Original Article

Warm Blood Cardioplegia Versus Histidine, Tryptophan, and Ketoglutarate Solution in Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease: A Meta-Analysis

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ABSTRACT

Background: Postoperative outcomes for those undergoing cardiac surgery with extracorporeal circulation are significantly influenced by myocardial protection. Administration of cardioplegic solution is the primary method for protecting the myocardium. Furthermore, myocardial hypothermia and cardiac arrest that follows significantly lower the myocardium's oxygen consumption by 95%. Consequently, a suitable and efficient cardioplegia technique must be achieved.

Patients and Methods: This review compiled data from randomized controlled trials and retrospective and prospective observational studies to assess and compare the therapeutic effects of Custodiol solution and warm blood cardioplegia in coronary artery bypass grafting (CABG) for left main coronary artery disease (CAD). The studies included in this meta-analysis all reported on populations that underwent coronary angioplasty (CABG) for patients who have left main CAD.

Results: The overall summary estimates from the common effect model (risk ratio=0.85, 95% CI: 0.74–0.98) suggest a significant reduction in postoperative inotropic support with Custodiol, while the random effects model (risk ratio=0.94, 95% CI: 0.70–1.26) shows no significant variation. High heterogeneity (I2=74%, *P*0.01) indicates substantial variability among the study results.

Conclusion: In comparing Custodiol solution with warm blood cardioplegia for left primary CAD cases undergoing CABG, our meta-analysis showed mixed results regarding creatine kinase and Tn-I levels, with Custodiol showing a significant reduction in creatine kinase levels at 4–7h postsurgery. While Custodiol indicated a potential benefit in reducing postoperative inotropic support, the variability in outcomes and lack of consistency across studies suggest caution in interpreting its superiority over warm blood cardioplegia. Further randomized controlled trials are warranted to validate these findings and address the limitations of heterogeneity and publication bias observed in the included studies.

Key Words: Acute kidney injury, Atrial fibrillation, Extracorporeal circulation, Low cardiac output syndrome, Ventricular fibrillation.

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INTRODUCTION

Postoperative outcomes for people undergoing cardiac surgery with extracorporeal circulation are significantly influenced by myocardial protection. The main way to preserve the myocardium is by giving a cardioplegic solution. Furthermore, myocardial hypothermia and cardiac arrest that follows significantly lower the myocardium's oxygen consumption by 95%. Consequently, a suitable and efficient cardioplegia technique must be achieved[1].

Myocardial protection during prolonged periods of ischemia and subsequent reperfusion is a matter of concern in cardiac surgery. Myocardial energy stores are preserved, osmotic and electrolyte imbalances are prevented, and acidosis is neutralized by cardioplegic solutions, which improve tolerance to ischemia and reperfusion[2].

Nowadays, multiple types of blood cardioplegia can be administered using various methods. Cardioplegia can be classified into several types, such as blood versus crystalloid, intermittent versus continuous, cold versus warm, antegrade versus retrograde versus combination, as well as a terminal warm shot[3].

The rationale behind warm blood cardioplegia is that it more closely resembles normal physiology, which means it can deliver oxygen to the myocardium or ensure less hemodilution compared with a crystalloid solution. This, in turn, means it could improve postoperative cardiac outcomes, making it a safe and reliable technique for myocardial protection[4].

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Both low sodium concentrations and high potassium concentrations are the foundations of crystalloid cardioplegia (CCP). An increase in extracellular potassium concentrations causes a depolarization of the myocardium's resting membrane potential, which in turn causes the fast sodium channels to become inactive and the heart to arrest during diastole[5].

Intracellular cardioplegic solutions include Custodiol. Custodiol interferes with the action potential of cardiac cells because its low sodium concentrations provide a weak diffusion gradient across their membranes. Due to its low calcium concentration, Custodiol causes cardiac arrest during the diastolic period by breaking the excitation–contraction relationship[6]. Transplantation of organs such as the heart, kidneys, livers, and pancreases required the use of Custodiol for perfusion and flushing. The low salt concentration and buffering capabilities of histidine, tryptophan, and ketoglutarate (HTK) make Custodiol an attractive option for long-term myocardial protection[7].

Aim:

The objective of the current meta-analysis is to compare the outcomes of Custodiol solution versus warm blood cardioplegia in coronary artery bypass grafting (CABG) for left main coronary artery disease (CAD) cases.

PATIENTS AND METHODS

Evaluation criteria for research included in this review

Type of study

To assess the clinical outcomes of Custodiol solution and tepid blood cardioplegia in CABG for left main CAD, the review analyzed observational studies that were either retrospective or prospective.

Types of participants

This review considered all studies reporting populations doing CABG for left main CAD patients.

Types of intervention

Interventions with Custodiol solution in addition to warm blood cardioplegia in CABG were focused on individuals with left main CAD.

Types of outcome measures

The primary outcomes of interest are laboratory and clinical assessments of myocardial damage, either directly or indirectly, exemplified by the measurement of creatine kinase-myocardial band (CK-MB) levels on the first postoperative day during a designated morning blood sample collection. Examples of secondary endpoints involve AKI, length of hospital or ICU stay, 30-day mortality, risk factors for myocardial protection (myocardial infarction, cardiac enzyme release, low cardiac output syndrome/use of inotropes), in addition to rhythm disturbances (VF as the initial rhythm post cross-clamp release, along with new postoperative AF).

Search strategy for the identification of studies

The search strategy was developed to encompass both electronic and manual data that was accessible. Up to 2024, electronic searches were conducted in PubMed, EMbase, CINAHL, as well as the Cochrane. The search was performed using Medical Subject Headings (MeSH) terms such as:

[warm OR normothermia OR normothermic] AND [cardioplegia OR "myocardial protection"] AND [("histidine-tryptophan-ketoglutarate" or "Bretschneider," or "Custodiol" OR "coronary artery bypass graft" OR "coronary artery bypass grafting" OR CABG OR "vein graft" OR "bypass graft" OR "surgical revascularization"]) AND ("randomized controlled trial" OR "clinical trial" OR "controlled clinical trials, randomized" OR "clinical trials, randomized" OR "trials, randomized clinical").

Data synthesis also included obtaining full-text versions of articles from publicly available medical journals and other published studies that met inclusion criteria according to title, abstract, and subject descriptors; this was done through a combination of a search, discussions with multiple investigators who were experts in the field, and published case reports.

Only studies written in English were considered for this review.

Reviews and studies using animals were not considered. Excluded from consideration were studies that did not include the intended outcome measures or that included patients treated with other methods, such as emergency or salvage procedures or percutaneous coronary intervention. Not all data points were considered. Excluded from the analysis were studies that used therapies other than warm blood cardioplegia and Custodiol solution.

Methods of the review

Locating and selecting studies

Articles that seemed to meet the inclusion criteria were retrieved in full after reviewing their abstracts using the above search approach. The study must provide data on a minimum of one outcome measure.

Data extraction

A cross-check was conducted between two assessors after the data was independently extracted.

Statistical consideration

Out of the data produced by each included randomized controlled trial, odds ratios (for categorical outcomes) or standardized mean differences (MD) (for data on continuous outcomes) with their respective 95% confidence intervals (CI) were computed whenever feasible. With the Cochrane Collaboration's Review Manager Software, we combined the findings of similar studies into a statistical meta-analysis when the data allowed it. We used the

conventional χ^2 test to look for heterogeneity in the pooled data. We used a random effect analysis based on the method given by DerSimonian and Laird (1986) when there was a lot of variation in the effect measure across the studies. The variation between studies is taken into consideration by the random effect analysis. We were given the results of the random effect analysis even though there was no significant heterogeneity, as the homogeneity test had low power.

Release 14.0 of the STATA statistical software (Stata Crop. 2015, College Station, Texas, USA) was used for all statistical analyses in the pooling of the studies.

Statistical analysis

The Open Meta [analyst] software was used to conduct the statistical analysis for the meta-analysis. Considering the fact that the genuine impact sizes of the studies varied, a grouped random effects model was used to compute the pooled mean outcome and generate forest plots showing the individual study means of the two modalities. To extend the findings beyond the papers that were part of the analysis, a random effects model was selected. It was also used to evaluate heterogeneity.

RESULTS

Study selection

Out of the 18 findings that were found in the original search, six were removed, leaving 12 for the final quantitative synthesis. Randomized controlled trials, prospective randomized studies, and retrospective analyses are all part of the study designs that were involved in these studies. General characteristics of the involved studies were as given below.

The included studies provide a comprehensive perspective, incorporating various study designs such as randomized controlled trials, retrospective cohorts, case series, and multicenter studies. Randomized controlled trials like those by Ali and colleagues and Gaudino and colleagues offer high-level evidence due to their rigorous design. Retrospective cohort studies, such as those by Cvetkovic and colleagues and Arslan and colleagues, provide valuable observational insights. Case series are well represented by studies such as those by *Mercan et al*. [8] and Kammerer and colleagues, offering detailed clinical insights. Multicenter studies like Demmy and colleagues enhance the generalizability of findings across different populations. Prospective randomized studies and randomized trials, such as those by Braathen and colleagues and Vivacqua and colleagues, further enrich the dataset.

Regarding medical history data of patients, the highest percentage of smokers is observed in the study by Beyersdorf and colleagues, with 58.3% in the Custodiol group and 66.7% in the Warm Blood Cardioplegia group. Ali and colleagues report the highest diabetes prevalence in the Custodiol group at 45%, while Mercan and colleagues show even higher rates in both groups. Cvetkovic and colleagues indicate the highest hypertension prevalence, with 74.1% in the Custodiol group and 88% in the Warm Blood Cardioplegia group. For hyperlipidemia, Vivacqua and colleagues record the highest incidence, with 70.9% in the Custodiol group and 81.5% in the Warm Blood Cardioplegia group (Tables 1–3).

Table (4) summarizes the NYHA classification of patients in the involved studies, indicating their functional status. In Ali and colleagues, the Custodiol group has a distribution of 5% in NYHA class 1, 35% in class 2, 50% in class 3, and 10% in class 4, whereas the Warm Blood Cardioplegia group shows 5% in class 1, 50% in class 2, 35% in class 3, and 10% in class 4. Gaudino and colleagues report 48.4% of the Custodiol group in class 3 and 29% in class 4, with the Warm Blood Cardioplegia group showing higher percentages in class 3(62.1%) and slightly lower in class 4(24.1%). Beyersdorf and colleagues find all patients in the Custodiol group in class 3, while the Warm Blood Cardioplegia group has 33.3% in class 2, 58.3% in class 3, and 8.3% in class 4.

Comparison between Custodiol and warm blood cardioplegia with regard to cardiac enzymes

Creatine kinase levels

A comparison of CK levels between Custodiol and warm blood cardioplegia across different time subgroups (47h, 24h, and 48h) shows mixed results. At 4–7h postsurgery, there is a significant reduction in CK levels with Custodiol across all studies, supported by both common and random effects models, despite high heterogeneity. At 24h, the results are inconsistent, with no significant overall difference and high heterogeneity. At 48h, no significant differences are observed, with moderate heterogeneity. The overall analysis indicates a substantial reduction in CK levels with Custodiol according to the common effect model, but the random effects model shows no significant variance, highlighting substantial variability among the study results.

Creatine kinase-myocardial band levels

A comparison of CK-MB levels between Custodiol and warm blood cardioplegia across different time subgroups (4–8h, 20–24h, and 44–48h) shows varying results. In the 4–8h subgroup, Beyersdorf and colleagues and Braathen and colleagues reported significant reductions in CK-MB levels with Custodiol, while Cvetkovic and colleagues found no significant difference. The overall common and random effects models indicate a significant reduction with Custodiol, despite high heterogeneity (I2=69%). In the 20–24h subgroup, none of the studies reported significant differences, and the common and random effects models confirm this with no significant overall difference and low heterogeneity (I2=0%). In the 44–48h subgroup, Beyersdorf and colleagues reported a

significant reduction, while Braathen and colleagues and Cvetkovic and colleagues found no significant differences. The overall common and random effects models indicate a significant reduction with Custodiol, with moderate heterogeneity (I2=74%). The overall analysis suggests a significant reduction in CK-MB levels with Custodiol according to the common effect model (MD=−2.98, 95% CI: −4.24 to −1.72), but the random effects model shows no significant distinction (MD=−1.79, 95% CI: −5.11 to 1.54), highlighting substantial variability among the study results.

Troponin-I levels

A comparison of troponin-I (Tn-I) levels between Custodiol and warm blood cardioplegia across different time subgroups (4 –7h, 24h, and 48h) shows no significant differences overall. In the 4–7h subgroup, Arslan and colleagues reported a significant increase in Tn-I levels with Custodiol (MD=2.50, 95% CI: 0.29–4.71), while Cvetkovic and colleagues and Demmy and colleagues found no significant differences. The overall common and random effects models for this subgroup show no significant differences, with high heterogeneity (I2=71%). In the 24h subgroup, none of the studies reported significant differences, and the overall common and random effects models confirm no significant differences with no heterogeneity (I2=0%). Similarly, in the 48h subgroup, no significant differences were reported by any study, and the overall common and random effects models show no significant differences with no heterogeneity (I2=0%). The overall analysis from both the common effect model (MD=−0.13, 95% CI: −0.58 to 0.32) and the random effects model (MD=−0.13, 95% CI: −0.58 to 0.32) indicates no statistically significant difference in Tn-I levels between Custodiol and warm blood cardioplegia, with low heterogeneity (I2=7.8%, *P*= 0.36).

Comparison between Custodiol and warm blood cardioplegia as regards outcome

Cardiopulmonary bypass time

A comparison between Custodiol and warm blood cardioplegia across seven studies shows no statistically significant differences in cardiopulmonary bypass time. Individual studies by Arslan and colleagues, Beyersdorf and colleagues, Careaga and colleagues, Gaudino and colleagues, Mercan and colleagues, and Vivacqua and colleagues all reported MDs with CIs crossing zero, indicating no significant difference. Cvetkovi and colleagues reported a slightly positive MD, suggesting a possible increase in cardiopulmonary bypass time with Custodiol, but this finding was not statistically significant. Overall summary estimates from both the common effect model (MD=0.90, 95% CI: −3.65 to 5.46) and the random effects model (MD=0.64, 95% CI: −4.50 to 5.78) further support the lack of significant variance between the two cardioplegia methods. The low heterogeneity (I2= 0%, *P*= 0.62) indicates consistency in the results across the included studies.

Aortic cross-clamping time

A comparison of aortic cross-clamping time between Custodiol and warm blood cardioplegia across seven studies shows varied results. Arslan and colleagues, Careaga and colleagues, Gaudino and colleagues, and Vivacqua and colleagues reported MDs with CIs crossing zero, indicating no statistically significant differences. Braathen and colleagues, Cvetkovic and colleagues, and Gallandat Huet and colleagues observed significant positive MDs, suggesting increased aortic cross-clamping time with Custodiol. The overall summary estimates indicate a substantial difference in favor of Custodiol with the common effect model showing a MD of 28.13 (95% CI: 26.96–29.30) and the random effects model showing an MD of 6.54 (95% CI: −4.81 to 17.90). However, the latter's CI crosses zero, indicating nonsignificance. High heterogeneity (I2=99%, *P*< 0.01) suggests significant variability among the study results.

Cardiac arrest beginning time<

A comparison of cardiac arrest beginning time between Custodiol and warm blood cardioplegia, based on two studies, shows mixed results. Arslan and colleagues reported a significant positive MD of 9.70 (95% CI: 0.53 to 18.87), indicating longer cardiac arrest beginning time with Custodiol. In contrast, Cvetkovic and colleagues found a nonsignificant negative MD of −0.40 (95% CI: −10.47 to 9.67), suggesting no meaningful difference. The overall summary estimates from the common effect model (MD= 5.12, 95% CI: −1.66 to 11.90) and the random effects model (MD= 4.87, 95% CI: −5.01 to 14.76) both indicate no significant variation in cardiac arrest beginning time between the two methods. Moderate heterogeneity (I2=53%, *P*= 0.15) suggests some variability between the study results, though it is not substantial.

Number of grafts

A comparison of the number of grafts between Custodiol and warm blood cardioplegia across four studies shows minimal differences. Arslan and colleagues reported a slight but significant negative MD of −0.50 (95% CI: −0.98 to −0.02), suggesting fewer grafts with Custodiol. Beyersdorf and colleagues observed no difference (MD=0.00, 95% CI: −0.74 to 0.74), while Cvetkovic and colleagues reported a small positive MD of 0.20 (95% CI: −0.13–0.53), and Mercan and colleagues found a slight negative MD of −0.10 (95% CI: −0.49–0.29), both indicating nonsignificant differences. The overall summary estimates from the common effect model (MD=−0.04, 95% CI: −0.25 to 0.17) and the random effects model (MD=−0.08, 95% CI: −0.40 to 0.24) both suggest no significant distinction in the number of grafts between the two cardioplegia methods. Moderate heterogeneity (I2=47%, *P*= 0.13) indicates some variability among the study results, but it is not substantial.

Postoperative inotropic requirement

A comparison of postoperative inotropic need between Custodiol and warm blood cardioplegia across seven studies shows mixed results. Ali and colleagues reported a significantly lower risk ratio (RR) of 0.62 (95% CI: 0.49 to 0.77) favoring Custodiol, while Beyersdorf and colleagues observed a wide CI (RR=0.20, 95% CI: 0.03 to 1.47), indicating high uncertainty. Braathen and colleagues, Cvetkovic and colleagues, Demmy and colleagues, Gaudino and colleagues, and Vivacqua and colleagues reported nonsignificant RRs, with CIs crossing one, indicating no clear difference. The overall summary estimates from the common effect model (RR=0.85, 95% CI: 0.74 to 0.98) suggest a significant reduction in postoperative inotropic support with Custodiol, while the random effects model (RR=0.94, 95% CI: 0.70 to 1.26) shows no significant difference. High heterogeneity (I2=74%, $P< 0.01$) indicates substantial variability among the study results.

Ejection fraction change

A comparison of ejection fraction (EF) change between Custodiol and warm blood cardioplegia across two studies indicates no significant difference. Ali and colleagues reported a MD of −0.21 (95% CI: −1.03 to 0.61), suggesting a slight, nonsignificant reduction in EF change with Custodiol. Cvetkovic and colleagues observed a MD of 0.36 (95% CI: −1.46 to 2.18), indicating a nonsignificant increase. There is no statistically significant distinction in the change of EF among the two cardioplegia procedures, depending on the overall summary estimates from both the common effect model (MD=−0.11, 95% CI: −0.86 to 0.64) and the random effects model (MD=−0.11, 95% CI: −0.86 to 0.64). There is little variation in the results across the research because of the small sample size (I2=0%, $P= 0.58$).

ECG changes

A comparison of ECG changes between Custodiol and warm blood cardioplegia across three studies shows no significant differences. Ali and colleagues reported a RR of 0.67 (95% CI: 0.37 to 1.21), indicating a nonsignificant reduction in ECG changes with Custodiol. Beyersdorf and colleagues observed an RR of 0.40 (95% CI: 0.10 to 1.67), also suggesting no significant variance. Demmy and colleagues reported an RR of 0.97 (95% CI: 0.70 to 1.35), indicating no difference. The overall summary estimate from the common effect model (RR=0.81, 95% CI: 0.61–1.09) shows no significant distinction in ECG changes among the two cardioplegia methods. The heterogeneity is low (I2=14%, P=0.31), suggesting consistent findings across the studies.

Postsurgical atrial fibrillation

A comparison of postsurgical atrial fibrillation between Custodiol and warm blood cardioplegia across five studies shows no significant differences. Beyersdorf and colleagues reported a RR of 0.50 (95% CI: 0.05 to 4.81), indicating high uncertainty. Braathen and colleagues observed an RR of 0.67 (95% CI: 0.31 to 1.44), suggesting no significant difference. Careaga and colleagues reported an RR of 0.20 (95% CI: 0.03 to 1.51), indicating a potential reduction but with high uncertainty. Demmy and colleagues and Vivacqua and colleagues found RRs of 1.15 (95% CI: 0.78 to 1.70) and 0.67 (95% CI: 0.38 to 1.17), respectively, showing no significant difference. The overall summary estimate from the common effect model (RR=0.82, 95% CI: 0.61 to 1.10) shows no significant distinction in postsurgical atrial fibrillation between the two cardioplegia methods. The heterogeneity is low to moderate (I2=27%, $P= 0.24$), indicating some variability among the study results but not substantial.

Hospital stay duration

A comparison of hospital stay duration between Custodiol and warm blood cardioplegia across two studies indicates a slight reduction in hospital stay with Custodiol. Ali and colleagues reported an MD of −0.51 (95% CI: −0.71 to −0.31), showing a statistically significant reduction in hospital stay. Cvetkovic and colleagues reported a nonsignificant MD of −0.30 (95% CI: −1.92 to 1.32), indicating no clear variance. The overall summary estimates from both the common effect model (MD=−0.51, 95% CI: −0.71 to −0.31) and the random effects model (MD=−0.51, 95% CI: −0.71 to −0.31) consistently show a significant reduction in hospital stay with Custodiol. The heterogeneity is low (I2=0%, $P= 0.80$), indicating consistent findings across the studies.

ICU stay duration

A comparison of ICU stay duration between Custodiol and warm blood cardioplegia across five studies shows varied results. Ali and colleagues reported an MD of −0.09 (95% CI: −0.15 to −0.03), indicating a statistically significant reduction in ICU stay with Custodiol. Cvetkovic and colleagues observed a nonsignificant MD of −0.60 (95% CI: −1.88 to 0.68), and Gaudino and colleagues reported an MD of 1.00 (95% CI: −0.05 to 2.05), suggesting a possible increase but with high uncertainty. Mercan and colleagues found a nonsignificant MD of −0.15 (95% CI: −0.58 to 0.28), and Vivacqua and colleagues reported no disparity (MD=0.00, 95% CI: −0.82 to 0.82). The overall summary estimates from the common effect model (MD=−0.09, 95% CI: −0.15 to −0.03) indicate a significant reduction in ICU stay with Custodiol, whereas the random effects model (MD=−0.07, 95% CI: −0.27 to 0.13) shows no significant variance. Low heterogeneity (I2=18%, $P= 0.30$) suggests consistency among the study results Figures (1–6).

Fig. 1: Flow diagram of the literature search and study selection processes.

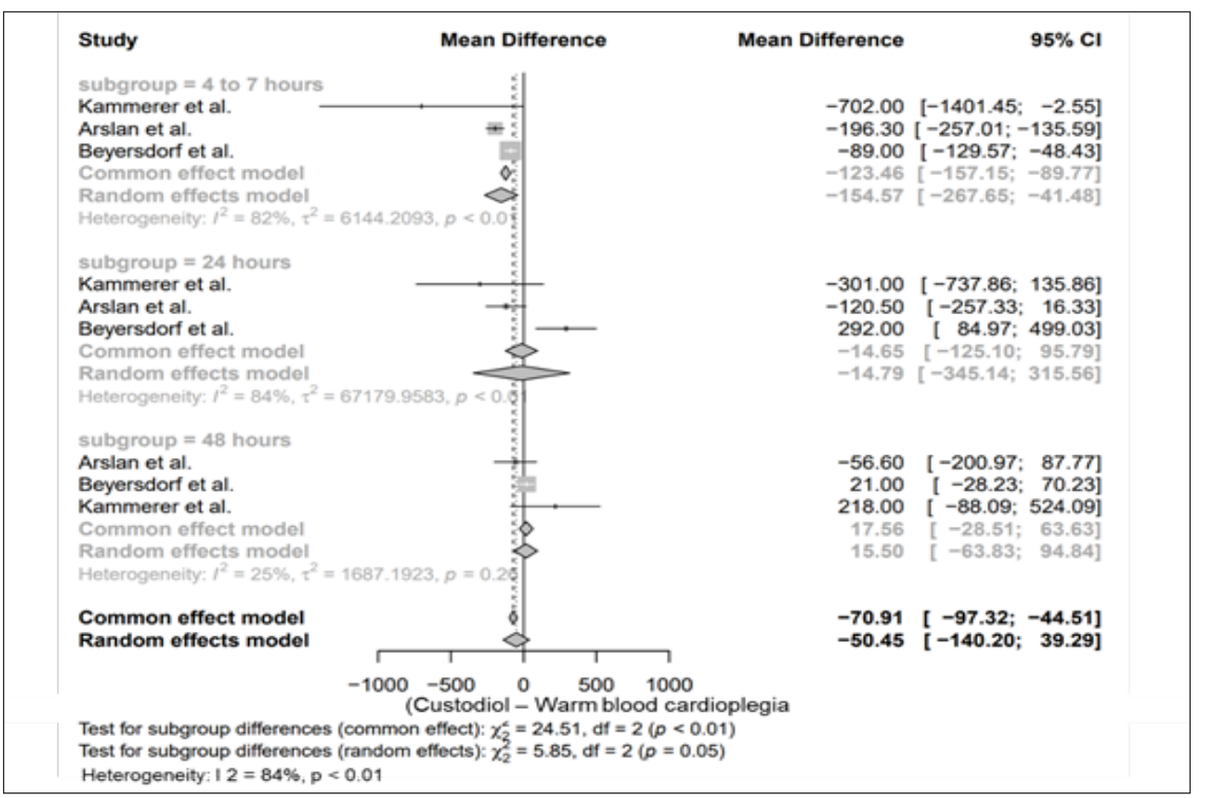

Figure 2: Forest plot of the comparison: Custodiol versus warm blood cardioplegia, CK level. CK-MB, creatine kinase-myocardial band.

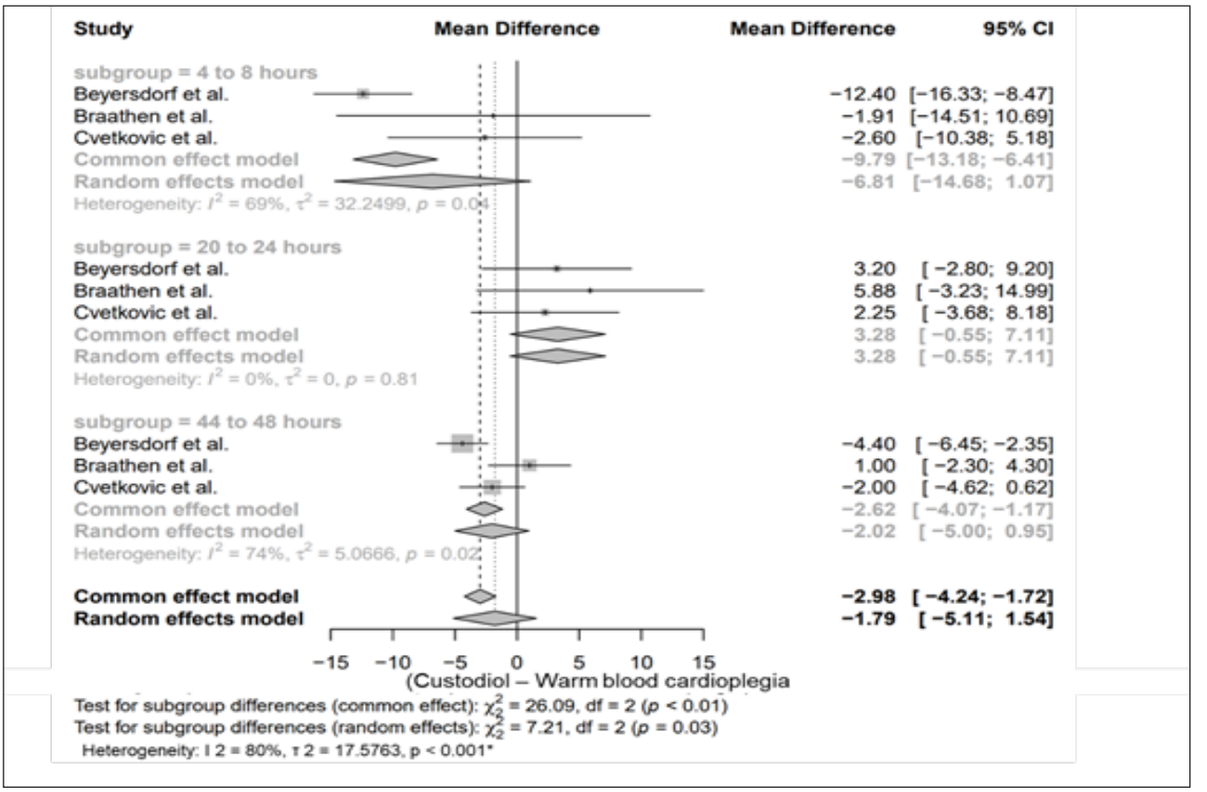

Figure 3: Forest plot of the comparison: Custodiol versus warm blood cardioplegia, CK-MB level. CK, creatine kinase.

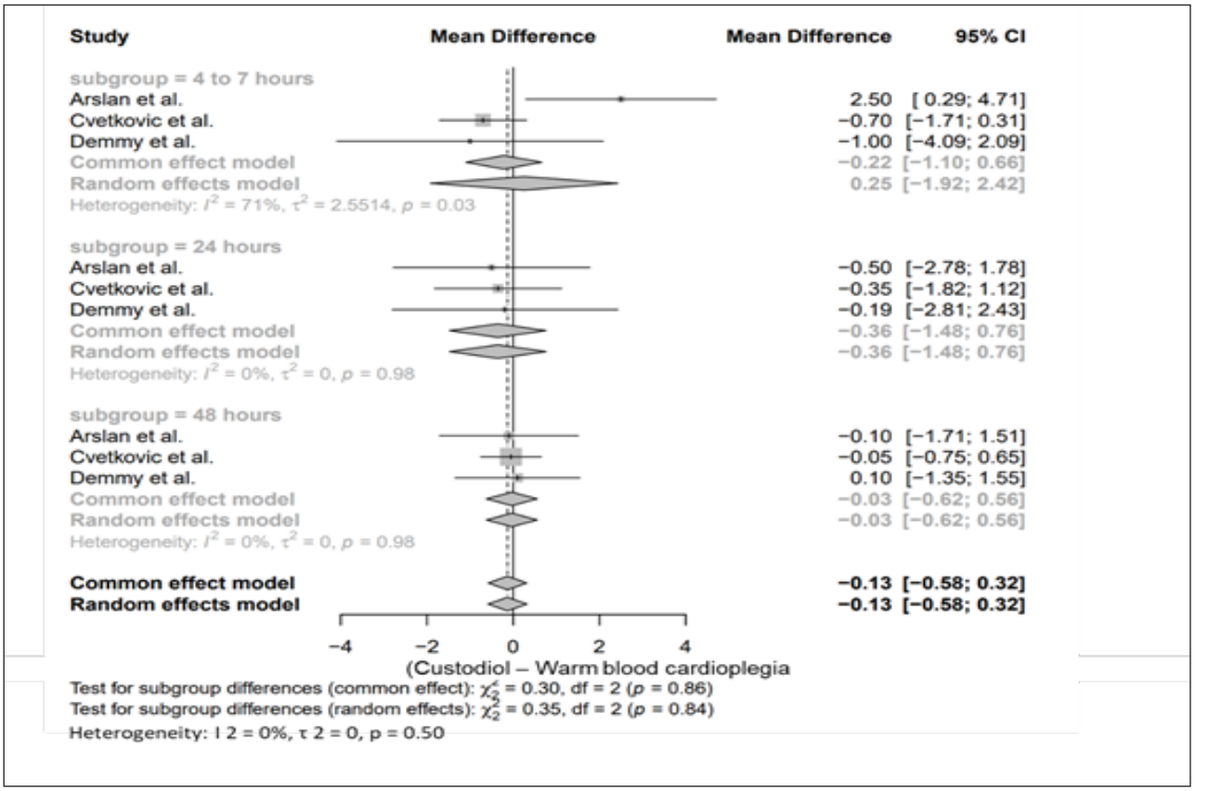

Figure 4: Forest plot of the comparison: Custodiol versus warm blood cardioplegia, Tn-I level.

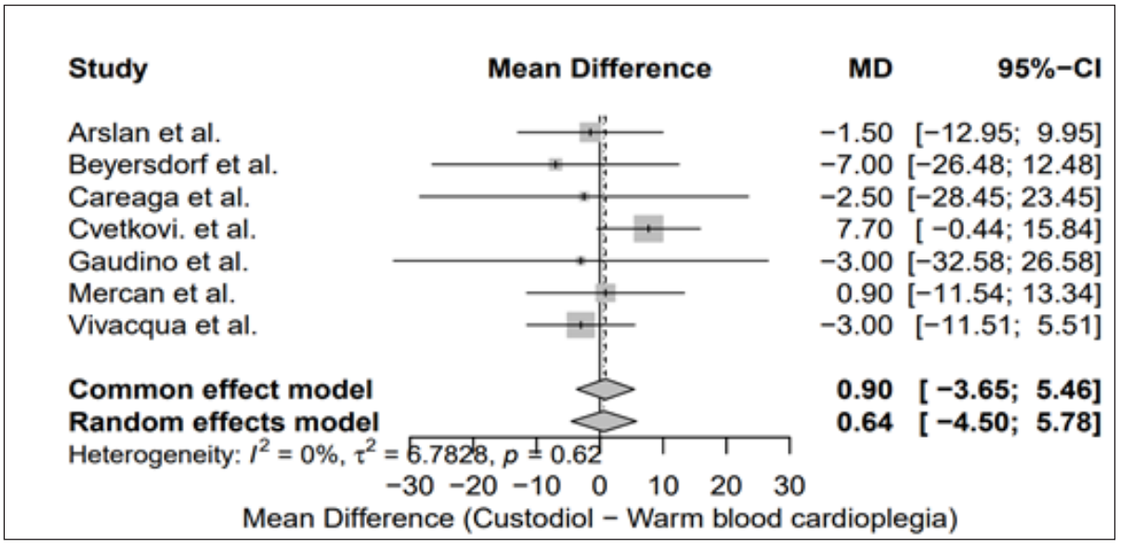

Fig. 5: Forest plot of the comparison: Custodiol versus warm blood cardioplegia, CPB time. CPB, cardiopulmonary bypass.

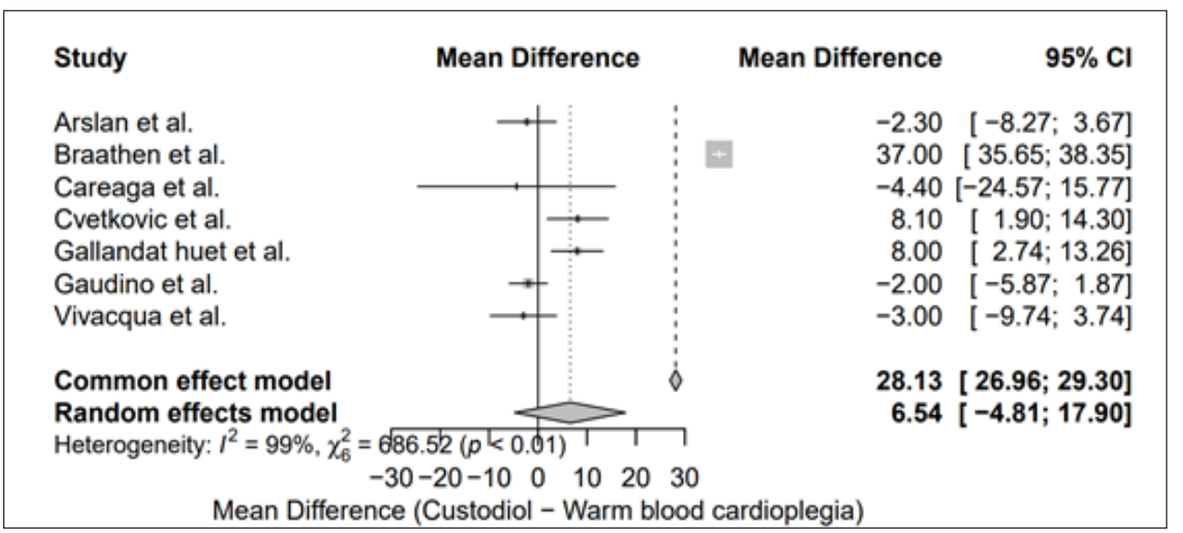

Fig. 6: Forest plot of the comparison: Custodiol versus warm blood cardioplegia, aortic cross-clamping time.

Table 1: General characteristics of the included studies.

References	Custodiol group (N)	Warm blood cardioplegia group (N)	Type of study
Ali and colleagues	160	160	Randomized controlled trial
Cvetkovic and colleagues	54	50	Retrospective cohort
Vivacqua and colleagues	110	55	Randomized study
Gaudino and colleagues	31	29	Randomized trial
Mercan and colleagues	25	25	Case series
Kammerer and colleagues	55	52	Case series
Braathen and colleagues	38	38	Prospective randomized study
Demmy and colleagues	68	68	Multicenter study
Arslan and colleagues	21	21	Retrospective cohort
Careaga and colleagues	15	15	Case series
Beyersdorf and colleagues	12	12	Case series
Gallandat huet and colleagues	132	117	Retrospective cohort

Table 2: Demographic data in included studies.

References	Study groups	Age (years)	Sex (Male %)	Weight (kg)
Ali and colleagues	Custodiol	44.19±11.63	118 (73.8)	–
	Warm blood cardioplegia	43.11±10.7	120 (75)	–
Cvetkovic and colleagues	Custodiol	64.5±6.5	40 (74.1)	–
	Warm blood cardioplegia	65.3±6.3	44 (88)	–
Vivacqua and colleagues	Custodiol	63±13	29 (52.7)	83±17
	Warm blood cardioplegia	70±11	35 (63.6)	90±22
Gaudino and colleagues	Custodiol	64±9	25 (80.7)	–
	Warm blood cardioplegia	61±5	21 (72.4)	–
Mercan and colleagues	Custodiol	60.1±7.8	19 (76)	–
	Warm blood cardioplegia	62.7±9.4	21 (84)	–
Kammerer and colleagues	Custodiol	65±14	31 (56.4)	74±13
	Warm blood cardioplegia	66±9	36 (69.2)	77±19
Braathen and colleagues	Custodiol	59±2	34 (89.5)	86±3
	Warm blood cardioplegia	59±2	25 (65.8)	80±2
Demmy and colleagues	Custodiol	62	67 (98.5)	–
	Warm blood cardioplegia		61 (89.7)	–
Arslan and colleagues	Custodiol	60.23±5.6	16 (76.2)	78.4±I 1.9
	Warm blood cardioplegia	60.38±7.3	19 (90.5)	75.6±13.2
Careaga and colleagues	Custodiol	53±19.75	21 (70)	–
	Warm blood cardioplegia			–
Beyersdorf and colleagues	Custodiol	58±7	9 (75)	–
	Warm blood cardioplegia	59±8	9 (75)	–
Gallandat huet and colleagues	Custodiol	60.7±8.8	107(81.1)	–
	Warm blood cardioplegia	60.7±7.6	94 (80.3)	–

According to demographic data of included studies, the age of participants in both Custodiol and Warm Blood Cardioplegia groups ranges from ~43 to 70 years. The sex distribution shows a higher percentage of males in most studies, with the male percentage ranging from 52.7 to 98.5%. Weight data is provided in a few studies, with variations observed between the groups.

Table 3: Medical history of included studies.

	Smoking	Diabetes mellitus	Hypertension	Hyperlipidemia
Ali and colleagues				
Custodiol	56 (35)	72 (45)	80 (50)	–
Warm blood cardioplegia	40 (25)	56 (35)	72 (45)	–
Cvetkovic and colleagues				
Custodiol	21 (38.9)	24 (44.4)	40 (74.1)	24 (44.4)
Warm blood cardioplegia	21 (42)	20(40)	44 (88)	24 (48)
Vivacqua and colleagues				
Custodiol	–	11 (20)	32 (58.2)	39 (70.9)
Warm blood cardioplegia	–	12(21.8)	45 (81.8)	44(81.5)
Mercan and colleagues				
Custodiol	–	12 (48)	17 (68)	9 (36)
Warm blood cardioplegia	–	13 (52)	12 (48)	12 (48)
Kammerer and colleagues				
Custodiol	–	5 (9.1)	–	–
Warm blood cardioplegia	–	4 (7.7)	–	–
Beyersdorf and colleagues				
Custodiol	7 (58.3)	0	3 (25)	7 (58.3)
Warm blood cardioplegia	8 (66.7)	2 (16.7)	4 (33.3)	10(83.3)

Table 4: NYHA classification of included studies.

	NYHA classification			
	1	2	3	4
Ali and colleagues				
Custodiol	8 (5)	56 (35)	80 (50)	16(10)
Warm blood cardioplegia	8 (5)	80 (50)	56 (35)	16(10)
Gaudino and colleagues				
Custodiol	–	–	15(48.4)	9 (29)
Warm blood cardioplegia	–	–	18(62.1)	7(24.1)
Beyersdorf and colleagues				
Custodiol	0	0	12 (100)	0
Warm blood cardioplegia	0	4 (33.3)	7 (58.3)	1 (8.3)

DISCUSSION

Cardioplegia is the principal technique used to protect myocardial function during cardiac surgery and to maintain a serene and bloodless surgical setting. Cardioplegia was initially introduced as a method for inducing hypothermic hyperkalemic arrest. Blood was subsequently recognized as an essential medium for administering potassium cardioplegia[9].

One safe and effective method for protecting the myocardium during surgery is warm blood cardioplegia. This technique is based on the idea that blood, rather than a crystalloid solution, may improve cardiac outcomes after the operation by mimicking normal physiology more closely, such as delivering oxygen to the myocardium and reducing hemodilution. Still, whether cardioplegia is superior for protecting the myocardium during cardiac surgeries remains open.

Some hospitals use Custodiol, an intracellular CCP solution, to preserve organs during transplant surgery and to protect the myocardium during complicated cardiac procedures. One of the reasons why HTK, also known as Bretschneider's or Custodiol, is appealing to cardiac surgeons is that it just requires a single dose to supposedly protect the heart for up to 3h, enabling complicated procedures to go forward unimpeded[10].

It is categorized as an intracellular, CCP as a result of its minimal calcium and sodium content. Cardiac arrest occurs during diastole as a result of hyperpolarization of the myocyte plasma membrane, which is induced by the depletion of sodium in the extracellular space. Unlike traditional "extracellular" cardioplegic solutions, which work by depolarizing the cell membrane to cause cardiac arrest, this one uses a different mechanism[11].

Results from CABG procedures with Custodiol solution and warm blood cardioplegia for patients with left main CAD were compared in this meta-analysis.

This review evaluated and compared the clinical effects of Custodiol solution in conjunction with warm blood cardioplegia in CABG for left main CAD. The data was sourced from randomized controlled trials, in addition to retrospective or prospective observational research. This review considered all studies reporting populations doing CABG for left main CAD patients.

After 320 patients underwent different types of cardiac operations [10], the safety and effectiveness of blood cardioplegia against HTK solution were evaluated. The HTK group had significantly shorter total bypass and cross-clamp times, along with reduced ICU and hospital stays, and shorter ventilation times compared with the blood cardioplegia group. Postoperative segmental wall motion abnormalities were more common in the blood cardioplegia group, which also had a higher incidence of patients requiring DC shocks and inotropic support. Although HTK cardioplegia was linked to a reduction in postoperative complications and a reduced recovery period, there were no significant variations in electrocardiographic changes, 30-day mortality, or readmissions among the two groups. HTK cardioplegia is a safe and effective alternative to blood cardioplegia, offering enhanced myocardial protection.

In 104 patients following primary isolated elective CABG, *Cvetkovic et al.,*[12] evaluated the myocardial protection offered by Custodiol and modified St Thomas cardioplegic solution. Although the Custodiol group had a longer cross-clamp duration (49.1 vs. 41.0min), the results for spontaneous rhythm restoration, levels of cardiac-specific enzymes, changes in EF, the frequency of MI, AF, and inotropic support were similar in both groups. Peak troponin-I and CK-MB levels were not significantly different across the groups, and no one died in either group. In CABG surgery, the cardioprotective benefits of Custodiol and modified St Thomas cardioplegic solutions were similar.

Another prospective noninferiority trial by *Vivacqua et al.* [13] compared the safety and efficacy of single-dose Custodiol HTK cardioplegia to repetitive cold blood cardioplegia in 110 patients undergoing various cardiac procedures. The study found no significant differences in cardiopulmonary bypass time, aortic cross-clamp time, cardiac biomarker levels (CK and troponin), or left ventricular function between the two groups. Postoperative outcomes, including ICU stay, incidence of atrial fibrillation, inotropic or vasopressor support, intubation time, and creatinine levels, were also similar. No deaths or myocardial infarctions occurred in either group. Their results indicated that single-dose Custodiol HTK is as effective as repetitive cold blood cardioplegia for myocardial protection during elective cardiac surgery.

Individuals with or without preoperative right ventricular (RV) dysfunction were the subjects of *Gaudino et al.,*[14], who compared the effectiveness of one-shot HTK cardioplegia with intermittent warm blood cardioplegia in protecting the RV during mitral valve surgery. There were no notable variations in postoperative RV function between the two cardioplegia procedures among 60 patients with preserved RV function (TAPSE ≥15). Nevertheless, mechanical ventilation and ICU hospitalizations were prolonged in patients with compromised RV function (TAPSE <15) compared with warm blood cardioplegia, due to the considerably worse RV ejection percentage, end-diastolic volume, and fractional area change observed with HTK. In a subset of patients with impaired RV function, adding intraoperative topical myocardial cooling to HTK cardioplegia significantly improved postoperative RV function. They concluded that while HTK cardioplegia is less effective for RV protection than warm blood cardioplegia, the inclusion of topical cooling can enhance its efficacy.

A different prospective study conducted by *Kammerer et al.,*[15] examined two strategies for myocardial protection in 107 individuals undergoing minimally invasive mitral valve surgery through right thoracotomy. One strategy was cold-CCP with Bretschneider's solution (Custodiol), while the other was warm blood cardioplegia using the Calafiore protocol. Both groups had similar demographic and operative characteristics, and hospitalization periods averaged 13 days. They found that cold-CCP resulted in significantly lower levels of cTN-I 48h postsurgery, although higher defibrillation rates were noted in the Bretschneider group (45 vs. 10%, $P< 0.001$). In addition, cardiac arrest was achieved faster with the Calafiore protocol, and one patient in the Calafiore group required an intra-aortic balloon pump. Despite these differences, the overall clinical mortality rate was similar between the groups (5%, $P= 0.673$). They suggested that as a minimally invasive alternative to warm blood cardioplegia, Bretschneider's cold-CCP provides better myocardial protection during mitral valve surgery.

Braathen et al.,[16] evaluated the efficacy of a single dose of cold antegrade HTK cardioplegia in providing comparable myocardial protection to repetitive antegrade cold blood cardioplegia in 80 individuals, who were undergoing elective mitral valve surgery. Myocardial injury was measured using troponin-T and CK-MB at several postoperative intervals. They showed no significant variances in these biomarkers among the HTK and blood cardioplegia groups. However, a notable correlation was found between ischemic time and myocardial injury markers in the HTK group, along with a higher incidence of spontaneous ventricular fibrillation after cross-clamping.

In mitral valve surgery, a single dose of HTK cardioplegia was determined to provide myocardial protection comparable to recurrent cold blood cardioplegia.

In a randomized, open-label trial across seven institutions by *Demmy et al.*,[17], 136 isolated coronary bypass patients were assigned to receive either a single dose of intracellular HTK cardioplegia or a standard extracellular multidose cardioplegia (Plegisol). Both groups had similar cross-clamp times and comparable hospital and ICU stays, as well as similar CK-MB curves, cardiac outputs, and adverse events. However, HTK was related to a lower incidence of defibrillation in contrast to Plegisol (64 vs. 91%, $P< 0.01$). Despite this, HTK treatment led to higher cardiac troponin-I levels at 6 h postprocedure (20.3±13.5 vs. 16.7±13.2μg/l, $P= 0.01$) and more frequent reinfusions due to cardiac warming. Logistic regression indicated that HTK was associated with higher cTn-I levels and more myocardial infarctions or adverse events. HTK offered prolonged protection with lower cTn-I release in fewer patients compared with Plegisol (17 vs. 27 patients, $P= 0.06$), suggesting that while HTK can be effective, it is linked to more structural protein release and adverse events.

In a study by *Arslan et al.*,[18] comparing myocardial protection between low-dose HTK and cold-CCP in isolated coronary bypass with short ischemic times, 21 patients were randomized to each group. HTK was administered antegrade at a lower dosage than typically used in the literature. They found similar aortic clamping times between the HTK (33.9±8.2min) and CCP groups (36.2±11.3min, $P> 0.05$). CCP individuals had lower lactate levels at 2 min, although HTK decreased malondialdehyde and CK levels at 24 h and 2 min, respectively. We could not find any statistically significant variations among the ischemic serum indicators. In contrast to CCP, which had a shorter period between aortic clamping and cardiac arrest (53.6±15.6 s, $P= 0.044$), HTK had a longer interval (63.3±14.7 s). Despite this longer time for fibrillation, HTK provided comparable myocardial protection to CCP for short clamping operations, with no significant biochemical or clinical differences.

In a study by *Careaga et al.*,[19] comparing myocardial protection using Bretschneider solution (HTK) versus conventional CCP in 30 patients undergoing elective open heart surgery, those in the HTK group (n=15) experienced significantly fewer postoperative arrhythmias ($P= 0.001$), reduced need for inotropic support ($P= 0.003$), and shorter ICU stays ($P= 0.037$) compared with the CCP group (n=15). No deaths occurred in either group. They suggested that Bretschneider solution provides adequate myocardial protection by lowering arrhythmia incidence, inotropic support requirements, and ICU length of stay.

In a study by *Beyersdorf et al.*,[20] of 37 patients undergoing coronary revascularization, three intraoperative myocardial protection protocols were compared: hypothermic ventricular fibrillation (HF), multidose blood cardioplegia, and single-dose Bretschneider's CCP. Myocardial ultrastructure, energy phosphate levels, and serum enzyme release were assessed, along with hemodynamic data. The blood cardioplegia group showed superior preservation of high-energy phosphates and better myocardial ultrastructure compared with HF and CCP. Rhythm disturbances were less frequent in the blood cardioplegia group (17%) in contrast to HF (25%) and CCP (42%). Functional recovery, as measured by cardiac index and stroke work index, was also better in the blood cardioplegia group. Higher release of MB-CK was observed in the HF group compared with the cardioplegia group. Although the clinical outcomes related to perioperative infarction, inotropic support, and low cardiac output were better with blood cardioplegia, differences between groups were not statistically significant. Overall, multidose blood cardioplegia provided superior myocardial protection compared with the other methods.

In a prospective research by *Gallandat et al.*,[21], the hemodynamic effects of two cardioplegic solutions were compared: Bretschneider cardioplegic HTK (group I, 132 patients) and St Thomas cardioplegic solution (group II, 117 patients) in CABG patients. Both groups experienced increased heart rate, cardiac output, pulmonary artery pressure, and pulmonary capillary wedge pressure postbypass, while systemic vascular resistance decreased in both groups. Group I had lower mean arterial pressure, pulmonary mean arterial pressure, and systemic vascular resistance compared with group II. Cardiac index was higher in group II (3.3 vs. 3.0 l/min/m^2), and sinus rhythm returned spontaneously in more patients in group I (39.5 vs. 20.4%, $P< 0.005$). In addition, temporary pacemaker use was more frequent in group I (6.3 vs. 1.1%). There was no significant correlation between hemodynamic data and aortic occlusion time within groups. Overall, Bretschneider cardioplegia was related to a greater incidence of spontaneous sinus rhythm but also a higher need for temporary pacing compared with St Thomas cardioplegia.

Based on the demographic data of the studies that were used in our analysis, the age range of the participants in both the Custodiol and warm blood cardioplegia groups is around 43–70 years. The sex distribution shows a higher percentage of males in most studies, with the male percentage ranging from 52.7 to 98.5%. Weight data is provided in a few studies, with variations observed between the groups.

A comparison of CK levels between Custodiol and warm blood cardioplegia across different time subgroups (4–7h, 24h, and 48h) shows mixed results. At 4–7h postsurgery, there is a significant reduction in CK levels with Custodiol across all studies, supported by both common and random effects models despite high heterogeneity. At 24h, the

results are inconsistent, with no significant overall difference and high heterogeneity. At 48h, no significant differences are observed, with moderate heterogeneity. The overall analysis indicates a significant reduction in CK levels with Custodiol according to the common effect model, but the random effects model shows no significant difference, highlighting substantial variability among the study results.

The overall common and random effects models for this subgroup show no significant differences, with high heterogeneity (I2=71%). In the 24h subgroup, none of the studies reported significant differences, and the overall common and random effects models confirm no significant differences with no heterogeneity (I2=0%). Similarly, in the 48h subgroup, no significant differences were reported by any study, and the overall common and random effects models show no significant differences with no heterogeneity (I2=0%). The overall analysis from both the common effect model (MD=−0.13, 95% CI: −0.58 to 0.32) and the random effects model (MD=−0.13, 95% CI: −0.58 to 0.32) indicates no statistically significant difference in Tn-I levels between Custodiol and warm blood cardioplegia, with low heterogeneity (I2=7.8%, *P*= 0.36).

The overall summary estimates indicate a substantial difference in favor of Custodiol with the common effect model showing an MD of 28.13 (95% CI: 26.96 to 29.30) and the random effects model showing an MD of 6.54 (95% CI: −4.81 to 17.90), though the latter's CI crosses zero, indicating nonsignificance. High heterogeneity (I2=99%, *P*< 0.01) suggests significant variability among the study results.

A comparison of cardiac arrest beginning time between Custodiol and warm blood cardioplegia, based on two studies, shows mixed results. Arslan and colleagues reported a significant positive MD (MD) of 9.70 (95% CI: 0.53–18.87), indicating longer cardiac arrest beginning time with Custodiol. The overall summary estimates from the common effect model (MD=5.12, 95% CI: −1.66–11.90) and the random effects model (MD=4.87, 95% CI: −5.01 to 14.76) both indicate no statistically significant difference in cardiac arrest beginning time between the two methods. Moderate heterogeneity (I2=53%, *P*=0.15) suggests some variability between the study results, though it is not substantial.

The overall summary estimates from the common effect model (RR=0.85, 95% CI: 0.74 to 0.98) suggest a significant reduction in postoperative inotropic support with Custodiol, while the random effects model (RR=0.94, 95% CI: 0.70 to 1.26) shows no significant difference. High heterogeneity (I2=74%, *P*< 0.01) indicates substantial variability among the study results.

CONCLUSION

In comparing Custodiol solution with warm blood cardioplegia for left main CAD patients undergoing CABG, our meta-analysis showed mixed results regarding CK and Tn-I levels, with Custodiol showing a significant reduction in CK levels at 4–7h postsurgery. While Custodiol indicated a potential benefit in reducing postoperative inotropic support, the variability in outcomes and lack of consistency across studies suggest caution in interpreting its superiority over warm blood cardioplegia. Further randomized controlled trials are warranted to validate these findings and address the limitations of heterogeneity and publication bias observed in the included studies.

CONFLICTS OF INTEREST

None declared .

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