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Assessment of the Need for Cardiac Support Using Custodiol HTK Cardioplegia versus Traditional Crystalloid Cardioplegia

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ABSTRACT

Introduction: Cardioplegia is responsible to prevent damage to the heart muscle during open heart operation, also to create a sterile, bloodless operating environment. The perfect cardioplegic solution for protection of the myocardium during operations on the heart is still controversial. **Aim:** To compare the intraoperative and postoperative requirement for an intra-aortic balloon pump between custodiol histidine-tryptophan-ketoglutarate (HTK) cardioplegia versus traditional crystalloid cardioplegia.

Methods: A prospective clinical trial investigation, conducted on 48 individuals underwent pump coronary artery bypass graft surgery. done in the routine cardiothoracic surgeries, Suez Canal University Hospital from 2020 to 2023.

Results: The mean lactate one minute and 15 minutes after CC removal was statistically significantly larger in Antegrade traditional cold crystalloid cardioplegia (ICCC) group than in HTK group. The mean CK-MB 15 minutes after reperfusion, 6, 12 and 1 day postoperatively was statistically significantly greater in ICCC group than in HTK group. The mean CTnI 15 minutes after reperfusion, and 6 hours postoperatively was statistically significantly more in ICCC group than in HTK group, group A was statistically significantly advanced in heart rate than group B regarding half an hour after weaning (p= 0.001), one hour after weaning (p= 0.001), sternal closure (p= 0.001) and skin closure (p= 0.002).. **Conclusion:** According to the biomarkers of myocardial injury, a single dose of custodiol HTK is more effective at preserving the myocardium during coronary artery bypass surgery than intermittent ante grade cold crystalloid cardioplegia. This was determined by comparing the two treatments.

Keywords: Lactate, Cardiac Troponin, Creatine Kinase.

INTRODUCTION

One of the most common contributing factors is injury to the myocardium that occurs after operation that lead to mortality and morbidity among individuals who have undergone heart operation. Significant advancements in cardiac surgery have been made possible in large part by the development of myocardial preservation technology. Utilization of warm vs cold cardioplegia, intermittent versus continuous perfusion, antegrade versus retrograde administration, versus crystalloid custodial cardioplegia, Histidine-Tryptophan-Ketoglutarate and their contrasts all remain controversial [(1)].

A key tactic for facilitating cardiac surgery and reducing intraoperative myocardial harm is cardioplegia. Cardioplegia was initially developed as a tool to facilitate hypothermic hyperkalemic arrest. In order to optimise the myocardium during this period of ischemia, several additives were investigated. Further research was done on the ideal cardioplegic temperature, timing, and delivery routes. While cardioplegia is widely acknowledged to be an essential instrument for myocardial protection during open-heart operations performed with the pump, there is still debate concerning a number of its components, temperatures, and methods of administration [(2)].

The solution used in conventional crystalloid cardioplegia is high in potassium. This cardioplegia is used to occasionally perfuse the coronary circulation after the start of cardiopulmonary bypass and aortic cross-clamping. The transmembrane potential is decreased as a result of the rise in extracellular potassium content. The heart eventually stops beating in the diastole. Due to the myocardium's slow washout and rewarming, cold cardioplegia must typically be repeated at intervals of roughly 30 minutes [(3)]. This is the method used in Suez Canal University Hospitals during cardiothoracic surgeries.

In the 1970s, **Bretschneider *er al.*** were the only researchers who initially proposed using histidine-tryptophan-ketoglutarate (HTK), a treatment that was based on the intracellular level of electrolytes [(4)].

The addition of mannitol reduces cellular edema, tryptophan stabilises the cell membrane, and the buffering effect of histidine may contribute to a rise in the effectiveness of anaerobic glycolysis. Nicotinamide adenine dinucleotide is produced from ketoglutarate [(5)].

Numerous investigations using experimental models or biochemical markers have demonstrated the effectiveness of the HTK solution. In various nations, HTK has recently been employed in cardiac surgery as a cardioplegia and multi-organ preservation solution [(6)].

Regarding the best procedures for myocardial protection during heart operation, there is still a lot of debate. Numerous investigations have contrasted standard crystalloid cardioplegia with custodial HTK cardioplegia for the preservation of the myocardium, however the results have been ambiguous [(1)].

Due to its well-integrated components that help the heart's myocardium stay healthy and regain its function, custodiol HTK rather than crystalloid cardioplegia may enhance postoperative cardiac

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outcomes. **Aarsaether *et al.*** in 2009 demonstrated that when it comes to maintaining a stable intracellular pH, protein buffers like histidine may be more effective than bicarbonate. This would make it possible for the recovery of biochemical along with mechanical parameters following ischemia [(7)].

During prolonged ischemia, the myocardium in the dilated heart that has been badly wounded may benefit from the buffering effect of histidine. Additionally, provision is made for a substantially larger buffer concentration due to the HTK solution's hypokalemic character and its low total ion concentration [(8)].

There is currently no agreement on the best way to provide cardioplegia to persons undergoing coronary artery bypass graft (CABG) in order to reduce myocardial damage. As repeated cardioplegia delivery might disrupt the technical flow of the process, a single dose cardioplegia may be a desirable choice in more complicated cardiac surgeries [(9)].

It has been demonstrated that custodiol HTK solution is easy to use, secure and practical when given as a single dosage. Furthermore, it is thought to provide enough myocardial protection for cardiac arrest lasting longer than two hours. Given the large number of surgeries carried out using these cardioplegic solutions globally, this is fairly surprising[(10)].

Aim of the work was to compare the intraoperative and postoperative requirement for an intra-aortic balloon pump between custodiol HTK cardioplegia versus traditional crystalloid cardioplegia.

PATIENTS AND METHODS

Between 2020 and 2023, Suez Canal University Hospital conducted this prospective, randomised clinical study during normal cardiothoracic procedures. Typically, one case was handled at a single location.

People undergoing on-pump CABG at Suez Canal University Hospital were randomly assigned to one of two groups using a random number table with an allocation ratio of one to one. On the day of operation, opaque randomised envelopes with the random sequence were unsealed.

Group (A): (24 patients) received intermittent antegrade traditional cold crystalloid cardioplegia (ICCC).

Group (B): (24 patients) received antegrade histidine–tryptophan–ketoglutarate (HTK).

Inclusion criteria: Patients of both sexes who required two or more coronary artery grafts and were older than 21 but younger than 60, patients with substantial systemic illness and some functional impairments who were classified as ASA III patients (American Society of Anesthesiologists physical status Grade III), as those whose ejection fraction was less than 40% and persons with a Body Mass Index (BMI) of 20 or above but below 34.

Exclusion criteria:

Patients who only needed one distal anastomosis, those with malfunction of the left ventricle, along with an ejection fraction of less than 45%, those who had recently suffered a myocardial infarction (8 to 30 days prior to surgery), or those with concurrent cardiac valve disease or unstable angina and were among the first group of patients and patients undergoing cardioversion before surgery, renal insufficiency (creatinine >3 mg/L), or cerebrovascular illness (internal carotid artery stenosis >80%).

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

Anesthetic protocol:

Midazolam (0.05 mg/kg) and morphine (0.01 mg/kg) were given as pre-medication to all patients, and intra-arterial monitoring through the right radial artery was set up under local anesthetic before general anesthesia was induced. Fentanyl (1-2 g/kg), thiopental (1-3 mg/kg), and rocuronium (0.6 mg/kg) were used to produce anesthesia and relax the muscles, respectively. Depending on the hemodynamic data, anesthesia was continued with fentanyl at a dose of 3 g/kg/h (around 10-20 g/kg total), midazolam (1-4 mg/h), rocuronium (0.3-0.4 mg/kg/h delivered by continuous infusion) and isoflurane gas at 0.5 to as high as 0.75 minimum alveolar concentration.

After induction, a standard central venous catheter was placed. If the patient's hemodynamic and gas exchange condition were adequate after surgery, anesthesia was kept intravenously and also the participants were then sent back to an intensive care unit on mechanical ventilation.

Surgical protocol:

The patient received standard cardiopulmonary bypass treatment. Non-pulsatile cardiopulmonary bypass was accomplished by using a single cannula that connected to both the right atrium and the ascending aorta in two stages, in addition to a disposable membrane oxygenator as well as an arterial line filter.

With a core temperature of mild hypothermia (32–28°C) and a systemic flow rate of 2.4 l/min/m^2, the perfusion circuit was primed with 2 L of Hartmann's electrolyte solution (Ringer's lactate solution). To obtain an active clotting time of >450s, systemic heparin (300 U/kg) was given.

In both groups, the same surgical method was employed. Every procedure was carried out through a median sternotomy. The left internal thoracic artery and venous grafts were utilized as the graft material for this procedure.

During the entire aortic cross-clamp on the stopped heart, distal anastomoses were established. By partially side-biting clamping the ascending aorta while the heart was beating, proximal anastomoses were accomplished. According to each patient's particular needs, further analgesia was given. Support for inotropes was not

frequently employed. 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), were given when hemodynamic support was needed.

Cardioplegia protocol:

In both groups, the delivery route was solely antegrade. Following aortic cross-clamping, antegrade cardioplegia was administered intravenously at a pressure of 60 to 100 mm Hg until cardiac arrest was attained. The heart normally stops beating within 30 to 60 seconds; any delays might be caused by issues with the solution's distribution or an undiagnosed case of aortic regurgitation [(14)].

Prospectively gathered information on cardioplegia, including the total volume provided, the duration of interruptions, and technique failure. The longest single ischemia period, measured in minutes per patient (longest time off cardioplegia, or LTOC), was used to operationalize intermittentness. The cumulative ischemia time as a percentage of the cross-clamp period for each patient (% of time off cardioplegia, PTOC) was another way to sum up intermittentness.

Group A (ICCC):

Traditional crystalloid cardioplegia solution was used to induce cardiac arrest at the following mEq/L concentrations: K = 16, Ca = 1.2, Na = 110, Cl = 160, and Hco3 = 10. The osmolality is 290 mosmol/L and the pH is 7.8. Every patient received a starting dosage of 20 mL/kg solution (potassium 20 mEq/L at 4°C) through each coronary ostium, followed by maintenance doses of 10 mL/kg (potassium 6 to 8 mEq/L) every 20 mins by antegrade perfusion. Using ice slush to cool the halted heart, repeated when the slush melts, completed the myocardial protection. A 30-32 °C systemic cooling was maintained [(15,16)].

Group B (HTK):

To induce cardioplegic arrest, individuals received 20 ml/kg of HTK cardioplegic solution following aortic cross-clamping. Each liter contains 15 mmol/l sodium chloride, 0.015 mmol/l calcium chloride, 18 mmol/l histidine hydrochloride, 10 mmol/l potassium chloride, 180 mmol/l tryptophan, 2 mmol/l magnesium chloride, as well as 1 mmol/l potassium hydrogen 2-ketoglutarate (osmolality 310/kg, pH 7.02–7.20). When the initial perfusion pressure varies amongst 80 and 100 mmHg, the cardioplegic solution was delivered in an antegrade method at a temperature of 4–8°C. During the time that the myocardium was at rest, the perfusion pressure was kept at a range of 40–60 millimeters. The new systemic temperature was 32 degrees Celsius.

Biomarkers of myocardial injury (Myocardial metabolism):

By drawing blood samples from the coronary sinus, myocardial metabolism was evaluated prior to aortic clamping (pre-XCL), 1 minute after the clamp was released (XCL off), and 15 minutes after reperfusion (Rep). Creatine kinase-MB and CTnI were also assessed in peripheral blood at 6-, 12- and 24-hours following surgery, in addition to pH, lactate, and creatine kinase-MB.

Ethical approval:

Following clearance from the Suez Canal University Hospital's Ethics Committee, the study's methods were carried out in conformity with the Declaration of Helsinki's principles for the ethical treatment of subjects in human research. There were no new negative effects because both methods of cardioplegia have previously been authorised by the Egyptian Society of Cardiothoracic Surgery and utilised in clinical practice.

A signed written informed patient consent outlining the purpose, effects, technique, and complications was obtained. Patients were free to leave the study at any time and without explanation, and doing so had no bearing on the level of medical care that was provided to them. All research participants' data and findings were kept confidential.

Statistical Analysis

Data were coded before being input into the statistical computer programme. For all of the statistical studies, the version (25) of the Statistical Package for the Social Sciences (SPSS) was utilized. Quantitative data were presented as mean and standard deviation, while qualitative data were presented as numbers and %. To check for normalcy, the Kolmogorov test was utilised. Quantitative variables regularly distributed were subjected to the (T) test, whereas those with non-normally distribution were subjected to the Mann-Whitney test. Chi square and Fisher's exact tests were used for qualitative variables. Statistical significance was set at a P value of 0.05.

RESULTS

The mean age of group A was statistically significantly lower than group B. There was no statistically significant difference between the two groups in the other measured parameters, e.g., sex, mean body mass index, the mean duration of surgery, the mean number of grafts, and the mean bypass time (table 1).

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
Intraoperative Defibrillation No. (%)		1 (4.2%)	3 (12.5%)	-	0.296
Intraoperative IABP No. (%)		0 (0.0%)	2 (8.3%)	-	0.149

Data are expressed as mean and standard deviation or as frequency and percentage. 95% CI: 95% confidence interval of the mean difference between both groups.

Figure 1 shows that regarding intraoperative heart rate assessment there was no statistically significant alteration amongst both groups regarding basal, after induction, 30 min after induction, 60 min after induction, or 90 min after induction. When compared to Group B, the results for Group A were statistically and substantially better 30 minutes after weaning (p= 0.001), 60 min after weaning (p= 0.001), sternal closure (p= 0.001), and skin closure (p= 0.002).

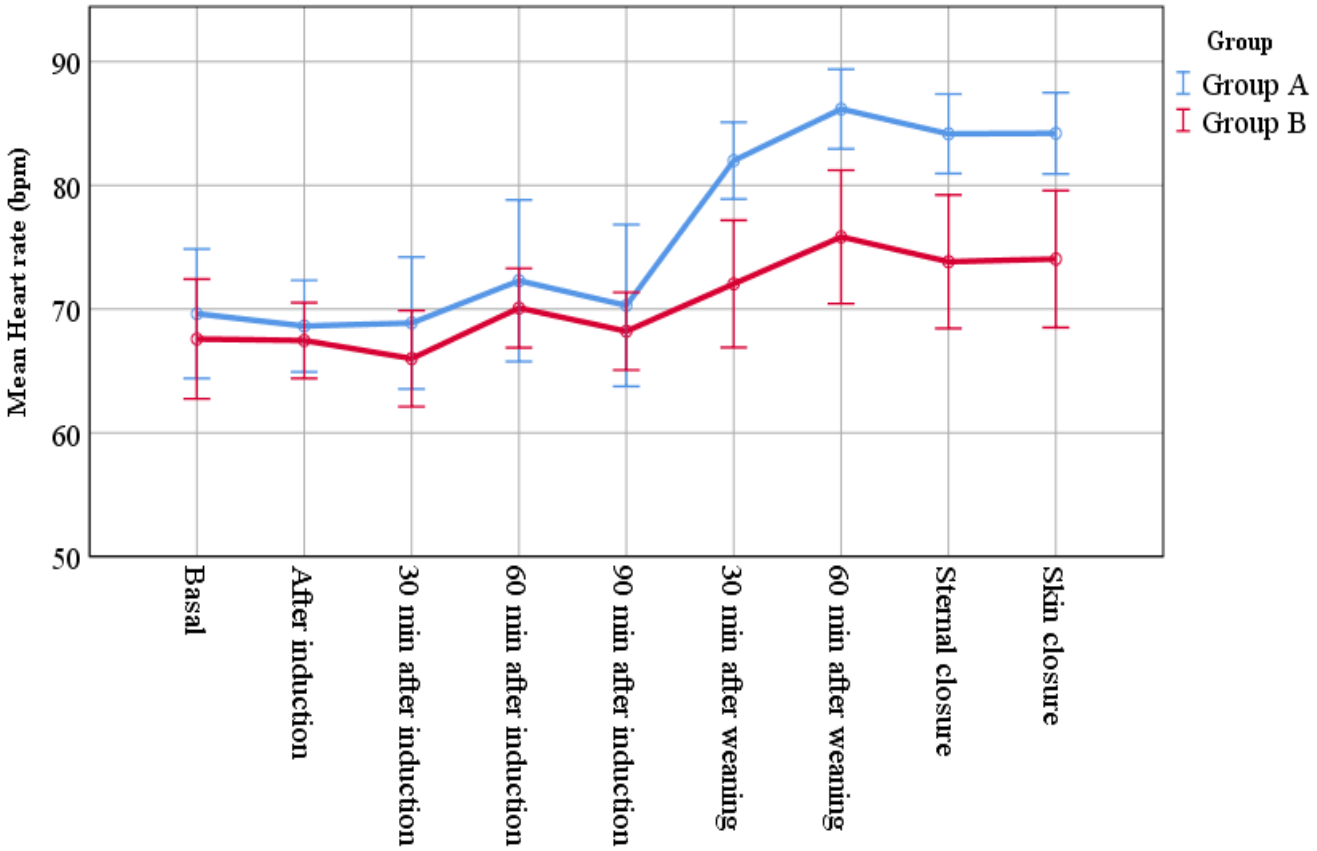

Figure (1) Intraoperative heart rate assessment

Figure 2 shows that regarding intraoperative MAP assessment there was no statistically significant variance among both groups regarding basal, after induction, 30 min after induction, 60 min after induction, or 90 min after induction. While Group A was statistically significantly lower than group B regarding 30 min after weaning (p= 0.001), 60 min after weaning (p= 0.001), sternal closure (p= 0.001), and skin closure (p= 0.003).

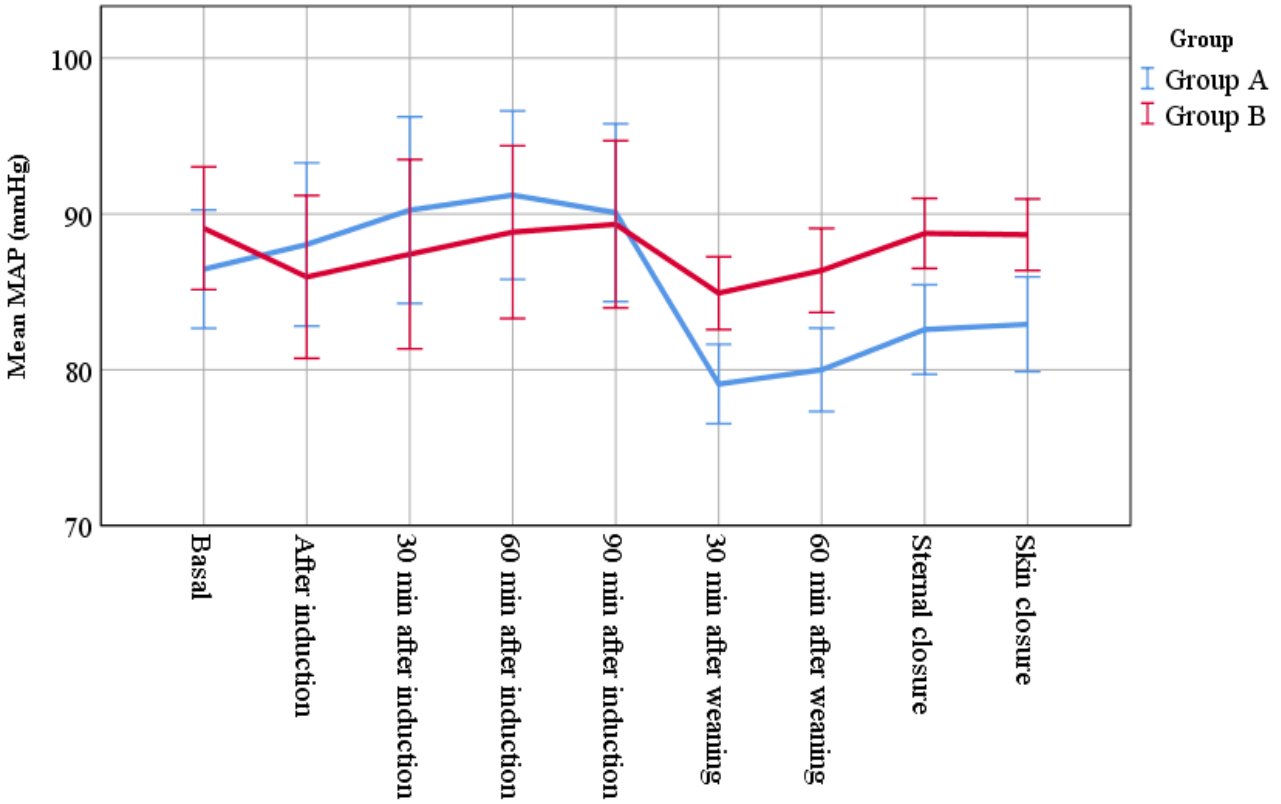

Figure (2) Intraoperative MAP (mmHg) assessment of the studied groups

Table 2 shows that there was no statistically significant alteration among both groups regarding mean baseline lactate. The mean lactate one and 15 minutes after CC removal in group A was statistically significantly increased than in group B. Regarding intraoperative CK-MB assessment there was no statistically significant change amongst both groups regarding baseline, or one minute after CC removal. While Group A was statistically significantly higher than group B regarding 15 minutes after reperfusion. Regarding intraoperative coronary CTnI assessment there was no statistically significant variance amongst either group regarding baseline. At 15 minutes post-reperfusion, Group A statistically outperformed Group B.

Table (2): Intraoperative coronary lactate, CK-MB, and CTnI assessment of the studied groups

		Group A (n= 24)	Group B (n= 24)	95% CI	P
Lactate (mmol/ L)	**Baseline**	1.08 ± 0.445	1.08 ± 0.487	-0.28, 0.26	0.961
	One minute after CC removal	2.83 ± 0.669	2.34 ± 0.668	0.1, 0.87	**0.016**
	15 minutes after Reperfusion	2.25 ± 0.669	1.77 ± 0.180	0.09, 0.87	**0.017**
CK-MB (IU/L)	**Baseline**	13.34 ± 4.894	14.13 ± 2.346	-3.48, 1.90	0.556
	One minute after CC removal	22.92 ± 1.289	19.39 ± 3.030	-1.59, 8.65	0.172
	15 minutes after reperfusion	32.48 ± 6.270	24.55 ± 1.261	-0.03, 15.84	**0.049**
CTnI (ng/L)	**Baseline**	0.02 ± 0.012	0.02 ± 0.014	-0.01, 0.00	0.381
	One minute after CC removal	0.03 ± 0.001	0.03 ± 0.001	-0.01, 0.01	0.573
	15 minutes after reperfusion	0.05 ± 0.001	0.04 ± 0.001	0.0, 0.02	**0.029**

Data are expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups.

Table 3 shows that regarding postoperative CK-MB assessment, it was statistically significantly higher in group A than group B regarding 6, 12, and 24 hours postoperatively. Regarding CTnI, there was no statistically significant alteration amongst either groups after 12 or 24 hours postoperatively. While Group A had statistically significantly more CTnI than group B after 6 hours postoperatively.

Table (3): Postoperative coronary CK-MB, and CTnI assessment of the studied groups

		Group A (n= 24)	Group B (n= 24)	95% CI	P
CK-MB (IU/L)	6 hours postoperative	51.58 ± 8.523	35.12 ± 7.101	2.80, 30.13	**0.019**
	12 hours postoperative	50.45 ± 8.141	34.22 ± 6.830	2.76, 29.70	**0.019**
	24 hours postoperative	48.40 ± 7.720	32.83 ± 5.584	2.51, 28.65	**0.020**
CTnI (ng/L)	6 hours postoperative	0.07 ± 0.003	0.05 ± 0.002	0.01, 0.04	**0.006**
	12 hours postoperative	0.07 ± 0.003	0.05 ± 0.002	-0.01, 0.03	0.089
	24 hours postoperative	0.07 ± 0.002	0.05 ± 0.002	-0.01, 0.03	0.070

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

DISCUSSION

One of the most frequent causes of morbidity and death following cardiac surgery is perioperative myocardial injury. Significant advancements in cardiac surgery have been made possible in large part by the development of myocardial preservation technology. However, concerns still exist over the use of warm vs cold, antegrade versus retrograde, intermittent versus continuous perfusion and HTK versus crystalloid custodial cardioplegia [(1)].

During cardiac surgery, proper myocardial protection using cardioplegic medications is crucial, especially when older patients and more severe diseases are involved [(5)].

In order to compare the ejection fraction using trans-esophageal echocardiography and the need for cardiac support between custodiol cardioplegic solution and traditional crystalloid solution in patients undergoing on-pump coronary artery bypass graft surgery using trans-esophageal echocardiography, this prospective randomised clinical trial study was conducted.

Our findings showed that the mean age of the ICCC group was statistically considerably lower than that of the antegrade HTK group, however when comparing the two groups based on sex or mean body mass index, there was no statistically significant change.

When comparing the two groups, we found no statistically significant variation in terms of surgical time, bypass time, graft count, or cross clamp duration.

This is in agreement with **Saber *et al.*** [(17)] study, in which neither the number of grafts nor the cross-clamp time were significantly different between the blood cardioplegia group and the custodiol-HTK crystalloid cardioplegia group.

However, our study is in disagreement with **Risk *et al.*** [(18)] who reported that the standard cardioplegia group's mean total bypass duration and mean total cross clamp time were both statistically significantly greater than those of the custodiol group.

Also, **Elnahas *et al.*** [(19)] study demonstrated that compared to the conventional group, the custodiol group had a considerably shorter ischemia and CPB time. These results can be explained by the necessity for additional reperfusion time following the removal of the cross-clamp as well as the multiple interruptions required for the recurrent delivery of conventional cardioplegia as opposed to the single dosage of HTK solution. Furthermore, a greater rate of first weaning failure from CPB resulted in a longer cumulative cross clamp time (CCT). They discovered that the usual coronary artery bypass grafting procedure requiring three grafts or a double valve replacement needed a mean CCT of more than 100 minutes, which was lengthy enough to disclose ischemia problems.

In a study by **de Haan *et al.*** [(20)] on patients undergoing cardiac surgery with prolonged CCT, in comparison to the St Thomas group, the CCT was much longer in the custodial group. They attributed this considerable variation in CCT to surgeon choice and case difference, which offer some bias in comparing the forms of cardioplegia, even if they did not detect any differences between the two groups in terms of postoperative complications or death.

In our investigation, the mean lactate was statistically substantially higher in the ICCC group than in the HTK group one minute and 15 minutes after CC removal.

However, in **Saber *et al.*** [(17)] study, at 1 and 6 hours following surgery, custodiol had considerably greater lactate concentrations. After that, lactate was cleared, and after 12 and 24 hours, there was no discernible difference between the two groups.

Because CPB is linked to decreased tissue oxygenation, it is possible that tissue hypoxia contributes to the development of early-onset hyperlactatemia. Early onset hyperlactatemia is a result of microcirculatory dysfunction, which develops as a result of the proinflammatory consequences of prolonged CPB.

Ascione *et al.* [(21)] found that, relative to preoperative values, a time-dependent rise in blood lactate was noticed right after the removal of the aortic cross-clamp and continued to be high at 48 hours later.

In order to assess the degree of myocardial damage brought on by heart surgery, troponin and CKMB are frequently employed. Heart troponin I is a good measure of the effectiveness of myocardial protection since it has been demonstrated to be the most sensitive biochemical marker of intraoperative myocardial damage [(22)].

This was in contrast to **Edelman *et al.*** [(23)], **Abdelmajeed *et al.*** [(24)] and **Mercan *et al.*** [(25)] studies in

which creatine kinase-MB and troponin I mean changes between the traditional and custodiol groups were not statistically significant.

According to the findings of our study, the mean CTnI at 6 hours after surgery was statistically substantially greater in the ICCC group than in the HTK group. This was in line with **Saber *et al.*** [17] study, thus, at 1 and 6 hours following surgery, custodiol leads to considerably decreased troponin levels.

After cardiac surgery, troponin levels are often higher, albeit this depends on the specific type of procedure. Troponin levels are frequently elevated six hours after heart surgery, although these levels are normalised to the 24-hour value [24].

Early troponin release can be linked to common causes, such as the impact of surgery, whereas persistent myocardial ischemia/necrosis that affects outcomes during and after surgery can also be reflected in continuous troponin release [25].

It has been demonstrated that with straightforward cardiac surgery, cardiac troponin I levels increase within the first six hours after surgery and then rapidly decline over the next 24 hours, reaching much lower levels. More extensive myocardial injury is indicated by a delayed release of CTnI. If, within 24 hours after operation, CTnI reached > 8.5 g/L, an adverse result was seen [26, 27].

CONCLUSION

According to the biomarkers of myocardial injury, a single dose of custodiol HTK is more effective at preserving the myocardium during coronary artery bypass surgery than intermittent ante grade cold crystalloid cardioplegia. This was determined by comparing the two treatments.

DECLARATIONS

- **Consent for publication:** I attest that all authors have agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** no conflicts of interest.

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