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Original Article

Clinical Outcomes of the Use of Custodiol versus Warm Blood Cardioplegia during Coronary Artery Bypass Grafting in Patients with Significant Left Main Coronary Artery Disease

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Abstract

Background: Patients who undergo coronary artery bypass graft (CABG) surgery, particularly those with significant left main coronary artery disease (LMCAD), require optimal myocardial protection. The selection between Custodiol and warm blood cardioplegia remains critical in enhancing surgical outcomes and improving postoperative quality of life. This study sought to compare Custodiol and warm blood cardioplegia regarding myocardial protection during CABG surgery.

Methods: This randomized controlled clinical trial was carried out on 100 patients with significant LMCAD. Patients underwent CABG surgery using either Custodiol (Group I, n= 50) or intermittent antegrade warm blood cardioplegia (Group II, n= 50). In Group I, 13 patients were female (26%); in Group II, 15 were female (30%).

Results: Both groups had comparable preoperative demographics. Use of hemofilter [8 (16%) vs. 1 (2%), p= 0.004], DC shock [6 (12%) vs. 1 (2%), p= 0.037] were more common in Group I. Arrhythmia occurred more frequently in Group I intraoperatively [9 (18%) vs. 2 (4%), p= 0.009]. No early mortality was observed in either group. Postoperative data revealed no significant differences between the groups in vital parameters, complications, echocardiographic data, or mortality.

Conclusion: Both Custodiol and warm blood cardioplegia demonstrated comparable efficacy and safety profiles for myocardial preservation during CABG surgery in patients with significant LMCAD. Custodiol could be an effective alternative to blood cardioplegia in patients with LMCAD.

KEYWORDS

Coronary artery bypass grafting; Custodiol; Warm blood cardioplegia; Myocardial protection; Left main coronary

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Introduction

Left main coronary artery disease (LMCAD) has a substantial prognostic risk since it affects a large portion of the myocardial territory. Diagnosing and managing significant LMCAD cases remain sources of clinical concern and uncertainty. In stable individuals who undergo coronary angiography, LMCAD is frequently detected in conjunction with other coronary artery disorders (CADs). The American College of Cardiology/American Heart Association and European Society of Cardiology have published current clinical practice guidelines that suggest revascularization for patients with ≥50% stenosis

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of the left main coronary artery (LM), irrespective of the presence of symptoms or the amount of ischemia associated with it [1].

Revascularization through surgery is usually beneficial for lesions involving the distal LM bifurcation or those connected to complex multivessel disease; however, isolated LMCA lesions pertaining to the ostium or shaft may benefit from coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) [2].

Cardioplegia is crucial in facilitating cardiac surgery while limiting intraoperative myocardial injury during CABG. Initially introduced for hypothermic hyperkalemic arrest, cardioplegia initially served as an agent, followed by the introduction of blood to deliver potassium to the heart. Several methods of delivering cardioplegia have been devised to minimize ischemia-reperfusion harm and maximize myocardial preservation. One of the most important factors for myocardial protection during CABG surgery is the temperature of the cardioplegia [3].

Physiological temperature blood cardioplegia might enhance postoperative outcomes by offering improved myocardial protection through increased oxygen availability. Additionally, blood enhances the carrying capacity of oxygen and is linked to reduced hemodilution [4].

Studies have shown that custodiol (HTK) solution can be safely employed as a cardioplegia solution and administered as a single dose, providing adequate myocardial protection for up to 3 hours. Custodiol is preferred among cardiac surgeons because it ensures uninterrupted open-heart procedures [5].

There is no consensus on the most effective tool for assessing myocardial protection. Real-time evaluation of myocardial protection is not routine. The evaluation of myocardial protection in the postoperative clinical setting is contingent upon indirect indicators, including but not limited to the following: troponin I/T or creatine kinase MB levels; ischemic electrical signs on the electrocardiogram; the frequency of myocardial infarction, stroke, and atrial fibrillation; low cardiac output; the length of stay in the intensive care unit; the need for inotropic support; the use of an intra-aortic balloon pump; the need for extracorporeal membrane oxygenation; and the myocardial function, as confirmed by echocardiography [6,7]. Many factors, such as the following, impact these indirect factors: anesthesia, surgery, critical care, and, in complex cardiopathies, the resulting physiology following surgical intervention or resolution. Isolating the role of each factor is impossible, rendering myocardial protection an idea without precise and measurable clinical markers [8].

Therefore, this study aimed to compare myocardial protection in patients with Custodiol and warm blood cardioplegia during CABG surgery.

Patients and Methods

Design and patients

This randomized controlled clinical trial was performed on 100 patients with significant LMCAD and underwent CABG with cardioplegia using either custodial or intermittent antegrade warm blood cardioplegia. The research was performed over two years, from July 2022 to June 2024.

The World Medical Association Declaration of Helsinki's guidelines were followed when conducting this study. The Ethics Committee approved the research protocol. Each participant in the study provided informed consent.

The inclusion criteria were patients with isolated left main coronary disease displaying stenosis exceeding 50%, individuals with both left main coronary stenosis exceeding 50% and additional coronary artery diseases such as multivessel disease (MVD), and patients exhibiting an ejection fraction (EF) greater than 30%. The exclusion criteria were patients with severe renal or hepatic dysfunction, recent emergency operations, infarctions, or coronary dissections. Patients who had both valve replacement/repair and simultaneous CABG were not included. Patients with residual deficits from a cerebrovascular accident, an ejection fraction less

Table 1: Comparison of demographic and preoperative data between patients who received custodial (Group I) and warm blood cardioplegia (Group II)

Demographic data	**Group I** (n= 50)	**Group II** (n= 50)	**P-value**
Age mean ± SD	57.7±7.4	61.6±5.3	0.538
Sex n (%)			
Female	13 (26%)	15 (30%)	0.641
Male	37 (74%)	35 (70%)	
Risk factors			
DM	33 (66%)	31 (62%)	0.688
HTN	32 (64%)	30 (60%)	0.423
Smoking	31 (62%)	29 (58%)	0.378
Hyperlipidemia	27 (54%)	29 (58%)	0.465
Preoperative ECHO			
FS	27.9±4.5	29.2±3.9	0.704
EF %	54.4±5.1	55.7±7.2	0.825
ESD/mm	32.04±6.1	30.6±5.7	0.736
EDD/mm	45.9±7.8	46.1±9.6	0.668
LA/mm	35.1±7.1	33.6±9.6	0.912
SWMA (N)	39	36	0.326
Angiography			
LM	50 (100%)	50 (100%)	0.603
LAD	42 (84%)	40 (80%)	0.527
LCX	37 (74%)	34 (68%)	0.829
RCA	24 (48%)	30 (60%)	0.116
Laboratory investigations			
Hb (gm/dl)	14.6±2.04	13.9±3.8	0.756
Serum creatinine	0.7±0.57	0.8±0.71	0.842
SGPT	12.2±3.4	15.7±4.2	0.092
HbA1c	7±1.7	6.8±2.2	0.289
CkMb (IU/l)	1.36±.74	1.46±0.51	0.873
Troponin I (ng/ml)	0.08±0.04	0.03±0.06	0.231

Shortening, EF%: Ejection Fraction Percentage, ESD: End-Systolic Dimension, EDD: End-Diastolic Dimension, LA: Left Atrium, SWMA: Segmental Wall Motion Abnormalities, LM: Left Main coronary artery, LAD: Left Anterior Descending artery, LCX: Left Circumflex artery, RCA: Right Coronary Artery, Hb: Hemoglobin, SGPT: Serum Glutamic Pyruvic Transaminase, HbA1c: Hemoglobin A1c, CkMb: Creatine Kinase-MB

than or equal to 30%, or a history of earlier cardiac surgeries were excluded.

Patients were randomly allocated into two groups. In Group A (n=50), patients underwent surgery for CABG using Custodiol myocardial protection. Group B (n= 50) patients underwent CABG using intermittent antegrade warm blood cardioplegia. The mean age of the patients in Group I was 57.7 years (±7.4 SD); 26% were females and 74% were males. Group II had a slightly older mean age of 61.6 years (±5.3 years), with 30% females and 70% males.

Study data and techniques

Preoperative data included a detailed history-taking and a series of investigations. The laboratory analyses included routine tests such as lipid profile, troponin I/T or creatine kinase MB, hepatic and renal function evaluations, HbA1c, and complete blood count (CBC) analysis. Further evaluations include an electrocardiogram (ECG), echocardiography, and a plain chest X-ray aiming for a detailed assessment covering regional wall motion abnormalities, left ventricular (LV) function, fraction shortening, ejection fraction, dimensions of the LV and left atrium, as well as an assessment of valvular function and lesions. Additionally, cardiac catheterization was carried out in patients to evaluate coronary lesions and ascertain the quality of targets for achieving optimal revascularization.

A comprehensive protocol was followed intraoperatively: hemodynamic monitoring involving radial artery catheters for continuous arterial blood pressure monitoring and a central venous catheter, blood gas sampling for aseptic monitoring, and a urinary catheter to track urine output. An incision through the median sternotomy was made under general anesthesia, after which the great saphenous vein and left internal mammary artery was removed. Cardiopulmonary bypass (CPB) was initiated through arterial and venous cannulas, with cardioplegia administered via a double-lumen cannula in the ascending aorta, inducing cardioplegia arrest. Two distinct cardioplegia methods, HTK Custodiol, and warm ante-grade cardioplegia, were employed, each with specific administration protocols that included perfusion pressure, temperature, and solution composition. Graft anastomosis was performed, prioritizing distal venous grafts before connecting the left internal mammary artery to the left anterior descending artery, with subsequent proximal venous graft anastomosis to the ascending aorta. Gradual weaning from CPB was facilitated, and inotropic support and intra-aortic balloon use were provided if necessary. Outcome assessment by the intraoperative need for defibrillators, inotropic support, or intra-aortic balloon pumps.

Postoperatively, patients were admitted to the Surgical Intensive Care Unit (SICU) and were intubated and mechanically ventilated. The length of time on mechanical ventilation, central venous pressure, mean arterial blood pressure, and urine output were monitored, and electrocardiograms and full laboratory investigations focused on cardiac enzymes such as troponin I/T or creatine kinase MB were conducted. The 6-hour postoperative troponin I/T level was assessed, and patients were admitted to the intensive care unit (ICU) and hospital while examining complications such as hemorrhage, neurological symptoms, hepatic or renal problems, arrhythmias, wound infections, and mortality. Furthermore, echocardiography was also employed.

Sample size calculation

According to the subsequent formula, n= Z2P(1-p)/d2. where n= sample size, Z= Z statistic for a level of confidence (for the level of confidence of 95%, Z value is 1.96), P= expected incidence of proportionality of one, and d=precision (0.05) (in a proportion of one; if 5% d= 0.05) [9].

Statistical analysis

SPSS v. 25 was utilized for statistical analysis (IBM Corp- Chicago- IL- USA). Standard deviations and means were utilized to summarize the numerical data. Categorical data are presented as numbers and percentages. The Mann–Whitney U test or independent t test was used for comparisons between normally distributed and nonnormally distributed variables. Fisher's exact test, when applicable, or the chi-squared test, was used to compare categorical variables. Every P value was two-sided. Significant P values were those that were less than 0.05.

Results

In this study, 126 patients were evaluated for eligibility; 19 did not match the inclusion criteria, and seven patients refused to join. The remaining 100 patients were recruited randomly into two groups of equal size (Figure 1).

Preoperative demographic data

There were no significant differences in sex or age between the groups. There were no statistically significant differences in the prevalence of diabetes mellitus, hypertension, smoking, or hyperlipidemia. No significant differences were observed between the two groups in preoperative echocardiographic data (ejection fraction, heart dimensions, pulmonary artery pressures, wall motion abnormalities) or in stenotic lesions across major coronary arteries in diagnostic angiography. Preoperative laboratory results (for hemoglobin, serum creatinine, and

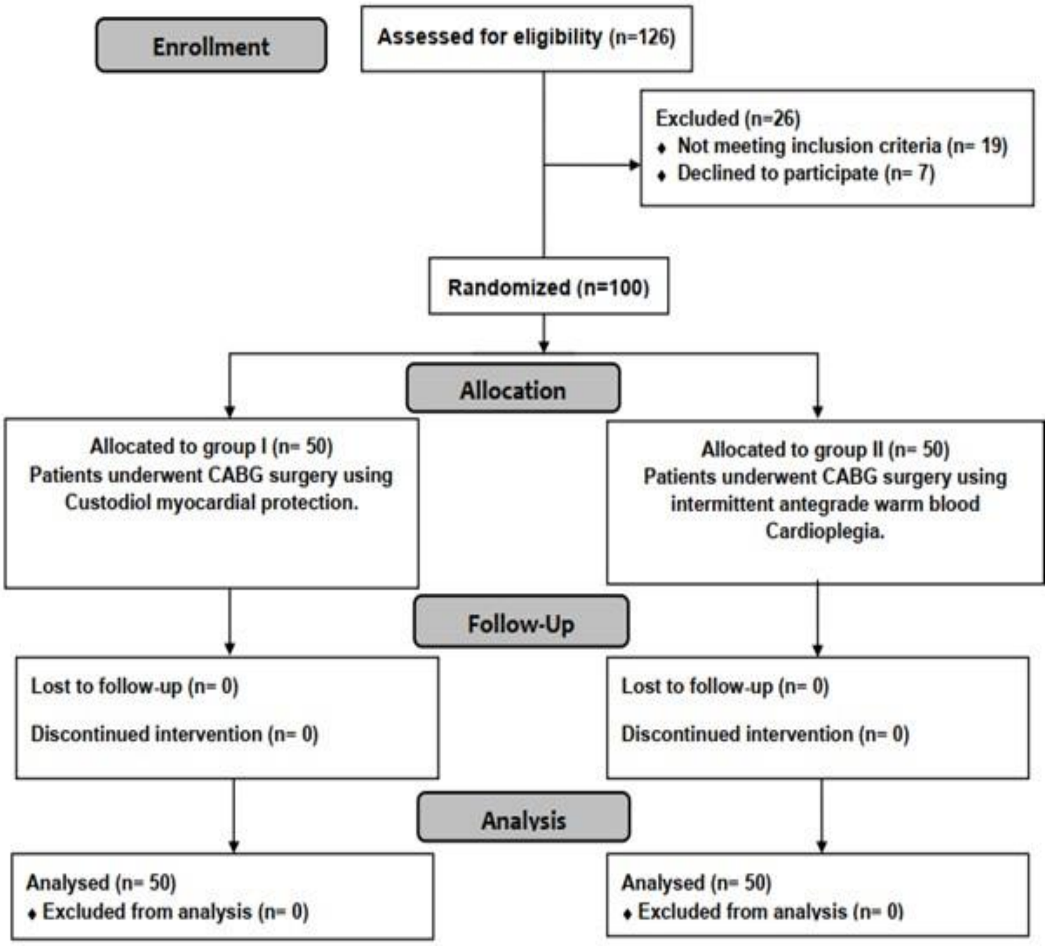

Figure 1: Consort flow diagram of patients who were enrolled

SGPT) also revealed no significant differences between the groups (Table 1).

Intraoperative evaluation

No statistically significant differences were noted in the number of grafts between the two patient groups. Cross-clamp time (ischemic time), total bypass time, difficulty weaning from CPB, and need for inotropic support (infusion of more than 50 ng of adrenaline) did not differ between groups. There was a significant difference regarding the need for hemofiltration after CPB, arrhythmias, and the need for DC shock; these conditions were more common in the custodial group (Table 2).

Table 2: Comparison of operative data between Group I and Group II. Data are presented as median (interquartile range) for quantitative variables and as frequency (percentage) for qualitative variables.

Variable	Group I (n= 50)	Group II (n= 50)	P
Clamp time	58 (45-75)	53 (37-66)	0.106
Total bypass time	106 (80-128)	89 (78-107)	0.069
Grafts	3 (2-4)	3 (1-4)	0.924
Use of hemofiter on CPB	8 (16%)	1 (2%)	0.004
Difficult weaning	10 (20%)	11 (22%)	0.766
Ionotropic support	10 (20%)	11 (22%)	0.766
IABP	4 (8%)	5 (10%)	0.944
Arrhythmias	9 (18%)	2 (4%)	0.009
DC shock	6 (12%)	1 (2%)	0.037
Intraoperative mortality	1 (2%)	2 (4%)	0.204

CPB: cardiopulmonary bypass, IABP: intra-aortic balloon pump, DC shock: direct current shock

Table 3: Comparison of postoperative data between patients who received custodial (Group I) and warm blood cardioplegia (Group II)

Laboratory investigations	Group I (n= 50)	Group II (n= 50)	P-value
Hb (gm/dl)	10.4±1.2	9.9±2.6	0.566
Serum creatinine	1.1±1.3	0.8±1.7	0.606
SGPT	16.5±3.4	21.1±4.3	0.389
CkMb (IU/l)	16.8±5.5	15.8±4.9	0.908
Troponin I (ng/ml)	2.1±0.95	2.3±0.84	0.168
ICU evaluation			
Ventilation time	5.5±2.8	6.1±3.8	0.706
ICU stay/days Median (range)	2.1(0-2.9)	2.6(0-3.2)	0.09
Postoperative Echocardiography			
FS	29.3±5.1	28.7±4.3	0.647
EF%	58.2±8.1	56.1±9.4	0.923
ESD/mm	31.09±7	32.8±6.9	0.782
EDD/mm	45.8±6.5	47.9±7.4	0.786
Postoperative Hospital stay	7.5±2.5	8.1±3.8	0.157

Hb: hemoglobin, SGPT: serum glutamic pyruvic transaminase, CkMb: creatine kinase-MB, ICU: intensive care unit, EF%: ejection fraction percentage, FS: fractional shortening, ESD: end-systolic dimension, EDD: end-diastolic dimension.

Postoperative outcomes

Postoperative evaluation in the intensive care unit showed no statistically significant differences between the two patient groups in terms of postoperative hemoglobin, serum creatinine, SGPT, CkMb, or troponin I levels six hours after surgery. Moreover, there were no statistically significant differences in postoperative ventilation time, ICU stay, or hospital stay among the groups under study. Additionally, postoperative echocardiography revealed no significant differences in ejection fraction, fractional shortening, heart dimensions, or estimated systolic pulmonary artery pressures (Table 3).

Postoperative complications such as wound infection, hemorrhage, and blood transfusion were not significantly different between the studied patient groups (Table 4).

Discussion

The debate over the ideal cardioplegia solution in cardiac surgery persists. Past comparisons favoring blood-based solutions excluded Custodiol, contributing to the ongoing discourse [7]. The mortality rates for high-risk patients with advanced coronary artery disease and significant LV dysfunction range drastically between 2.7% and 33%, prompting individualized approaches in cardioplegia selection [10,11]. Surgeons aim to optimize outcomes and reduce complications by tailoring their choice of cardioplegia [12].

With its unique composition of inducing diastolic cardiac arrest, Custodiol offers a comprehensive strategy for myocardial preservation, while warm blood cardioplegia, which has evolved over several decades, provides optimal myocardial protection [13,14].

Table 4: Comparison of postoperative complications between patients who received custodial (Group I) and warm blood cardioplegia (Group II)

	Group I (n= 50)	Group II (n= 50)	P
Hemorrhage/ml	621.3±151.9	763.7±317.1	0.268
Blood transfusion (units)	2 (4%)	4 (8%)	0.104
Wound infection	4 (8%)	5 (10%)	0.727
Postoperative mortality	0	0	0

Comparative studies, such as a meta-analysis of 14 trials, suggested increased ventricular arrhythmias with Custodiol, but these findings were not statistically significant [15].

This study sought to compare Custodiol and warm blood cardioplegia in terms of myocardial protection during CABG surgery. One hundred patients with significant left main coronary artery disease participated in this randomized, controlled clinical trial. Patients underwent CABG surgery using either Custodiol or intermittent antegrade warm blood cardioplegia.

In terms of the preoperative demographic and clinical data of the studied groups, there were no statistically significant differences between the groups. Several studies, including those performed by Ali et al. [5], Nardi et al. [16], and Refaie et al. [17], have consistently reported no significant disparities in preoperative demographic, clinical, echocardiographic, or laboratory data between groups of patients undergoing cardiac surgeries with varying cardioplegia solutions. Regardless of the specific solution used—warm blood cardioplegia, Custodiol cardioplegia, or cold crystalloid cardioplegia—age, sex distribution, prevalence of comorbidities such as diabetes mellitus, hypertension, smoking, and hyperlipidemia, as well as echocardiographic parameters and laboratory results—did not significantly differ across the cohorts studied. Similarly, Ali et al. reported statistically significant differences in the preoperative laboratory parameters, except for the serum creatinine concentration, which was significantly greater in the warm blood group than in the custodiol group (1.05 ± 0.32 vs. 0.86 ± 0.22, respectively) [5].

Regarding the intraoperative evaluation, the two patient groups did not significantly differ concerning the number of grafts, cross-clamp time (ischemic time), total bypass time, difficulty weaning from CPB, or the need for inotropic support (infusion of more than 50 nanograms of adrenaline). However, the Custodiol group had higher incidences of hemofilter use for CPB, arrhythmias, and DC shocks than did the warm blood cardioplegia group. In support of our findings, Ali et al. reported no statistically significant differences in bypass time (P=0.465), cross-clamp time (P=0.65), number of grafts (P=0.27), the incidence of intraoperative death (P=1.00), or utilization of the IABP (P=0.37) between the Custodiol and Warm blood groups [5]. In their study, Nardi et al. reported that the warm blood cardioplegia group exhibited a longer cardiopulmonary bypass time (95.5±33.3 vs. 80.3±28.3 minutes; p=0.017) and received more cardioplegia doses (2.5±1.0 vs. 1.8±0.7; p<0.0001) than did the cold crystalloid cardioplegia group. Cross-clamp times showed a trend, but not significantly, between the groups (73.2±27.0 vs. 65.4±20.2 minutes; p=0.123). Post-CPB, the warm blood cardioplegia group had higher hemoglobin levels than did the cold crystalloid cardioplegia group (9.0±1.1 vs. 8.5±1.1 g/dL; P=0.047) [16].

In the present study, postoperative evaluations in the ICU revealed no statistically significant differences between patient groups regarding hemoglobin, serum creatinine, SGPT, CkMb, or troponin I levels at six hours post-surgery showed no significant changes. Similarly, the studied groups did not significantly differ in ventilation time, ICU stay, hospital stay, echocardiography findings, and postoperative complications such as wound infection, hemorrhage, and blood transfusion. In a meta-analysis by Kot et al., no significant disparities in postoperative outcomes, including mortality rates, cardiac issues, and other complications, were found between warm and cold cardioplegia patients [18].

Ali et al. noted comparable use of inotropic support during intensive care unit care but reported a significant increase in postoperative arrhythmia in the Custodiol group. However, there were no significant differences in various cardiac parameters or postoperative complications between the groups, except for this notable arrhythmia disparity and slightly different mortality rates [5]. Nardi et al. observed enzymatic differences between cold crystalloid cardioplegia and warm blood cardioplegia groups; however, postoperative complications remained similar between the two groups, except for a greater incidence of primary respiratory pulmonary failure in the cold crystalloid cardioplegia group [16].

In a study comparing Custodiol versus blood cardioplegia, Refaie et al. found no significant differences in defined endpoints, including complications such as prolonged ventilation, reintubation, intra-aortic balloon pump insertion, atrial fibrillation, pacemaker necessity, myocardial infarction, stroke, renal failure, 30-day mortality, or hospital readmission [17].

In a prospective randomized study involving 345 patients who underwent aortic valve replacement, Ovrum and colleagues found no difference in the outcomes of retrograde cold blood cardioplegia or retrograde cold crystalloid cardioplegia with regard to bleeding, blood transfusion requirements, stroke, perioperative myocardial infarction, kidney function, infections, or death [19].

Hoyer and colleagues conducted a propensity score-matched analysis of almost 7,000 patients after aortic valve replacement. The study revealed no significant differences with regard to operative mortality, postoperative complications, or long-term survival between cold crystalloid cardioplegia Custodiol and cold blood cardioplegia patients [20]. However, another study performed by Boros compared Custodiol cardioplegia versus 4:1 blood cardioplegia in 229 adult patients who underwent cardiac surgeries. The outcomes showed no significant variation in 30-day mortality or hospital stay. There was a significantly greater need for fresh frozen plasma in patients with custodial cardioplegia during the perioperative phase [21].

In a study performed by Prathanee and colleagues, custodial cardioplegia was compared to those with blood cardioplegia in 125 CABG patients. They concluded that Custodiol cardioplegia preserved the myocardium in patients undergoing CABG as safely as tepid blood cardioplegia. Additionally, they observed that the custodial group had a greater rate of ventricular fibrillation during the reperfusion phase [22].

Interestingly, some studies suggest utilizing Custodiol cardioplegia in adult patients. The myocardial protection offered by Custodiol is more likely to be the same as that offered by warm blood cardioplegia. Moreover, single-dose administration provides great advantages, especially in long and complex cardiac procedures [17]. According to two meta-analyses conducted by Guru, Jacob, and colleagues, cold blood cardioplegia was connected to a lower frequency of low cardiac output syndrome and CK-MB release; however, the frequency of myocardial infarction and death remain similar [7,23]. Two additional meta-analyses by Fan, Abah, and associates revealed no difference in short-term mortality between warm and cold cardioplegia [8,24].

In a study involving 200 patients who underwent CABG, Jacquet, and colleagues reported that antegrade warm cardioplegia provided superior myocardial protection to combined antegrade and retrograde cold crystalloid cardioplegia on the release of cardiac enzymes. However, the duration of ischemic arrest was significantly shorter in the warm group [25].

Ovrum et al. did not find any differences in clinical outcome among 1,440 patients who underwent coronary artery bypass surgery in their large prospective randomized study. The mean cross-clamp time, however, was only 34 minutes, which might be insufficient to demonstrate a possible variation [26].

Warm blood cardioplegia was related to greater long-term survival and fewer late myocardial infarctions than cold blood cardioplegia was, according to an intriguing observational study by Mallidi et al. [27]. Abah et al. and Zeng et al. performed two recently published meta-analyses on 2,866 patients and 5,897 patients who underwent heart surgery. The findings of the first meta-analysis showed that warm and cold cardioplegia produced similar short-term mortality and clinical results, while the second meta-analysis showed that cold blood cardioplegia decreased the frequency of perioperative myocardial infarction compared to cold crystalloid cardioplegia [24,28]. Kaul et al. observed a notable decrease in the release of the AST enzyme during cold blood cardioplegia as opposed to cold crystalloid or ischemic cardiac arrest in 123 patients who underwent combined valve (aortic or mitral) and coronary artery bypass surgery [29]. Ascione et al. observed a significant decrease in the release of cardiac troponin I at 1, 24, and 48 hours after surgery when cold blood cardioplegia was utilized as opposed to warm blood cardioplegia [30].

The multicenter design of our study is a significant strength, as it provides diverse perspectives and potentially enhances the generalizability of our findings. However, the study's limited sample size represents a notable constraint, potentially restricting the broader applicability of our conclusions. Therefore, additional randomized clinical trials with larger sample sizes should be considered in future studies.

Conclusion

Both Custodiol and warm blood cardioplegia demonstrated comparable efficacy and safety profiles in myocardial preservation during CABG surgery for patients with significant LMCAD. No significant differences were found in the various parameters between the two cardioplegia techniques. Custodiol could be an effective alternative to blood cardioplegia in patients with LMCAD.

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