Comparison between the Impact of Traditional Cold Crystalloid Cardioplegia and Histidine-Tryptophan-Ketoglutarate Solution Cardioplegia on Myocardial Protection during on Pump Coronary Artery Bypass Surgery Assessed by Transesophageal Echocardiography

Fatma Ibrahim Amin Ibrahim[1], Ezzat Mohamed EL-Taher[2], Mohamed Emad EL-Din Abdel-Ghaffar[2], Nihal Adel Nasr[3], Hassan Salah Hassan[4].

1. M.B. B.CH. (2009), master's degree (2015), Assistant Lecturer, Department of Anesthesia and Intensive Care, Faculty of Medicine, Suez Canal University.
2. Professor of Anesthesiology and Intensive Care, Faculty of Medicine, Suez Canal University.
3. Lecturer of Anesthesiology and Intensive Care, Faculty of Medicine, Suez Canal University.
4. Lecturer of Cardiothoracic Surgery, Faculty of Medicine, Suez Canal University.

Abstract

Introduction: Cardioplegia is responsible for myocardial protection during open heart operation and provides static and bloodless field to facilitate surgical procedures. The perfect cardioplegic solution for myocardial protection during cardiac operation is still controversial. Aim: To compare the ejection fraction using trans-esophageal echocardiography, need for cardiac support, and postoperative complications of custodiol cardioplegic solution versus traditional crystalloid solution in cases having a coronary artery bypass graft (CABG) operation while on the pump using aid of trans-esophageal echocardiography. Methods: This prospective randomized clinical trial study involved 48 cases who underwent on-pump coronary artery bypass graft operation, they were randomly selected for one of the two groups, group (A) who received intermittent ante grade traditional cold crystalloid cardioplegia (ICCC), and Group (B) who received ante grade histidine–tryptophan–ketoglutarate (HTK). It was conducted in the routine cardiothoracic surgeries, Suez Canal University Hospital from 2020 to 2023. Results: Regarding the intraoperative SWMA assessment, 5, 30 minutes after CC release, at sternal closure, and skin closure were shown to be substantially greater in ICCC group than in HTK group. The intraoperative mean ejection fraction, fractional shortening, and fractional area change were shown to be substantially higher in ICCC group than in HTK group 30, 60 min after weaning, at sternal closure, and skin closure. No substantial variance was shown among both groups regarding any of the relevant postoperative complications, mortality, MI, CHF, LOS, stroke, or AF. Conclusion: A single dose of custodiol HTK is superior to intermittent ante grade cold crystalloid cardioplegia in protecting the myocardium in coronary artery bypass operation as exhibited by the biomarkers of myocardial damage. There were no substantial variances in after surgery mortality and morbidity using custodiol cardioplegia when compared with intermittent ante grade cold crystalloid cardioplegia for CABG.

KeyWords: Ejection Fraction, Fractional Shortening, Fractional Area Change.

DOI Number: 10.48047/nq.2023.21.6.NQ23133 **NeuroQuantology2023;21(6): 1305-1314**

Introduction:

Perioperative myocardial damage is a major contributor to cardiac surgery-related morbidity and mortality. Substantial progress in cardiac surgery has been made thanks in large part to improved myocardial preservation techniques. However, there is still debate about whether antegrade or retrograde delivery, warm or cold cardioplegia, intermittent or continuous perfusion, and crystalloid vs Histidine-Tryptophan-Ketoglutarate (HTK) custodial cardioplegia is best (1).

In order to do cardiac surgery with a low likelihood of myocardial damage during the procedure, cardioplegia is commonly used. The use of cardioplegia as an agent for inducing a hypothermic hyperkalemic arrest was pioneered. In an effort to improve myocardial function during ischemia, many compounds were tested. Cardioplegic temperature, timing, & administration methods were investigated further. Cardioplegia is widely acknowledged as a necessary tool for myocardial protection during on-pump cardiac operation, but its content, temperature, and manner of distribution are still the subject of debate (2).

The potassium content of crystalloid cardioplegia used historically. This cardioplegia is intermittently perfused into the coronary circulation after cardiopulmonary bypass and aortic cross-clamping have been initiated. The transmembrane potential drops caused by an increase in extracellular potassium concentration. The heart eventually stops beating during diastole. Due to the slow washout and rewarming of the myocardium, cold cardioplegia must be repeated at intervals, frequently every 30 minutes (3). In the hospitals affiliated with Suez Canal University, this is the standard procedure for cardiothoracic operations.

The intracellular Level of electrolytes was first postulated by Bretschneider in the 1970s, and it forms the basis for the HTK solution (4).

Tryptophan stabilizes the cell membrane; the addition of mannitol reduces cellular edema; and ketoglutarate is a precursor of nicotinamide adenine dinucleotide. Histidine has a buffering impact and may increase the effectiveness of anaerobic glycolysis (5).

The efficacy of the HTK solution has been proven in a variety of studies, either through the use of biochemical markers or via the use of physiological evaluation in experimental models. In addition to its traditional usage as cardioplegia in cardiac surgery, HTK has been increasingly used as a multi-organ preservation strategy in recent years (6).

Myocardial protection strategies during cardiac surgery continue to be a contentious topic. Inconclusive findings have been found when comparing custodiol HTK cardioplegia with standard crystalloid cardioplegia for myocardial preservation (1).

In comparison to crystalloid cardioplegia, the well-integrated components of custodiol HTK may enhance postoperative cardiac outcomes by aiding in myocardial preservation and functional recovery. When it comes to restoring biochemical and mechanical functions after an ischemia event, protein buffers like histidine may be more effective than bicarbonate. This was demonstrated by Aarsaether et al. in 2009 (7).

Heavily damaged myocardial in a dilated heart during prolonged ischemia may benefit from the buffering action of histidine. The HTK solution is hypokalemic, with a low overall ion concentration, hence a much greater buffer concentration is built in (8).

There is currently no agreement on how best to provide cardioplegia to patients undergoing CABG operation in order to reduce myocardial damage. Due to the technical difficulties associated with re-administering cardioplegia during a more sophisticated cardiac surgery, a single dose of cardioplegia may be preferable (9).

In one study, custodiol HTK solution was shown to be easy to use, safe, and practically applicable. More than two hours of cardiac arrest is thought to be protected against myocardial damage. Considering how frequently these cardioplegic treatments are used in surgeries across the world, this finding comes as something of a surprise. So, we're doing this trial to see how the HTK solution stacks up against the standard crystalloid cardioplegia we've been using for the past decade or so (10).

Aim of the work: To contrast the ejection fraction using trans-esophageal echocardiography, need for cardiac support, and postoperative complications of custodiol cardioplegic solution versus traditional crystalloid solution in cases undergoing on-pump CABG operation using aid of trans-esophageal echocardiography.

Patients and Methods:

This prospective randomized clinical trial was carried out in Suez Canal University Hospital in the routine cardiothoracic surgeries. One case usually was done in single setting.

Cases who had CABG performed at Suez Canal University Hospital were chosen at random to one of two groups using a table of random numbers with a distribution ratio of one-to-one, with departmental research committee approval and informed patient consent. The random sequence was concealed in opaque randomed envelopes that was opened in the day of surgery.

After receiving approval from the Research and Ethics Committees of the Faculty of Medicine, Suez Canal University, and obtaining written informed patient consent explaining the objective, effects, method, and complications, patients were recruited and allocated at random to one of two equal groups on an alternating basis. Group (A): (24 cases) received intermittent ante grade traditional cold crystalloid cardioplegia (ICCC). Group (B): (24 patients) received ante grade histidine–tryptophan–ketoglutarate (HTK).

Inclusion criteria: Patients who need 2 or more coronary artery grafts, more than 21 and less than

60 years of age, of both sexes. ASA III patients (American Society of Anesthesiologists physical status Grade III) = (cases with moderate systemic disease and some functional limitations) and in cases with low ejection fraction less than 40% and patients of Body Mass Index (BMI) more than 20 and less than 34.

Exclusion criteria: Patients requiring only one distal anastomosis, cases with left ventricular (LV) dysfunction with an ejection fraction of fewer than 45% that, cases with recent myocardial infarction (8 to 30 days prior surgery) or patients with concomitant heart valve disease or unstable angina. Patients with cerebrovascular disease (internal carotid artery stenosis >80%), renal insufficiency (creatinine >3 mg/L) and/or cardioversion before surgery.

Based on the calculation that the sample size was equivalent to 24 cases for each group (11-13).

Anesthetic protocol

Before inducing anesthesia, we premedicated all cases with morphine (0.01mg/kg) and midazolam (0.05 mg/kg); intra-arterial monitoring was set up via the right radial artery with a local anesthetic. Muscles were relaxed with rocuronium (0.6 mg/kg), and anesthesia was produced with thiopental (1-3 mg/kg) and fentanyl (1-2 g/kg). Based on hemodynamic data, anesthesia was sustained with fentanyl at a dosage of 3 g/kg/h (10-20 g/kg total), midazolam at a dosage of 1-4 mg/h, rocuronium at a dosage of 0.3-0.4 mg/kg/h provided through continuous infusion, and isoflurane gas at a dosage of 0.5 to up to 0.75 minimum alveolar concentrations.

After the patient was put under, standard central venous catheters were placed. If the case's hemodynamic and gas-exchange state permits, surgery was completed with intravenous anesthetic maintenance, and the case was given over to an ICU for continued mechanical ventilation.

Surgical protocol

Regular procedures for cardiopulmonary bypass were used on the case. Using a single two-stage right atrial and ascending aortic cannula, a disposable membrane oxygenator, and an arterial line filter, we were able to achieve non-pulsatile cardiopulmonary bypass.

After introducing 2 liters of Hartmann's electrolyte solution (Ringer's lactate solution) into the perfusion circuit, the systemic flow rate was kept at 2.4 l/min/m2 while the core temperature was maintained at mild hypothermia (32-28 degrees Celsius). To obtain an active clotting time of >450s, systemic heparin (300 U/kg) was given.

Both cohorts underwent the identical surgical procedure. The median sternotomy was used for every procedure. Grafts were taken from the left internal thoracic artery and veins.

During the time the heart was stopped in a complete aortic cross-clamp, distal anastomoses were performed. Ascending aorta proximal anastomoses were accomplished using partial side-bite clamping while the heart was still beating. According to each patient's specific needs, further analgesia was given. The usage of inotropic assistance was uncommon. Dobutamine (5-10 g/kg/min) or trideal (0.3-0.7 g/kg/min) with or without epinephrine (0.01-0.1 g/kg/min) was given when hemodynamic support was necessary.

Cardioplegia protocol

In both cohorts, antegrade delivery was the only option.

After aortic cross-clamping, an instantaneous injection of 60 to 100 mm Hg of antegrade cardioplegia was made into the aortic root to induce cardiac arrest. Within 30 to 60 seconds, the heart stops beating; any longer than that may suggest a difficulty with the solution's distribution or undiagnosed aortic regurgitation (14).

The entire amount of cardioplegia given, the duration of any interruptions, and any technique failures were all recorded prospectively. The duration of a single ischemia episode was used as a measure of intermittency (longest time off cardioplegia, LTOC). Total ischemia time or cumulative ischemic time expressed as a percentage of cross-clamp time per case (% of time off cardioplegia, PTOC) was another way that intermittency was summed up.

Group A (ICCC): For the induction of cardiac arrest traditional crystalloid cardioplegia solution was used in the after concentration in mEq/L (K = 16, Ca = 1.2, Na = 110, Cl = 160, Hco3 = 10). The pH = 7.8 and osmolality = 290 mosmol/L. Each patient received an initial dose of 20 mL/kg solution (potassium 20 mEq/L at 4°C) via each coronary ostium and maintained with 10 mL/kg (potassium, 6 to 8 mEq/L) every 20 minutes by ante grade perfusion. Extra topical cardiac cooling using ice slush over the arrested heart, repeated after the slush melts, was used to fully preserve the myocardium. Systemic temperatures were kept between 30 and 32 degrees Celsius. (15,16).

Group B (HTK): Cases were given 20 ml/kg of HTK cardioplegic solution following aortic cross-clamping to elicit cardioplegic arrest. Each liter contained 15 mmol/l sodium chloride, 10 mmol/l potassium chloride, 18 mmol/l histidine hydrochloride, 180 mmol/l histidine, 4 mmol/l magnesium chloride, 2 mmol/l tryptophan, 30 mmol/l mannitol, 0.015 mmol/l calcium chloride, and 1mmol/l potassium hydrogen 2-ketoglutarate (osmolality 310 /kg, pH 7.02-7.20).The cardioplegic solution was given in an antegrade method at an initial perfusion pressure of 80-100 mmHg and a temperature of 4-8 c. Myocardial perfusion pressure was held constant from 40 to 60 mmHg throughout quiescence. The inside temperature was reduced to 32 degrees Celsius.

Intraoperative myocardial ischemia

New segmental wall motion abnormalities (SWMAs) on two-dimensional TEE and/or ST segment alterations on ECG were used to make the diagnosis.

Standardized to 10 mm/mV, a 6-leads electrocardiographic system was linked to the cases in the operation room. Before administering any sedatives, the case had a baseline ECG taken from leads I, II, III, aVR, aVL, aVF, and V5.

A 3.5 MHz ultrasonic transducer probe was inserted into the esophagus after the endotracheal tube had been properly placed. To get a cross-sectional image of the LV at the level of the papillary muscles, it will be placed behind the heart.

After the transducer was placed, echocardiographic pictures were taken. ECG were also recorded concurrently. Before making any incisions in the skin, we collected a baseline echocardiogram for each subject.

After the sternum was divided, before cardiopulmonary bypass was started, after 5 minutes of bypass was stopped, after 30 minutes of bypass (if the ribcage continued to be open), and before the sternum was closed, recordings were taken. During skin closure, the final echocardiography and ECG were obtained for all cases.

On the ECG data, the standard parameters for the diagnosis of ischemia were applied, involving the presence of a horizontal or down-sloping ST segment depression of at least 1 mm or an increase over one millimeter in the ST segment (contrast with baseline) 80 msec following the J point.

All echocardiograms were transcribed into a uniform format for research purposes.

If there was substantial wall thickening and the imaginary radius to the center of the LV shrank by over 30%, we judged that section to have undergone typical contraction.

When the radius is shortened by more than 10% but less than 30% & the wall is thickened, mild hypokinesia is diagnosed.

If the wall just slightly thickened and the radial shortening was less than 10%, a diagnosis of severe hypokinesia was made.

Akinetic segments were identified as those in which the wall did not thicken during systole; dyskinetic segments were identified as those in which the wall bulged and otherwise acted during systole.

Visual estimations of endocardial motion and myocardial thickness were used in this qualitative analysis approach.

Using the original echocardiography as a reference, we determined that an area was ischemia if it deteriorated by two or more classes after the first recording.

If the condition improved before the skin healed, it was classified as temporary; otherwise, it was thought to be chronic.

It was determined that an echocardiogram was illegible if the short-axis view could not be obtained, the orientation was altered, or the image resolution was insufficient to detect wall thickening.

Post-operative adverse cardiac events: All-cause death during and after surgery up to 7 days was considered postoperative mortality. Myocardial infarction (confirmed by ECG and/or enzyme) after surgery; heart failure after surgery. Definition of **low output syndrome (LOS):** systolic blood pressure 90 mm Hg for 60 minutes in conjunction with the necessity for inotropic medicine or intra-aortic balloon pump (IABP) counter pulsation. Stroke, AF, or the requirement for renal dialysis (in cases who were not on dialysis before surgery) incidence

Hospital stay in days: The number of days a patient spent in the hospital (including the ICU and inward) was noted.

Statistical Analysis: The data was encoded and input into the statistical computer program. All statistical analyses were performed using version

25 of the Statistical Package for the Social Sciences (SPSS). To describe the quantitative variables, descriptive statistics in numerical form (mean, SD, or percentages) were utilized. When applicable, tabular representations were utilized to characterize qualitative variables. Tables were utilized to display the data. Quantitative data were presented as mean ± SD, while qualitative data were presented as numbers and percentages. The Kolmogorov test was utilized to examine normality. As required, both parametric and nonparametric tests were utilized. The (T) Test was utilized for normally distributed quantitative variables, whereas the Mann-Whitney test was utilized for non-normally distributed quantitative variables. For qualitative variables, the Chi square and Fisher's exact tests were used. A P value of less than 0.05 was substantial.

Results:

Table 1 the mean age of group A was (49.42 ± 5.332 years) statistically significantly lower than group B (53.71 ± 5.916 years) (p= 0.011). The majority of group A 18 (75.0%), and group B 15 (62.5%) were males while 6 (25.0%) of group A and 9 (37.5%) of group B were females, without substantial distinction among both groups (p = 0.350). The mean body mass index of group A was (25.94 ± 3.517 kg/m2), and (27.74 ± 3.711 kg/m2) in group B without substantial variance among both groups (p = 0.092). The mean duration of surgery was (5.04 ± 1.318 hours) in both groups. The mean number of grafts was (2.79 ± 0.509) in group A while it was (3.00 ± 0.659) in group B, without substantial variance among both groups (p= 0.227). The mean bypass time was (75.42 ± 18.113 min) in group A while it was (86.04 ± 22.505 min) in group B, without substantial variance between both groups (p= 0.078).

Table 2 revealed that there was no substantial variance among both groups regarding baseline (p= 0.637), skin incision (p= 0.712), sternal split (p= 0.381), or before CC (p= 0.755). While Group A was statically considerably greater than group B regarding 5 minutes after CC release (p= 0.001), 30 minutes after CC release (p= 0.012), sternal closure (p= 0.028), and skin closure (p= 0.033).

Table 3 revealed that there was no substantial variance among both groups regarding basal (p= 0.873), after induction (p= 0.568), 30 min afterward induction (p= 0.530), 60 min afterward induction (p= 1), or 90 min after induction (p= 0.644). While Group A was statically considerably lower than group B regarding 30 min after weaning (p= 0.007), 60 min afterward weaning (p= 0.010), sternal closure (p= 0.019), and skin closure (p= 0.022). There was no substantial variance among both groups regarding basal (p= 0.712), after induction (p= 0.479), 30 min after induction (p= 0.466), 60 min afterward induction (p= 0.880), or 90 min afterward induction (p= 0.542). While Group A was statically considerably lower than group B regarding 30 min after weaning (p= 0.033), 60 min after weaning (p= 0.036), sternal closure (p= 0.023), and skin closure (p= 0.023).

Figure 1 illustrated that there was no substantial distinction among both groups regarding basal (p= 0.550), afterward induction (p= 0.886), 30 min following induction (p= 0.429), 60 min afterward induction (p= 0.557), or 90 min afterward induction (p= 0.749). While Group A was statically considerably lower than group B regarding 30 min after weaning (p= 0.004), 60 min after weaning (p= 0.012), sternal closure (p= 0.038), and skin closure (p= 0.038).

Table 4 showed that 12 (50.0%) of group A and 6 (25.0%) of group B had inotropic support >24 h without substantial variance among both groups (p = 0.074). 1 (4.2%) of group A and 7 (29.2%) of group B had arrythmia with substantial variance among both groups (p = 0.020). The mean mechanical ventilation in group A (17.38 ± 3.201 h) was considerably greater than in group B (11.88 ± 3.314 h) (p < 0.001). The mean ICU stay in group A (86.00 ± 18.359 h) was considerably greater than in group B (64.25 ± 15.269 h) (p < 0.001). The mean post-operative hospital stay in group A was (9.29 ± 2.053 days), while it was (8.25 ± 1.917 days) in group B without substantial variance among them (p= 0.076). No statistically substantial variance was found among both groups regarding any of the relevant postoperative complications; mortality (p= 0.551), MI (p= 0.312), CHF (p= 0.296), LOS (p= 0.156), stroke (p= 1), or AF (p= 0.296).

Table (1): Demographic characteristics and operative details of the studied groups

		Group A (n= 24)	Group B (n= 24)	95% CI	P
Age (years)		49.42 ± 5.332	53.71 ± 5.916	-7.56, -1.02	**0.011**
Sex	**Male no (%)**	18 (75.0%)	15 (62.5%)	-	0.350
	Female no (%)	6 (25.0%)	9 (37.5%)		
Weight (kg)		76.17 ± 12.349	83.14 ± 13.558	-14.5, 0.56	0.069
Height (m)		1.71 ± 0.080	1.73 ± 0.070	-0.06, 0.03	0.424
Body mass index (kg/m^2)		25.94 ± 3.517	27.74 ± 3.711	-3.90, 0.31	0.092
Duration of surgery (hours)		5.04 ± 1.318	5.04 ± 1.170	-0.7, 0.7	1
Number of grafts		2.79 ± 0.509	3.00 ± 0.659	-0.5, 0.1	0.227
Bypass time (minutes)		75.42 ± 18.113	86.04 ± 22.505	-22.4, 1.2	0.078
Cross clamp time (minutes)		60.00 ± 19.224	71.25 ± 22.996	-23.5, 1.0	0.072
Cardioplegia volume (ml)		318.75 ± 91.856	368.75 ± 124.946	-114, 14	0.121
Intra-operative Defibrillation No. (%)		1 (4.2%)	3 (12.5%)	-	0.296
Intra-operative IABP No. (%)		0 (0.0%)	2 (8.3%)	-	0.149

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.

Table (2): Intraoperative segmental wall motion abnormalities assessment of the studied groups

Segmental wall motion abnormalities		Group A (n= 24)	Group B (n= 24)	P
Baseline No. (%)	**Mild hypokinesia**	3 (12.5%)	2 (8.3%)	0.637
Skin incision No. (%)	**Mild hypokinesia**	5 (20.8%)	4 (16.7%)	0.712
Sternal split No. (%)	**Mild hypokinesia**	7 (29.2%)	4 (16.7%)	0.381
	Severe hypokinesia	0 (0.0%)	1 (4.2%)	
Before CC No. (%)	**Severe hypokinesia**	7 (29.2%)	8 (33.3%)	0.755
5 minutes after CC release No. (%)	**Mild hypokinesia**	7 (29.2%)	8 (33.3%)	**0.001**
	Severe hypokinesia	9 (37.5%)	0 (0.0%)	
	Akinesia	2 (8.3%)	0 (0.0%)	
30 minutes after CC release No. (%)	**Mild hypokinesia**	10 (41.7%)	8 (33.3%)	**0.012**
	Severe hypokinesia	6 (25.0%)	0 (0.0%)	
Sternal closure No. (%)	**Mild hypokinesia**	15 (62.5%)	7 (29.2%)	**0.028**
	Severe hypokinesia	1 (4.2%)	0 (0.0%)	
Skin closure No. (%)	**Mild hypokinesia**	8 (33.3%)	2 (8.3%)	**0.033**

Data is expressed as percentage and frequency. P is significant when < 0.05.

Table (3): Intraoperative ejection fraction and fractional shortening of the studied groups

		Group A (n= 24)	Group B (n= 24)	95% CI	P
Ejection fraction (%)	**Basal**	31.75 ± 4.821	31.54 ± 4.107	-2.39, 2.81	0.873
	After induction	29.08 ± 5.315	28.29 ± 4.144	-1.98, 3.56	0.568
	30 min after induction	32.38 ± 4.753	31.54 ± 4.364	-1.82, 3.48	0.530
	60 min after induction	29.04 ± 5.607	29.04 ± 4.506	-2.96, 2.96	1
	90 min after induction	32.04 ± 4.704	31.42 ± 4.605	-2.08, 3.33	0.644
	30 min after weaning	28.21 ± 6.318	33.13 ± 5.848	-8.45, -1.38	**0.007**
	60 min after weaning	27.88 ± 6.752	32.63 ± 5.436	-8.31, -1.19	**0.010**
	Sternal closure	29.08 ± 7.083	33.54 ± 5.587	-8.16, -0.75	**0.019**
	Skin closure	29.08 ± 7.095	33.50 ± 5.718	-8.16, -0.67	**0.022**
Fractional shortening (%)	**Basal**	17.90 ± 3.059	17.57 ± 3.153	-1.47, 2.14	0.712
	After induction	16.36 ± 3.121	15.74 ± 2.908	-1.13, 2.37	0.479
	30 min after induction	18.26 ± 3.074	17.58 ± 3.326	-1.18, 2.54	0.466
	60 min after induction	16.30 ± 3.111	16.16 ± 3.154	-1.68, 1.96	0.880
	90 min after induction	18.07 ± 3.016	17.50 ± 3.359	-1.29, 2.42	0.542
	30 min after weaning	15.94 ± 3.864	18.47 ± 4.081	-4.83, -0.22	**0.033**
	60 min after weaning	15.74 ± 4.013	18.15 ± 3.746	-4.67, -0.16	**0.036**
	Sternal closure	15.92 ± 4.197	18.68 ± 3.893	-5.11, -0.40	**0.023**
	Skin closure	15.91 ± 4.181	18.66 ± 3.921	-5.11, -0.39	**0.023**

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.

Table (4): Postoperative outcome and relevant complications of the studied groups

	Group A (n= 24)	Group B (n= 24)	95% CI	P
Inotropic support >24 h No. (%)	12 (50.0%)	6 (25.0%)	-	0.074
Arrhythmia No. (%)	1 (4.2%)	7 (29.2%)	-	**0.020**
Mechanical ventilation (h)	17.38 ± 3.201	11.88 ± 3.314	3.61, 7.39	**< 0.001**
ICU stay (h)	86.00 ± 18.359	64.25 ± 15.269	11.94, 31.56	**< 0.001**
Post-operative hospital stay (days)	9.29 ± 2.053	8.25 ± 1.917	-0.11, 2.20	0.076
Mortality No. (%)	2 (8.3%)	1 (4.2%)	0.48	0.551
MI No. (%)	1 (4.2%)	0 (0.0%)	0.5	0.312
CHF No. (%)	3 (12.5%)	1 (4.2%)	0.3	0.296
LOS No. (%)	4 (16.7%)	1 (4.2%)	0.22	0.156
Stroke No. (%)	0 (0.0%)	0 (0.0%)	1	1
AF No. (%)	3 (12.5%)	1 (4.2%)	0.3	0.296

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.

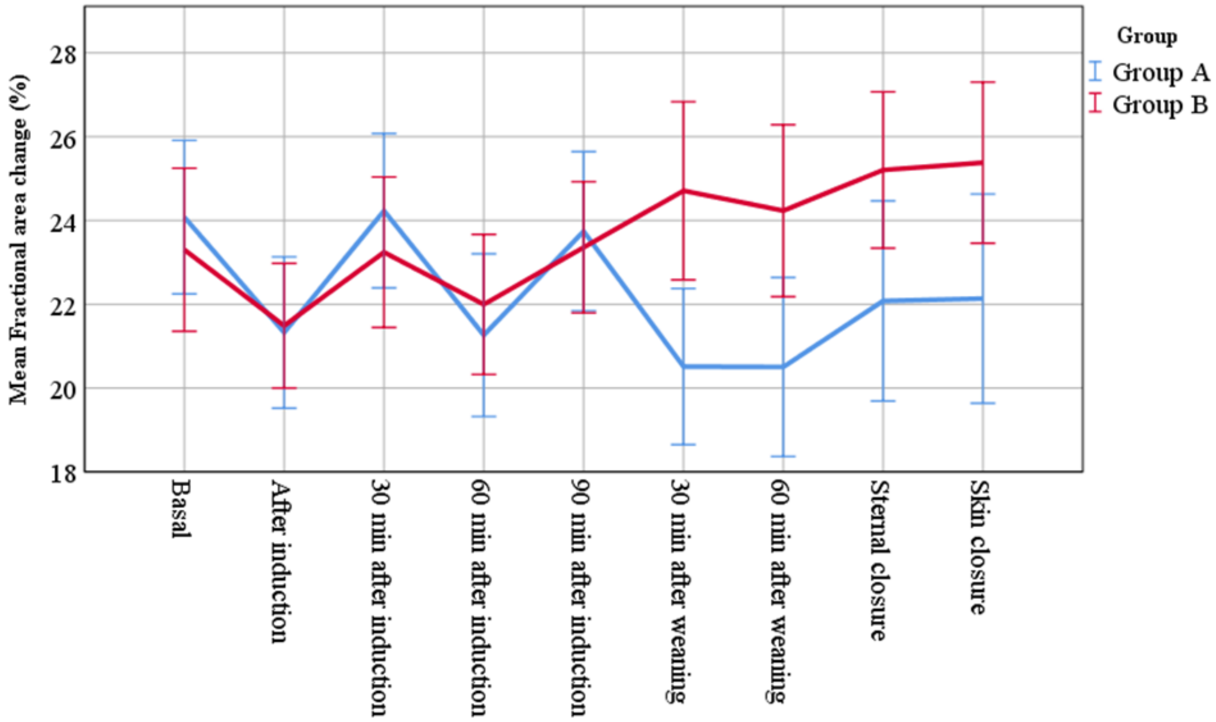

Figure (1) Intraoperative fractional area changes assessment of the studied groups

1311

Discussion:

After heart operation, perioperative myocardial injury is one of the leading causes of morbidity and mortality. The enhancement of myocardial preservation techniques has substantially contributed to substantial improvements in cardiac operations. Nevertheless, concerns persist concerning the use of crystalloid as opposed to HTK custodial cardioplegia, warm as opposed to cold cardioplegia, antegrade as opposed to retrograde delivery, and intermittent as opposed to continuous perfusion (1).

Proper myocardial protection with cardioplegic solutions is an essential step during cardiac surgery, especially with inclusion of elderly patients and more severe conditions (5).

Therefore, this prospective randomized clinical trial research was done to contrast the ejection fraction using Trans-esophageal echocardiography and need for cardiac support of custodiol cardioplegic solution versus traditional crystalloid solution in cases undergoing on-pump CABG operation using aid of trans-esophageal echocardiography.

Our results have revealed that the mean age of ICCC group was statistically considerably lesser than ante grade HTK group, while no statistically substantial variance was found among both groups concerning sex, mean body mass index.

In this study, no substantial variance was found among groups regarding and of their operative details (the duration of surgery, number of grafts, bypass time, or cross clamp time).

In agreement with Saber et al. (17) study, in which no substantial variance was found among blood cardioplegia and custodiol-HTK crystalloid cardioplegia groups regarding number of grafts, or cross clamp time.

However, in disagreement with Risk et al. (18) who reported that both of the mean total bypass time mean total cross clamp time were substantial greater in traditional cardioplegia group than in custodiol group.

Also, Elnahas et al. (19) study showed that the custodiol group had a significantly lower both ischemic and CPB time than the conventional group. These results can be attributed to the frequent interruptions required for the repeated administration of conventional cardioplegia as opposed to the single dose of HTK solution and the requirement for more reperfusion time following removing the cross-clamp. Furthermore, the cumulative cross clamp time (CCT) was prolonged due to a higher incidence of initial weaning failure from CPB. They have found that the mean CCT required for an average three-graft coronary artery bypass grafting or double-valve replacement is beyond 100 min, which was prolonged enough to reveal ischemic complications.

In a study by de Haan et al. (20) on cases undergoing cardiac operation with prolonged CCT, the CCT was considerably longer in the custodiol than in the St Thomas group. Although they did not find substantial variances among the two groups regarding postoperative complications or mortality, they referred this great difference in CCT to surgeon preference and case difference, which give some bias in comparing the types of cardioplegia.

In the current study the intraoperative mean ejection fraction was found to be statistically considerably lower in ICCC group than in HTK group 30, 60 min after weaning, at sternal closure, and skin closure.

In accordance with Risk et al.'s (18) research, their postoperative echocardiograms data, including EF and LV capacity, were better in the HTK group than in the cardioplegia group, demonstrating that a single dose of HTK arrangement provides superior myocardial security in double valve replacement over constant blood cardioplegia dosages.

A limited, randomized study by Gaudino et al. (21) Casts doubt on the sufficiency of Custodiol's preservation of the right ventricular myocardium compared to conventional cardioplegia (intermittent warm blood). Cases with poor pre-operative RV function (as measured by tricuspid annular plane systolic excursion—TAPSE) who were randomized to receive myocardial protection with Custodiol had a lower RV ejection fraction and volumes, and a worse clinical outcome (lower cardiac indices, higher pulmonary pressures, and a longer time on inotropes) than those protected with whole blood cardioplegia. There was no difference in consequence among cases protected by Custodiol or intermittent blood who had normal preoperative RV function.

Our study results have revealed that no substantial variance was found among both groups regarding any of the relevant postoperative complications, mortality, MI, congestive heart failure, LOS, stroke, or AF.

This was in line with Saber et al. (17) study that did not find a substantial variance in post-operative complications and mortality between blood and Custodiol cardioplegia, except for significantly greater frequency of VF in the Custodiol group (26% vs. 8%), the reason for an increased rate of VF after reperfusion with Custodiol-HTK cardioplegia was unclear in their study.

And similar to Edelman et al. (22) systematic review which evaluated the effectiveness of custodiol to that of standard cardioplegia for adult heart operations. For both the custodiolplegic group (n = 925) and the control group (n = 911), the risk of death was identical.

Similarly, Kuslu et al. (23) found that the two groups had comparable outcomes with regard to the length of mechanical ventilation and length of stay in the ICU.

Cardioplegia with Custodiol for stopping hearts, on the other hand, has been shown to result in greater spontaneous recovery without the need of a defibrillator and less need for inotropic medicines than cold blood cardioplegia.

In addition, Risk et al. (24) found that in contrast to the standard cardioplegia group, the custodial group had less complications during surgery and thereafter. These complications included longer ICU stays, less use of intraaortic balloon pumps, fewer cases of sternal damage illness, fewer readmissions to the ICU and the clinic, and a reduced 30-day readmission and death rate. Postoperative complications, such as sternal wound infection leading to mortality, were more common in the blood cardioplegia group. They also discovered that the incidence of AF after surgery was much greater in the custodial group.

HTK cardioplegia was associated with shorter ER stays and lower mortality compared to conventional cardioversion, as demonstrated by Liu et al. (25).

Patients who used custodiol during difficult cardiovascular medical operation had a decreased death rate compared to patients who used blood cardioplegia, as reported by Sansone et al. (26).

In Elnahas et al. (19) study, although statistically nonsignificant, the rate of mortality as a primary outcome was greater in the conventional group than in the custodiol group. The rates of complications were also higher with conventional plegia starting by failure of weaning from CPB, the rate of intraaortic balloon pump use, the need for high inotropic support, prolonged ventilation time, and prolonged ICU and hospital-stay times.

The strength of our research is that it is a prospective randomized clinical trial. However, we acknowledge that there are some potential pitfalls in our study, the absence of long-term follow-up with inability to compare our results of using two different solutions on long term, and high cost of custodiol cardioplegia. Also, the study was conducted at one hospital only.

Conclusion:

It has been shown by biomarkers of myocardial injury that a single dosage of custodiol HTK is more effective at preserving the myocardium during coronary artery bypass surgery than intermittent ante grade cold crystalloid cardioplegia. When it comes to protecting the heart during CABG operation, custodiol is just as safe and effective as the ante grade cold crystalloid cardioplegia. Mortality and morbidity rates after CABG surgery utilizing custodiol cardioplegia were similar to those after employing intermittent ante grade cold crystalloid cardioplegia. Despite having a longer cross-clamp period, the custodiol group experienced significantly less issues after surgery.

Conflict of interest statement

The authors affirm that they do not have any competing interests.

Ethical approval

After getting clearance from the Suez Canal University Hospital's Ethics Committee, the researchers carried out the study in a way that followed the Helsinki Declaration's principles for conducting scientific research with human subjects. All parents or legal guardians gave their agreement in writing before their child participated in the study after receiving a thorough explanation of the potential risks and advantages of the treatments. The Egyptian Society of Cardiothoracic Surgery has previously given its blessing to the use of both forms of cardioplegia in clinical practice; therefore its usage poses no extra risks. Cases were free to decline participation in the research at any time, and their medical care would not be affected. Similarly, patients were free to withdraw from the study at any time without providing an explanation. Confidentiality of data and results of all the study population was preserved.

Author's contribution

All authors are equally contributed.

REFERENCES

1. **Fan Y, Zhang A-M, Xiao Y-B, Weng Y-G, Hetzer R.** Warm versus cold cardioplegia for heart surgery: a meta-analysis. European Journal of Cardio-Thoracic Surgery. 2010;37(4):912-9.
2. **Guru V, Omura J, Alghamdi AA, Weisel R, Fremes SE.** Is blood superior to crystalloid cardioplegia? A meta-analysis of randomized clinical trials. Circulation. 2006;114(1 suppl):I-331-I-8.
3. **Butterworth IV JF, Mackey DC, Wasnick JD.** Morgan & Mikhail's. Clinical Anesthesiology. 2013.
4. **Bretschneider H, Kübler W, Spieckermann P.** Influence of dipyridamol (Persantin) on myocardial adenosine metabolism. Journal of molecular and cellular cardiology. 1970;1(1):23-38.
5. **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. The Journal of thoracic and cardiovascular surgery. 2011;141(4):995-1001.
6. **Murashita T, Yasuda K.** Comparison of the protective prorerties of St. Thomas', Tyers', and Bretschneider's cardioplegic solutions in the neonatal rabbit heart. [Zasshi][Journal] Nihon KyobuGeka Gakkai. 1996;44(11):2019-26.
7. **Aarsæther E, Stenberg TA, Jakobsen Ø, Busund R.**Mechanoenergetic function and troponin T release following cardioplegic arrest induced by St Thomas' and histidine-tryptophan-ketoglutarate cardioplegia–an experimental comparative study in pigs. Interactive cardiovascular and thoracic surgery. 2009;9(4):635-9.
8. **Takeuchi K, Buenaventura P, Cao-Danh H, Glynn P, Simplaceanu E, McGowan FX, et al.** Improved protection of the hypertrophied left ventricle by histidine-containing cardioplegia. Circulation. 1995;92(9):395-9.
9. **Arslan A, Sezgin A, Gultekin B, Ozkan S, Akay T, Uguz E, et al., editors.** Low-dose histidine-tryptophan-ketoglutarate solution for myocardial protection. Transplantation proceedings; 2005: Elsevier.
10. **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. 2012;43(3):526-31.
11. **Campbell MJ, Julious SA, Altman DG.** Estimating sample sizes for binary, ordered categorical, and continuous outcomes in two group comparisons. BMJ. 1995;311(7013):1145-8.
12. **Ramadan M, Abdelgawad A.** Clinical Impact of Custodiol Cardioplegic Solution on Patients Undergoing Complex Cardiac Surgery With Mild to Moderate Impairment of Left Ventricular Systolic Function. European Scientific Journal, ESJ. 2017;13(30).
13. **Lansman SL, Cohen M, Galla JD, Machac J, Quintana CS, Ergin MA, et al.** Coronary bypass with ejection fraction of 0.20 or less using centigrade cardioplegia: long-term follow-up. The Annals of thoracic surgery. 1993;56(3):480-6.
14. **Allen BS, Winkelmann JW, Hanafy H, Hartz RS, Bolling KS, Ham J, et al.** Retrograde cardioplegia does not adequately perfuse the right ventricle. The Journal of thoracic and cardiovascular surgery. 1995;109(6):1116-26.
15. **Ibrahim MF, Venn GE, Young CP, Chambers DJ.** A clinical comparative study between crystalloid and blood-based St Thomas' hospital cardioplegic solution. European journal of cardio-thoracic surgery. 1999;15(1):75-83.
16. **Geissler HJ, Mehlhorn U.** Cold crystalloid cardioplegia. Multimedia Manual of Cardio-Thoracic Surgery. 2006;2006(0109):mmcts. 2004.001040.
17. **Saber WA, El-Ghannam M, Mubarak YS, Mahdy HH, Khorshid RM.**Custodiol-HTK Solution Vs. Conventional Cardioplegia for Myocardial Protection During Coronary Artery Bypass Grafting Following Recent ST-Elevation Myocardial Infarction. Bali Journal of Anesthesiology. 2022 Apr 1;6(2):97.
18. **Risk YE, Abdelgawad BM, Elnahas AM, Melad MM.** Comparative Study between Cardioplegic Solution (Custodiol) versus Conventional Cardioplegic Solutions in CABG Patients. Benha Journal of Applied Sciences. 2021 Feb 1;6(1):263-6.
19. **Elnahas AM, Abdelgawad BM, Ali MM, Khedr AN, Sobhy MG, Omar I.** Benefits of custodiol cardioplegia in the context of cardiac surgery training. The Egyptian Journal of Surgery. 2021 Oct 1;40(4):1338-42.
20. **de Haan M, van Straten A, Overdevest E, de Jong M, Soliman-Hamad M.** Safety of Custodiol cardioplegia: a cohort study in patients undergoing cardiac surgery with elongated aortic cross-clamp time. Perfusion. 2020 Oct;35(7):591-7.
21. **Gaudino M, Pragliola C, Anselmi A, Pieroni M, De Paulis S, Leone A, De Caterina AR, Massetti M.** Randomized trial of HTK versus warm blood cardioplegia for right ventricular protection in mitral surgery. Scandinavian Cardiovascular Journal. 2013 Dec 1;47(6):359-67.
22. **Edelman JJ, Seco M, Dunne B, Matzelle SJ, Murphy M, Joshi P, Yan TD, Wilson MK, Bannon PG, Vallely MP, Passage J.** Custodiol for myocardial protection and preservation: a systematic review. Annals of cardiothoracic surgery. 2013 Nov;2(6):717.
23. **Kuslu S, Zeyneloglu P, Pirat A, Camkiran A, Ozkan M, Arslan G.** Comparison of the effects of histidine-triptophan-ketoglutarate solution and crystalloid cardioplegia on myocardial protection during pediatric cardiac surgery. Critical Care. 2014 Feb;18(1):1-82.
24. **Risk YE, Abdelgawad BM, Elnahas AM, Melad MM.** Comparative Study between Cardioplegic Solution (Custodiol) versus Conventional Cardioplegic Solutions in CABG Patients. Benha Journal of Applied Sciences. 2021 Feb 1;6(1):263-6.
25. **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 Journal. 2008 Sep 1;54(5):470-3.
26. **Sansone F, Punta G, Parisi F, Dato GM, Zingarelli E, Flocco R, Forsennati PG, Bardi GL, del Ponte S, Casabona R.** Right minithoracotomy versus full sternotomy for the aortic valve replacement: preliminary results. Heart, Lung and Circulation. 2012 Mar 1;21(3):169-73.