study interventions and procedures

For this study, 60 patients undergoing double valve surgery were divided into two groups: 30 patients were assigned to group A and underwent a single dose of antegrade custodial cardioplegia with severe hypothermia of 30 °C, to be repeated in 3 h. 30 patients were assigned to group B, which received intermittent antegrade cold blood cardioplegia with periodic repetitions of moderate hypothermia (28–32)°C.

Transthoracic echocardiography, clinical/laboratory assessments, and arterial blood gas exams were performed on all patients before and after surgery to assess their myocardial and respiratory function.

2.3. Study outcomes

Comparison of study groups in terms of age, sex, cardiac pathology, cardiopulmonary bypass, cross clamping times, need for hemofiltration on bypass, hyponatremia during cardiopulmonary bypass (CPB), return of spontaneous rhythm, need for intraoperative blood transfusion, arrhythmias, lactate l, and safety of custodiol cardioplegia during double valve surgery 24 h after surgery. Some of the problems that may develop following bypass surgery include hospitalization (days), postoperative atrial fibrillation, wound seroma, length of inotropic support in the ICU in days, intensive care stay (days), and mechanical ventilation (h). Following surgery, arrhythmia, hemorrhage, and re-exploration, blood transfusion, renal impairment, stroke, and mortality, as well as postoperative echocardiographic data.

2.4. Statistical analysis

The data was evaluated using SPSS Inc.'s statistical program for social sciences, version 23.0 (Chicago, Illinois, USA). The quantitative data included the mean, standard deviation, and ranges. Qualitative factors were also represented numerically and as percentages. The following experiments were carried out: Independent-samples when comparing two means, the significance test (t-test) was used. The χ^2 test of significance was used to compare the proportions of qualitative measures. The allowed margin of error was set at 5%, with a 95% confidence interval. As a result, the P value was determined to

be significant as follows: *P* values less than 0.05 were considered significant.

3. Results

3.1. Demographic and preoperative data between two groups

Table 1.

This table shows no statistically significant difference between groups according to demographic and preoperative data, with *P* value ($P > 0.05$).

3.2. Preoperative echocardiography

Table 2.

This table shows no statistically significant difference between both groups according to preoperative echocardiography ejection fraction (EF%), mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation, Tricuspid regurgitation, tricuspid annular plane systolic excursion (TAPSE), pulmonary artery pressure (PAP), Left atrial diameter (cm), Left vent end-systolic diameter (ESD) (cm) and Left vent end-diastolic diameter (EDD) (cm), with *P* value ($P > 0.05$).

3.3. Intraoperative data

Table 3.

This table shows statistically significant lower mean value of cardiopulmonary bypass time 'min' in group A comparing to group B, with *P* value ($P = 0.009$); also statistically significant increase frequency of hyponatremia during CPB in group A comparing to group B, with *P* value ($P = 0.008$); additionally, there was a statistically significant increase frequency of post bypass defibrillator device shock in group A comparing to group B, with *P* value ($P = 0.039$), also, statistically significant increase frequency of return of spontaneous rhythm in group B comparing to group A, with *P* value ($P = 0.040$). While the rest have parameters in significant difference between groups, with *P* value ($P > 0.05$).

3.4. Postoperative data

Table 4.

Table 1. Demographic and preoperative data between two groups.

	Group A: HTK group ($N = 30$) [n (%)]	Group B: Cold blood group ($N = 30$) [n (%)]	t-test value	*P* value
Age (y)	47.50 ± 8.08	49.50 ± 8.76	0.919	0.362
Sex				
Male	12 (40.0)	10 (33.3)	0.072	0.789
Female	18 (60.0)	20 (66.7)		
BMI [wt/(ht)2]	27.72 ± 2.37	25.52 ± 2.58	1.762	0.171
Pathology				
RHD	28 (93.9)	27 (90.0)	0.000	1.000
Degenerative	2 (6.7%)	3 (10.0)		
Ischemic	0	0		
Risk factors				
DM	2 (6.7)	2 (6.7)	0.000	1.000
HTN	3 (10.0)	2 (6.7)	0.210	0.647
NYHA class				
1	2 (6.7)	2 (6.7)	1.231	0.746
2	11 (36.7)	15 (50.0)		
3	15 (50.0)	11 (36.7)		
4	3 (10.0)	3 (10.0)		
Preoperative rhythm				
Sinus	5 (16.7)	7 (23.3)	0.104	0.747
Atrial Fibrillation	25 (83.3)	23 (76.7)		
Coronary angiography >40 years				
Normal	30 (100.0)	30 (100.0)	0.000	1.000
Abnormal	0	0		
Cardiac enzymes				
CKmb in ng/ml	11.63 ± 3.98	12.09 ± 3.06	0.502	0.618
Troponin level in ng/ml	0.023 ± 0.002	0.022 ± 0.002	0.682	0.738

Using: t-Independent Sample *t*-test for Mean ± SD.
χ^2: Chi-square test for Number (%) or Fisher's exact test, when appropriate.
P value greater than 0.05 is insignificant.
**P* value less than 0.05 is significant.
***P* value less than 0.001 is highly significant.

Table 2. Preoperative echocardiography finding between two groups.

	Group A: HTK group ($N = 30$) [n (%)]	Group B: Cold blood group ($N = 30$) [n (%)]	t-test value	P-value
EF%	57.33 ± 6.41	57.75 ± 5.15	0.280	0.781
Mitral stenosis	30 (100.0)	28 (93.9)	1.856	0.174
Mitral regurgitation	30 (100.0)	30 (100.0)	0.000	1.000
Aortic stenosis	12 (40.0)	17 (56.7)	1.647	0.199
Aortic regurgitation	30 (100.0)	30 (100.0)	0.000	1.000
Tricuspid regurgitation				
No	3 (10.0)	4 (13.3)	1.738	0.628
Mild	10 (33.3)	14 (46.7)		
Moderate	5 (16.7)	3 (10.0)		
Severe	12 (40.0)	9 (30.0)		
TAPSE	19.43 ± 0.63	19.01 ± 0.53	1.794	0.107
PAP	60.90 ± 10.19	57.23 ± 13.02	1.216	0.229
Left atrial diameter (cm)	4.73 ± 1.05	5.04 ± 0.63	1.387	0.171
Left vent ESD (cm)	3.26 ± 0.42	2.94 ± 0.42	1.951	0.095
Left vent EDD (cm)	5.95 ± 1.01	6.09 ± 1.04	0.529	0.599

Using: t-Independent Sample t-test for Mean ± SD. EDD, end-diastolic diameter; ESD, end-systolic diameter; PAP, pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.
χ^2: Chi-square test for Number (%) or Fisher's exact test, when appropriate.
P value greater than 0.05 is insignificant.
*P value less than 0.05 is significant.
**P value less than 0.001 is highly significant.

Table 3. Comparison between two groups according to intraoperative data.

	Group A: HTK group ($N = 30$) [n (%)]	Group B: Cold blood group ($N = 30$) [n (%)]	Test value	P value
Cardiopulmonary bypass time (min).	145.86 ± 28.56	165.24 ± 27.54	2.675	0.009[a]
Cross clamping time in minutes	131.58 ± 27.54	141.78 ± 23.46	1.544	0.128
Hemofiltration on bypass	10 (33.3)	7 (23.3)	0.727	0.394
Hyponatremia during CPB	18 (60.0)	8 (26.7)	6.660	0.008[a]
Rhythm after DC shock				
Sinus	10 (33.3)	4 (13.3)	3.301	0.069
Nodal	2 (6.7)	2 (6.7)	0.000	1.000
Atrial fibrillation	8 (26.7)	5 (16.7)	0.868	0.351
Ventricular tachycardia	0	1 (3.3)	0.990	0.319
Return of spontaneous rhythm	10 (33.3)	18 (60.0)	4.225	0.040[a]

Using: t-Independent Sample t-test for Mean ± SD. CPB, cardiopulmonary bypass.
χ^2: Chi-square test for Number (%) or Fisher's exact test, when appropriate.
P value greater than 0.05 is insignificant.
**P value less than 0.001 is highly significant.
[a] P value less than 0.05 is significant.

This table shows statistically significant higher mean value of duration of inotropic support in ICU 'days' in group B comparing to group A, with P value ($P = 0.002$), also statistically significant higher mean value of intensive care stay 'days' in group B comparing to group A, with P value ($P < 0.001$), additionally, there was a statistically significant higher mean value of hospital stay 'days' in group B

Table 4. Comparison between two groups according to postoperative data.

	Group A: HTK group ($n = 30$)	Group B: Cold blood group ($n = 30$)	Test value	P value
Needs for pharmacological inotropic support	12 (40.0%)	19 (63.3%)	3.207	0.073
Duration of inotropic support in ICU in days	1.96 ± 1.23	2.92 ± 1.05	3.251	0.002[a]
Mechanical ventilation (h)	14.48 ± 5.60	15.26 ± 4.99	0.570	0.571
Intensive care stay (days)	3.12 ± 1.10	4.22 ± 1.20	3.701	<0.001[b]
Hospital stay (days)	8.24 ± 1.03	13.39 ± 3.09	8.660	<0.001[b]

Using: t-Independent Sample t-test for Mean ± SD.
χ^2: Chi-square test for Number (%) or Fisher's exact test, when appropriate.
P value greater than 0.05 is insignificant.
[a] P value less than 0.05 is significant.
[b] P value less than 0.001 is highly significant.

comparing to group A, with P value ($P < 0.001$). While the rest have parameters in significant difference between groups, with P value ($P > 0.05$).

3.5. Postoperative echocardiographic

Table 5.

This table shows statistically significant higher mean value in group B: cold blood group than group A: HTK group according to left atrial diameter of postoperative, after 3 months and after 6 months, with P value ($P < 0.05$). Also, there was a statistically significant higher mean value in group A: HTK group than group B: cold blood group according to LVESD of postoperative, after 3 months and after 6 months, with P value ($P < 0.05$). While, there is no statistically significant difference between groups according to EF%, wit P value ($P > 0.05$ insignificant).

4. Discussion

Heart surgery requires intraoperative myocardial preservation because purposeful ischemia causes adenosine triphosphate depletion, which causes myocardial acidosis, cell swelling, and lasting structural damage.[10]

The most prevalent myocardial protection strategies are currently hypothermia and hyperkalemic cardioplegia.[11]

In patients undergoing aortic surgery, Dawoud and colleagues compared cold crystalloid single dosage HTK (Custodiol) cardioplegia to cold blood multidose cardioplegia. Custodial and cold blood cardioplegic therapies were reported to provide good myocardial protection in patients undergoing thoracic aortic surgery. Custodiol use was associated with lower troponin levels, shorter inotropic support durations, and shorter ICU stays. There was no statistically significant difference between the two groups in terms of early mortality or morbidity. Their study comprised 100 patients who had both elective and emergency aortic surgery. The remaining 50 patients (group B) received cold blood cardioplegia, while the 50 patients in group A received Custodiol cardioplegic solution. Troponin I peak release, length of inotropic support, and critical care unit hospitalization were all higher in the cold blood group. Custodiol patients required more hemofiltration and intraoperative blood product transfusions. There was no difference in cross-clamp time, arrhythmias, postoperative EF%, or in-hospital mortality. Intraoperatively, cross-clamp and total bypass time were comparable between the two groups.[12]

Rapid administration of an excessive dose of Custodiol (Na+ 15 mmol/l) has been connected to substantial hyponatraemia and acidosis. There was no data on blood sodium levels or outcomes from any of the comparison studies included in the meta-analysis that could be used to predict clinical hyponatraemia. Similarly, none of the series reporting (or researching) hyponatraemia was large enough to meet the inclusion requirements for this analysis.[6,13]

Lindner and colleagues measured blood sodium and osmolality in 25 patients at 11 intra- and postoperative intervals. Patients' serum sodium (15 mmol/l) levels declined significantly (and quickly), indicating isotonic hyponatremia. However, osmolality did not vary significantly.[14]

In a series of cardiac procedures, Ali and colleagues evaluated the efficacy and safety of blood cardioplegia and the HTK solution. Total 320 patients undergoing various cardiac operations were randomly assigned to either the HTK or blood cardioplegia groups. They discovered that using HTK

Table 5. Comparison between two groups according to postoperative echocardiographic data.

Postoperative echocardiographic	Group A: HTK group ($n = 30$)	Group B: Cold blood group ($n = 30$)	t-test	P-value
Ejection fraction (%)				
Postoperative (pre discharge)	60.46 ± 5.77	59.84 ± 7.21	0.368	0.714
3 months	60.15 ± 5.46	59.53 ± 7.00	0.383	0.704
6 months	59.23 ± 5.97	58.81 ± 6.28	0.265	0.792
Left atrial diameter (cm)				
Postoperative (pre discharge)	4.64 ± 0.31	4.94 ± 0.62	2.370	0.021[a]
3 months	4.43 ± 0.31	4.74 ± 0.62	2.449	0.017[a]
6 months	4.33 ± 0.31	4.74 ± 0.52	3.709	<0.001[b]
LVESD (cm)				
Postoperative (pre discharge)	3.19 ± 0.41	2.88 ± 0.31	3.303	0.002[a]
3 months	3.19 ± 0.52	2.88 ± 0.31	2.805	0.007[a]
6 months	3.09 ± 0.41	2.78 ± 0.31	3.303	0.002[a]

Using: *t*-Independent Sample t-test.
P value greater than 0.05 is insignificant.
[a] P value less than 0.05 is significant.
[b] P value less than 0.001 is highly significant.

cardioplegia reduced the time required for cross-clamp, bypass, mechanical ventilation, ICU stays, and hospital stays significantly. When compared with blood cardioplegia, it is associated with a lower incidence of postoperative segmental wall anomalies and a lesser need for inotropic support. Custodiol cardioplegia is a safe and effective alternative to blood cardioplegia for improving myocardial protection.[10]

In contrast to the current study's findings, Edelman and colleagues concluded that despite extensive clinical use, the evidence for Custodiol's advantage over other kinds of cardioplagia for myocardial protection or organ preservation is lacking. Custodiol and conventional cardioplegia were tested in 14 trials to maintain the myocardium after adult cardiac surgery. Although there was no difference in mortality, there was a trend toward greater ventricular fibrillation in the Custodiol group, which was not statistically significant. In trials comparing them, there was no difference between Custodiol and other types of cardioplagia.[15]

However, Veres and colleagues agreed with us and discovered that the novel HTK cardioplegic solution (Custodiol-N) improved myocardial and endothelial function during cardiopulmonary bypass with hypothermic cardiac arrest. According to the demonstrated protective benefits, custodiol-N may be the next-generation cardioplegic therapy for preventing ischemia-reperfusion injury in cardiac surgery. Custodiol-N cardioplegic solution avoided myocardial dysfunction following cardiac arrest by boosting coronary blood flow (587 ml/min vs. 263).[16]

Sharah and Raslan recommended custodiol cardioplegia while treating adult patients. Custodiol's myocardial protection is expected to be comparable to warm blood cardioplegia. Furthermore, single-dose administration is advantageous, particularly in long and difficult cardiac procedures.[17]

In 2021, in a prospective study involving 301 patients undergoing double valve surgery, two groups were compared: group A received Custodiol cardioplegia ($n = 135$), while group B received cold blood cardioplegia ($n = 166$). Patients in group A were notably younger, and although there was no significant difference in se distribution, the total bypass time was longer in group B. Cross-clamp time was similar between the groups. Group A exhibited shorter durations of mechanical ventilation, ICU stay, and hospital stay. Additionally, group A experienced lower rates of postoperative wound seroma and mortality compared with group B. In accordance with our results this study suggests that Custodiol cardioplegia is a safe option for double valve surgery.[18]

On the other hand, another prospective cohort trial reported a limited evidence supporting the superiority of custodial over cold crystalloid cardioplegia, they compared the effectiveness of Custodiol cardioplegia and cold crystalloid cardioplegia in providing myocardial protection during Double Valve Replacement Surgery and reported that Custodiol had shorter CPB time, fewer defibrillator device shocks, shorter ICU stay, and lower troponin levels, suggesting potential benefits.[19]

It is still debatable which sort of cardioplegia is more useful. Weisel contends that while selecting a cardioplegic strategy, the patient's health and the type of cardiac procedures to be performed should be considered in order to ensure adequate myocardial protection, improve postoperative outcomes, and prevent difficulties.[20]

4.1. Conclusion

Cold HTK solution performed better in myocardial preservation than hypothermic hyperkalemic blood cardioplegia in the repair or replacement surgical procedures with double valve defects. It is proposed as a possible technique for preserving myocardium during surgical treatments to correct or replace double valve abnormalities.

Conflicts of interest

There are no conflicts of interest.

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