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Custodiol versus Cold Blood Cardioloplegia in Minimally Invasive Aortic Valve Surgery: A Comparative Study

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Abstract

Background: Myocardial protection is a critical concern during aortic valve replacement. Custodiol cardioplegia and cold blood cardioplegia represent two primary strategies for myocardial preservation. This study sought to compare Custodiol and blood cardioplegia results for myocardial protection in aortic valve replacement.

Methods: This prospective study included 200 patients who were evenly divided into two groups based on the cardioplegia solution used: the Custodiol group (Group A) and the cold blood cardioplegia group (Group B). The study evaluated postoperative mechanical ventilation duration, ICU and overall hospital stay lengths, and echocardiographic findings at three and six months postoperatively.

Results: Compared with Group B, Group A had significantly shorter ventilation times (min-max: 6-9 vs. 9-15 hours), ICU stays (3-3 vs. 4-5 days), and hospital stays (7-9 vs. 10-20 days) ($p<0.001$ for all). Group A exhibited shorter cardiopulmonary bypass times (179 ± 9 minutes vs. 216 ± 14 minutes, $p<0.001$) and cross-clamp times (137 ± 8 minutes vs. 176 ± 18 minutes, $p<0.001$). Postoperative atrial fibrillation was more common in Group A (66% vs. 20%, $p<0.001$), while ventricular tachycardia and nodal rhythm post-defibrillation were greater in Group B. Mortality was lower in Group A (2% vs. 9%, $p=0.03$). However, at three and six months postoperatively, echocardiographic findings were significantly different in terms of left atrial diameter and left ventricular end-systolic diameter between Group A and Group B ($p<0.001$).

Conclusion: Custodiol cardioplegia could be associated with superior postoperative outcomes, including shorter ventilation times, ICU and hospital stays, and lower mortality rates, compared to cold blood cardioplegia in minimally invasive aortic valve replacement surgery.

KEYWORDS
Custodiol; Cold Blood Cardioplegia; Myocardial Protection; Aortic Valve Replacement; Cardiopulmonary

Introduction

Myocardial protection during aortic valve replacement surgery is paramount to patient outcomes and the long-term success of the procedure [1]. The advent of cardioplegia has significantly advanced the field of cardiac surgery by enabling surgeons to operate on a still and bloodless heart, thus reducing myocardial ischemia and improving postoperative cardiac function [2]. Among the various cardioplegia solutions available, Custodiol (histidine-tryptophan-ketoglutarate [HTK] solution) and cold

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blood cardioplegia have emerged as prominent options, each with distinct mechanisms of action and purported benefits [3,4]. While Custodiol offers the convenience of a single dose with prolonged protection, cold blood cardioplegia is recommended for its physiological composition and potential for replenishing the myocardium with oxygenated blood during the procedure [5,6].

The comparative effectiveness of these two cardioplegia strategies, especially in minimally invasive aortic valve surgery, has been the subject of ongoing research and debate [7]. Custodiol cardioplegia, characterized by an extended period of myocardial protection without repeated doses, is an attractive option for complex cardiac procedures requiring longer operative times [5,8]. Conversely, cold blood cardioplegia, administered in multiple doses throughout surgery, is believed to provide a more tailored approach to myocardial preservation, potentially minimizing ischemic injury through intermittent reperfusion and cooling of the myocardium [9].

Despite their widespread use, there remains a lack of consensus on which cardioplegia solution yields superior outcomes regarding myocardial protection, postoperative recovery, and long-term cardiac function [7,10]. This debate is particularly relevant in the setting of minimally invasive aortic valve replacement surgery. This technique has gained popularity due to its association with reduced trauma, shorter recovery times, and comparable surgical outcomes to traditional open-heart procedures. The choice of cardioplegia solution in this context is critical, as it must accommodate the nuances of minimally invasive techniques while ensuring optimal myocardial protection [11,12].

Given the evolving landscape of cardiac surgery and the continuous quest for improving patient outcomes, this study aimed to compare the outcomes of patients undergoing minimally invasive aortic valve replacement surgery with those of patients receiving Custodiol and blood cardioplegia for myocardial protection.

Patients and Methods

Study Design and Participant Selection

This research was an investigation involving 200 individuals who underwent aortic valve replacement. Participants were divided into two categories based on the type of cardioplegia solution administered. The first group, Group A, consisted of 100 patients treated with Custodiol, while the second group, Group B, included 100 patients who received cardioplegia via cold blood. The choice of cardioplegia was influenced by the surgeon's preference and the patient's age. The eligibility of patients for the study was limited to those who underwent minimally invasive aortic valve surgery and had an ejection fraction greater than 50%. The exclusion criteria included patients who underwent revision surgery, emergency procedures, double valve replacement, or simultaneous coronary artery bypass grafting.

Procedure Details:

The incisions used in this study for all patients who underwent minimally invasive aortic valve replacement were J-shaped mini sternotomy, arterial cannulation through the ascending aorta, and venous cannulation through the right atrial appendage. For patients in Group A, a single administration of HTK solution at 4°C, dosed between 20-25 ml/kg, was applied over 5–8 minutes, subsequently reducing the systemic temperature to 30°C. The cardioplegia solution was administered antegrade, starting with an initial perfusion pressure between 80–100 mmHg, which was reduced to 40–60 mmHg following the induction of cardiac arrest. In contrast, Group B patients received cold blood cardioplegia directly through the aortic root, with systemic temperatures decreased to 28-30°C and hematocrit levels maintained at 21-25%. Blood cardioplegia was prepared in a 1:4 ratio with the cardioplegia solution. It was reapplied every 20 minutes, with an infusion speed of 150-180 ml/min for the initial liter, followed by 500 ml for each subsequent dose until the mechanical aortic valve replacement was complete.

Study Objectives:

The primary endpoints assessed in this study were the duration of postoperative mechanical ventilation, length of ICU stay, and overall hospitalization period. Echocardiographic evaluations were conducted three and six months after the surgery to monitor outcomes.

Ethical Approval and Consent

The Research Ethics Committee granted approval for this study. Before their participation, all individuals provided informed written consent.

Statistical analysis

Statistical analyses and data handling were conducted using IBM SPSS version 28 (IBM Corp- Chicago, IL, USA). The Kolmogorov–Smirnov test and visual inspection methods were utilized to evaluate the distribution of the quantitative data. Based on the distribution, quantitative data are presented as mean values with standard deviations or medians with their respective ranges. Categorical data are presented as frequencies and percentages. Quantitative data was compared across different groups using either the independent t-test or the Mann–Whitney U test, depending on whether the data followed a normal distribution. For categorical variables, comparisons were made using either the chi-square test or Fisher's exact test, as appropriate. A multivariate logistic regression analysis was carried out to assess the likelihood of mortality, with the computation of odds ratios and their 95% confidence intervals. All the statistical tests applied were bidirectional, and a p-value threshold of less than 0.05 was used to determine statistical significance.

Results

General characteristics

Both groups were comparable in terms of age (p = 0.313), sex (p = 0.203), smoking status (p = 0.174), diabetes status (p = 0.626), chronic obstructive pulmonary disease (COPD) status (p = 0.147), aortic stenosis (p = 0.0.157), and aortic regurgitation. (Table 1)

Group A had a shorter average CBT (179 ± 9 minutes) than Group B (216 ± 14 minutes), with a p-value of <0.001. Similarly, the average CCT for Group A was 137 ± 8 minutes, which was significantly less than that for Group B (176 ± 18 minutes), with a p-value of <0.001. (Table 1)

Post-bypass and postoperative findings

Atrial fibrillation was significantly more prevalent in Group A (66%) than in Group B (20%), with a p-value <0.001. Conversely, ventricular tachycardia (VT) showed the opposite trend, being significantly greater in Group B (80%) than in Group A (34%). Post-defibrillation (DC), nodal rhythm occurrence was significantly greater in Group B (80%) than in Group A (7%), with a p-value of <0.001, while sinus rhythm was more common in Group A (93%) than in Group B (14%). (Table 2)

Table 1: General characteristics of the Custodiol group (Group A) and the cold blood cardioplegia group (Group B)

		Group A (n = 100)	Group B (n = 100)	p-value
Age (years)	Mean ±SD	46 ±9	47 ±9	0.313
Sex				
Male	n (%)	48 (48)	57 (57)	0.203
Female	n (%)	52 (52)	43 (43)	
Smoking	n (%)	28 (28)	37 (37)	0.174
DM	n (%)	24 (24)	27 (27)	0.626
COPD	n (%)	10 (10)	17 (17)	0.147
AS	n (%)	47 (47)	57 (57)	0.157
AR	n (%)	100 (100)	100 (100)	-
CBT (min)	Mean ±SD	179 ±9	216 ±14	**<0.001**
CCT (min)	Mean ±SD	137 ±8	176 ±18	**<0.001**

SD: standard deviation; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; AS: aortic stenosis; AR: aortic regurgitation; CBT: cardiopulmonary bypass time; CCT: cross clamp time

Table 2: Postbypass and postoperative findings in the Custodiol group (Group A) and the cold blood cardioplegia group (Group B)

		Group A (n = 100)	Group B (n = 100)	p-value
Post bypass arrhythmia				
AF	n (%)	66 (66.0)	20 (20.0)	**<0.001**
VT	n (%)	34 (34.0)	80 (80.0)	
DC	n (%)	100 (100)	100 (100)	-
After DC				
Nodal	n (%)	7 (7)	80 (80)	**<0.001**
Sinus	n (%)	93 (93)	14 (14)	
VT	n (%)	0 (0)	6 (0)	
Vent time (hrs)	Median (range)	7 (6 - 9)	12 (9 - 15)	**<0.001**
ICU stay (days)	Median (range)	3 (3 - 3)	4 (4 - 5)	**<0.001**
Hospital stay (days)	Median (range)	8 (7 - 9)	13 (10 - 20)	**<0.001**
Wound seroma	n (%)	5 (5)	36 (36)	**<0.001**
Death	n (%)	2 (2)	9 (9)	**0.03**

AF: Atrial Fibrillation; VT: Ventricular Tachycardia; DC: Direct Current; Nodal: Nodal Rhythm; Sinus: Sinus Rhythm; Vent time: Ventilation Time; ICU: Intensive Care Unit.

Group A had a shorter median ventilation time (7 hours), ICU stay (3 days), and hospital stay (8 days), all with p-values <0.001, than Group B, which had a median of 12 hours for ventilation time, four days for ICU stay, and 13 days for hospital stay. Wound seroma was significantly greater in Group B (36%) than in Group A (5%), and the mortality rate was greater in Group B (9%) than in Group A (2%), with P values of <0.001 and 0.03, respectively. Table 2

Postoperative echocardiographic findings

Echocardiographic evaluations after surgery revealed that the ejection fractions were consistent and similar across both groups immediately following surgery (Group A: 58.7 ± 5.5, Group B: 58 ± 6.8 %; p= 0.394), at the three-month mark (Group A: 58.5 ± 5.1, Group B: 57.7 ± 6.6 %; p = 0.378), and at six months postoperation (Group A: 57.5 ± 5.6, Group B: 57 ± 6%; p = 0.548). (Table 3)

Nonetheless, there were notable distinctions in the measurements of the left atrial diameter and the left ventricular end-systolic diameter (LVESD). Specifically, the left atrial diameter was consistently lower in Group A than in Group B at every measured interval: immediately after the operation (4.5 ± 0.3 cm vs. 4.8 ± 0.6 cm; p < 0.001), at three months (4.3 ± 0.3 cm vs. 4.6 ± 0.5 cm; p < 0.001), and at six months (4.2 ± 0.3 cm vs. 4.6 ± 0.5 cm; p < 0.001). (Table 3)

Similarly, LVESD values were significantly lower in Group A than in Group B after surgery (3.1 ± 0.4 cm vs. 2.9 ± 0.3 cm; p < 0.001), at the three-month follow-up (3.1 ± 0.5 cm vs. 2.8 ± 0.3 cm; p < 0.001), and at six months after the procedure (3.0 ± 0.4 cm vs. 2.7 ± 0.3 cm; p < 0.001). (Table 3)

Prediction of mortality

Multivariate logistic regression analysis was performed to predict mortality. Moreover, controlling for age, sex, smoking status, and diabetes, custodial cardioplegia was associated with an 83.3% reduction in the risk of mortality (OR = 0.167, 95% CI = 0.032 – 0.861, p= 0.032).

Discussion

In this research involving 200 participants, the effectiveness of Custodiol cardioplegia was compared against that of intermittent cold blood cardioplegia. The findings indicated that cardiopulmonary cardioplegia led to fewer arrhythmias following bypass surgery, reduced durations of mechanical ventilation, and shorter stays in the ICU and hospital overall. While cold blood cardioplegia is traditionally employed for myocardial protection, its application necessitates pausing the surgical procedure every 15–20 minutes for additional doses.

Table 3: Postoperative echocardiographic data in the Custodiol group (Group A) and the cold blood cardioplegia group (Group B)

		Group A (n = 100)	Group B (n = 100)	p-value
Ejection fraction (%)				
Postoperative	Mean ±SD	58.7 ±5.5	58 ±6.8	0.394
Three months	Mean ±SD	58.5 ±5.1	57.7 ±6.6	0.378
Six months	Mean ±SD	57.5 ±5.6	57 ±6	0.548
Left atrial diameter (cm)				
Postoperative	Mean ±SD	4.5 ±0.3	4.8 ±0.6	**<0.001**
Three months	Mean ±SD	4.3 ±0.3	4.6 ±0.5	**<0.001**
Six months	Mean ±SD	4.2 ±0.3	4.6 ±0.5	**<0.001**
LVESD (cm)				
Postoperative	Mean ±SD	3.1 ±0.4	2.9 ±0.3	**<0.001**
Three months	Mean ±SD	3.1 ±0.5	2.8 ±0.3	**<0.001**
Six months	Mean ±SD	3 ±0.4	2.7 ±0.3	**<0.001**

For complex surgeries such as aortic valve replacement, where uninterrupted operations are preferred, Custodiol has emerged as a favorable choice. Nonetheless, the surgical community lacks consensus on the optimal cardioplegia solution. The choice of cardioplegia in this study was influenced by the surgeons' personal preferences and convictions, with some surgeons favoring blood cardioplegia for its perceived superior myocardial protection in patients of advanced age or those with a hypertrophied left ventricle, which contributed to variations in age and valve lesion characteristics across the study groups.

The occurrence of arrhythmias during bypass was notably greater in the group receiving cold blood cardioplegia. According to Del Nido and colleagues, postsurgical conduction abnormalities may result from insufficient myocardial protection during surgery, suggesting that effectively protected hearts often naturally return to a normal rhythm without the need for defibrillation [13]. In line with this, research by Sakata and his team on the use of HTK solution in complex cardiac surgeries reported a greater incidence of natural heart rhythm restoration and a reduced need for inotropic medication compared to cold blood cardioplegia [14].

In our study, a remarkable 93% of patients in the Custodiol group successfully reverted to a normal sinus rhythm after undergoing direct current (DC) cardioversion, in stark contrast to only 14% of patients who received cold blood cardioplegia. A comparative analysis of the biomarkers for myocardial damage revealed that cardiopulmonary cardioplegia provides myocardial protection comparable to that achieved with repeated doses of antegrade cold blood cardioplegia during elective aortic valve replacement surgeries. Braathen and colleagues noted an increased incidence of spontaneous ventricular fibrillation following the cross-clamp removal in patients treated with HTK, suggesting this was due to oxidative stress and alterations in the electrolyte balance across cell membranes. Cardiac conduction issues were associated with inadequate myocardial protection during the operation, which could be attributed to inconsistent reperfusion and diminished ATP reserves. However, it was observed that the occurrence of spontaneous ventricular fibrillation did not influence the levels of myocardial enzyme release compared to the use of blood cardioplegia [15].

Our findings revealed that ventricular fibrillation (VF) was the initial rhythm observed after reperfusion in patients with cold blood cardioplegia, echoing the observations made by Liu and their team. The underlying cause remains unclear, although some researchers propose that VFs upon reperfusion could signal inadequate protection of the myocardium [16].

Statistically notable disparities were observed between the two groups under study in terms of ventilation duration, hospitalization period, and length of ICU stay. Li and their team reported a reduction in ICU stay duration and mortality rates with Custodiol cardioplegia compared to cold blood cardioplegia, attributing these outcomes to a decreased need for inotropic support and fewer postoperative complications in complex cardiac surgery patients [17]. On the other hand, Kuslu and colleagues reported no significant difference between groups concerning mechanical ventilation time and ICU stay length, although their research focused on pediatric patients with congenital heart disorders [18].

This research revealed a significant difference in arterial blood gas levels between the two groups. The group treated with cold blood cardioplegia frequently experienced acidosis and hyperkalemia. In contrast, while other investigations noted a reduction in serum sodium levels, osmolality remained unchanged, indicating the presence of isotonic hyponatremia. It has been proposed that incorporating a hemofilter into the cardiopulmonary bypass setup could effectively address hyponatremia following the use of custodiol.

Furthermore, the research noted greater complications, such as cloudy seroma formation at the wound site, primarily among patients treated with cold-blood cardioplegia. Consistent with our results, Sansone and colleagues reported a lower death rate in patients subjected to intricate cardiac procedures using Custodiol than in those who received cold blood cardioplegia [19,20].

Postoperative echocardiographic evaluations, including left ventricular function and dimensions, revealed no significant differences between the groups. Saitoh and colleagues demonstrated that the protective effects of Custodiol solution extend to both the myocardium and coronary artery endothelium [21]. In addition, Von Oppell and associates conducted studies on human endothelial cell cultures maintained in various cardioplegia solutions at various temperatures and concluded that Custodiol is the most effective at preserving endothelial cells under hypothermic conditions, which is consistent with the findings of other studies [22].

Study limitations:

The research was not conducted as a randomized controlled trial, leading to potential bias in the allocation of patients to groups based on the surgeons' preferences. Various factors beyond the type of cardioplegia used may have influenced the results. Additionally, the findings of these investigations are limited by the fact that they were performed within a single institution. Despite these limitations, this research successfully demonstrated the safety and effectiveness of custom-free cardioplegia for minimally invasive aortic valve operations.

Conclusion

Custodiol cardioplegia could be associated with superior postoperative outcomes, including shorter ventilation times, ICU and hospital stays, and lower mortality rates, compared to cold blood cardioplegia in minimally invasive aortic valve replacement surgery. These findings suggest that Custodiol provides more effective myocardial protection during surgery. This study underscores the importance of selecting an appropriate cardioplegia solution to optimize patient outcomes in aortic valve replacement surgeries.

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