ORIGINAL ARTICLE

Custodial HTK Cardioplegia in conventional cardiac surgery: A retrospective analysis From UiTM

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ABSTRACT

Introduction: Custodial-HTK (Histidine-Tryptophan-Ketoglutarate) solution and blood cardioplegia are both established methods for myocardial protection during cardiac surgery. However, their utility in patients undergoing complex cardiac surgery is not extensively study. This study compares clinical outcomes between patients receiving Custodial-HTK and blood cardioplegia in one of the tertiary Malaysian cardiac center.

Materials and Methods: We retrospectively analyzed data from 79 patients who underwent elective, on-pump, cross-clamp cardiac surgeries at Faculty of Medicine, Universiti Teknologi MARA (UiTM) from August 2022 to July 2023. Patients undergoing emergency procedures, off-pump, or incomplete records were excluded. Patients receiving Custodial-HTK were typically those with impaired LVEF or requiring complex surgeries.

Results: Custodial-HTK was used in 12% of cases. These patients had slightly higher mean age (61.9 ± 7.6 vs. 59.9 ± 8.8 years) and higher mean EuroSCORE II, although the latter was not statistically significant (p = 0.115). Comorbidities including diabetes, hypertension, stroke, and renal disease were comparable between groups. The Custodial group showed significantly lower mean LVEF (43.7 ± 14.7%) and greater use of pre-induction intra-aortic balloon pump (IABP) (20%). Complex procedures were more frequent (50%), with longer mean cardiopulmonary bypass (181.7 ± 65.1 minutes) and cross-clamp durations (131.3 ± 50.4 minutes). Despite these differences, postoperative complication rates, ICU stay, total hospital stay, and 30-day mortality did not differ significantly between groups.

Conclusion: Although patients receiving Custodial-HTK had higher surgical complexity and poorer baseline cardiac function, postoperative outcomes were within acceptable clinical range to the blood cardioplegia group. These findings support the use of Custodial-HTK as a safe and effective alternative in high-risk cardiac surgery patients.

KEYWORDS:
Custodial HTK solution; cardioplegia; myocardial protection; cardiac surgery; blood cardioplegia; clinical outcomes

INTRODUCTION

Myocardial protection is pivotal in cardiac surgery, preserving the myocardium during periods of ischaemia that normally encounter during cardiopulmonary bypass.[1] Myocardial protection during cardiopulmonary bypass relies primarily on two key strategies: hypothermia[2], which reduces myocardial oxygen demand, and potassium-induced electromechanical arrest, which halts the heart's electrical and mechanical activity to prevent energy depletion.[3]

Although blood cardioplegia remains a standard myocardial protection strategy in cardiac surgery, Custodiol-HTK—a single-dose, crystalloid cardioplegia—has gained increasing acceptance for its prolonged protective effect and simplified delivery, allowing an uninterrupted operative field.[4] In smaller cardiac centers such as ours, managing complex or high-risk cases, particularly in patients with significantly reduced ejection fraction, poses substantial challenges. With limited resources and intra-aortic balloon pump (IABP) support as the only available mechanical circulatory device, the extended duration of myocardial arrest afforded by Custodiol-HTK offers practical advantages by reducing interruptions and facilitating operative efficiency. Moreover, its biochemical properties provide reliable myocardial protection during lengthy or technically demanding procedures. Despite these advantages, evidence regarding its performance in high-risk populations, including those with low LVEF or requiring IABP support which remains limited. Therefore, this study aims to evaluate the perioperative outcomes associated with Custodiol-HTK compared with traditional blood cardioplegia within our institution.

MATERIALS AND METHODS

The authors conducted an observational cohort study was conducted in all patients undergoing an elective, conventional cardiac surgery, using an on-pump and cross-clamp techniques. The study was conducted at the Cardiovascular and Thoracic Department, Faculty of Medicine, Universiti Teknologi Mara (UITM).

This study includes cohort of patients from August 2022 to July 2023. Patients who underwent as emergency or urgent surgery, patients with off-pump and on-pump beating heart techniques, and patient with incomplete records were excluded in this study.

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The decision to use Custodiol-HTK cardioplegia was made collaboratively by the operating surgeon, perfusionist, and attending anesthesiologist. In our institution, Custodiol-HTK is preferentially selected for patients with poor left ventricular systolic function, defined as a left ventricular ejection fraction (LVEF) <40%, or for complex cardiac procedures, which we defined as operations involving two or more concomitant interventions. In Coronary Artery Bypass Grafting patient, poor coronary targets were not classified as complex, as no standardized SYNTAX scoring was performed to objectively assess coronary anatomical complexity. All remaining patients received our institution's standard myocardial protection strategy using conventional blood cardioplegia. For analysis, patients were categorized into two groups: Group 1, consisting of those who received Custodiol-HTK, and Group 2, comprising patients who received standard blood cardioplegia.

Data Collection and Analysis: Data on patient demographics, comorbidities, intraoperative variables, and postoperative outcomes were collected for analysis. Group comparisons were performed using the Independent t-test for continuous variables and the Chi-square test for categorical variables. A two-tailed p-value of <0.05 was considered statistically significant.

Primary outcome of this study is to compare the 30-day Mortality between each group, whereas the secondary outcome will be mean duration of ICU stay, mean duration of hospital stay and also post-operative complications such as postoperative arrhythmias, mediastinal bleeding, renal failure, pulmonary complication, post-operative stroke, transaminitis, new heart failure and surgical site infection.

RESULTS

Patient Demographics and Baseline Characteristics

This study was conducted at UiTM from August 2022 to July 2023. A total of 79 patients were assessed retrospectively and the elegibility criteria includes electives patients on conventional on-pump, cross-clamp cardiac surgery. Exclusion criteria were emergency cardiac surgeries, as well as off-pump surgeries and on-pump beating heart surgeries where cardioplegia is not used in these 2 methods. Out of these 79 patients, 10 patients received Custodial-HTK solution as cardioplegic myocardial protection, whereas the other 70 patients received conventional blood cardioplegia.

Mean age was 61.9 ± 7.6 years in the Custodiol group and 59.9 ± 8.8 years in the blood cardioplegia group. The 95% confidence interval for the between-group difference ranged from –7.83 to 3.85, with no significant difference observed (p = 0.493). Male gender is more prevalent in Custodial group (90.0% vs 79.9%). EuroSCORE II was higher in the Custodiol group (2.39) compared with the blood cardioplegia group (1.44), with a 95% confidence interval for the mean difference ranging from –1.77 to –0.14 (p = 0.115), although the difference was not statistically significant. Mean ejection fraction was significantly lower in the Custodiol group (43.7) compared with the blood cardioplegia group (49.09), with a 95% confidence interval for the mean difference of –1.2 to 11.7 (p = 0.001), with 50% of the Custodial group cohort have EF less than 40% (p value: 0.006). Requirement of IABP preinduction was seen statistically higher in the Custodial group (20.0% vs 1.44%, p = 0.041) as compared to the Blood group.

There were no significant differences in NYHA or CCS class, nor in prevalence of diabetes, hypertension, smoking, renal disease, stroke, or left main disease between the 2 groups. On the hand, Custodial group have shown to have numbers of patient requiring inotrope preinduction and history of Cardiogenic shock although it does not achieve statistical significant.

Intraoperative Data

More than 90% patient in Blood group underwent isolated CABG, with only 1.4% from the cohort underwent double valve procedure, compared to Custodial group which only 50% of the cohort underwent isolated CABG while the other 50% underwent more complex procedures such as double valve procedures and CABG with valve procedures. In regard to cardiopulmonary bypass (CPB) and aortic cross-clamp durations, patients in the Custodial group had significantly longer CPB time (181.7 ± 65.1 minutes; 95% CI: –78.01 to –24.87) and cross-clamp time (131.3 ± 50.4 minutes; 95% CI: –56.76 to –16.28) compared to the Blood group, achieving statistical significance (p < 0.001). This finding is expected, as Custodial solution is more commonly used in patients undergoing more complex surgical procedures.

Postoperative Outcomes

Primary outcome of 30- day mortality is similar in both Custodial and Blood group (10.00 vs 10.14, p value: 0.734). For the secondary outcome, the mean duration of ICU stay was similar between the Custodial and Blood groups (6.42 ± 6.81 vs. 6.90 ± 4.40 days; 95% CI: –4.91 to 3.95), with no statistically significant difference (p = 0.973). The Custodial group recorded a shorter mean duration of hospital stay compared to the Blood group (8.9 ± 5.5 vs. 10.67 ± 9.44 days); however, this difference was not statistically significant (p = 0.708), with a 95% confidence interval of –4.34 to 7.88. For the post-operative complications outcome such as arrhythmias, renal failure, pulmonary complication, transaminitis and new onset of heart failure is higher in the Custodial group, however it was statistically not significant.

DISCUSSION

This retrospective study presents our early institutional experience with the use of Custodiol-HTK solution as a cardioplegic agent, compared to conventional blood cardioplegia, as part of the myocardial protection strategy. In our centre, blood-based cardioplegic solutions such as St. Thomas' extracellular cardioplegia and Del Nido cardioplegia are routinely employed to achieve myocardial protection during cardiac surgery. Both solutions have demonstrated excellent myocardial preservation by inducing diastolic arrest during aortic cross-clamping.

The St. Thomas' cardioplegic solution, first introduced in 1976, is an extracellular, potassium-based formulation designed to induce rapid and sustained myocardial arrest. In 1981, the solution was modified by increasing its potassium

Table I: Baseline Characteristics, Demographic and Preoperative Variables

Variable	Blood (N=69)	Custodial (N=10)	p-value	Confidence Interval
Age, mean (SD)	59.9 ± 8.805	61.9 ± 7.62	0.439	(-7.83, 3.85)
Male (%)	79.70	90.00	0.392	
Euroscore, mean (SD)	1.44 (1.14)	2.39 (1.67)	0.115	(-1.77, -0.14)
MI < 90 days (%)	52.17	30.00	0.166	
Diabetic (%)	55.07	50.00	0.512	
Smoking (%)	49.27	30.00	0.213	
Hypertension (%)	84.05	90.00	0.528	
Dyslipidemia (%)	62.31	60.00	0.573	
Renal Disease (%)	26.08	20.00	0.510	
Stroke (%)	2.89	0	0.759	
Sinus Rhythm (%)	95.65	80.00	0.78	
LM Disease (%)	43.47	40.00	0.558	
EF Good >50% (%)	52.00	50.00	0.006	
EF Moderate 40-49% (%)	34.80	0	0.006	
EF Impaired <40% (%)	13.00	50.00	0.006	
EF Mean (SD)	49.09 ± 8.89	43.7 ± 14.7	0.001	(-1.2, 11.7)
Inotropes Pre-Induction (%)	0	10.00	0.127	
Cardiogenic Shock (%)	4.34	10.00	0.425	
IABP Preinduction (%)	1.44	20.00	0.041	

Table II: Intraoperative Variables

Variable	Blood (N=69)	Custodial (N=10)	p-value	Confidence Interval
Isolated CABG (%)	92.75	50.00	<0.001	
Single Valve Procedure (%)	2.89	0	<0.001	
CABG + Valve Procedure (%)	0	40.00	<0.001	
Double Valve/Other (%)	1.44 / 2.89	10.00 / 0	<0.001	
2 Grafts (%)	17.18	22.22	0.896	
3 Grafts (%)	67.18	66.66	0.896	
4 Grafts (%)	15.62	11.11	0.896	
CPB Time, mean (SD)	130.26 ± 34.64	181.70 ± 65.12	<0.001	(-78.01, -24.87)
Aortic Cross Clamp Time, mean (SD)	94.78 ± 26.18	131.3 ± 50.43	<0.001	(-56.76,-16.28)

Table III: Postoperative Outcomes

Variable	Blood (N=69)	Custodial (N=10)	p-value	Confidence Interval
Arrhythmias (%)	18.84	40.00	0.209	
Mediastinal Bleeding (%)	13.04	0	0.594	
Renal Failure (%)	15.94	30.00	0.377	
Pulmonary Complication (%)	31.88	40.00	0.722	
Post-op Stroke (%)	4.35	0	0.663	
Transaminitis (%)	18.84	30.00	0.415	
New Heart Failure (%)	4.34	10.00	0.425	
Surgical Site Infection (%)	14.49	0	0.345	
30-day Mortality (%)	10.14	10.00	0.734	
ICU Stay, mean (SD)	6.42 ± 6.81	6.9 ± 4.4	0.973	(-4.91, 3.95)
Duration of Hospitalization, mean (SD)	10.67 ± 9.44	8.9 ± 5.5	0.708	(-4.34, 7.88)

concentration and reducing its sodium content to enhance myocardial protection. The modified St. Thomas' solution remains widely used in contemporary cardiac surgery, providing effective myocardial protection with a recommended redosing interval of approximately 20 minutes.[7]

The Del Nido cardioplegic solution was developed in the 1990s by Dr. Pedro Del Nido. It is an extracellular crystalloid solution formulated with Plasma-Lyte as the base, supplemented with magnesium sulfate, sodium bicarbonate, potassium chloride, and lidocaine. In contrast to the St. Thomas' solution, Del Nido cardioplegia provides prolonged myocardial protection, allowing a single dose to maintain electromechanical arrest for up to 90 minutes.[8]

Custodiol-HTK solution is a widely used crystalloid cardioplegia developed originally for organ preservation in 1970s.[6] Custodial-HTK is intracellular-type cardioplegic solution that induces diastolic arrest primarily through hyperpolarization, achieved by its low sodium and calcium composition.[4,5]

Custodial-HTK solution formulation reduces intracellular calcium overload, thereby minimizing ischemia-induced cellular injury. Histidine acts as a buffer to maintain acid-base balance, tryptophan stabilizes cell membranes, ketoglutarate serves as a metabolic substrate to support ATP regeneration, and mannitol reduces edema and scavenges free radicals.[5] Together, these components provide prolonged myocardial protection with a single-dose administration, often effective for up to 2 hours, making it especially useful in complex or prolonged cardiac surgeries unlike blood cardioplegia which need to be administered repeatedly every 15-30 minutes.[5] The extended duration of myocardial protection provided by Custodiol-HTK solution minimizes the need for repeated dosing, thereby preventing intraoperative interruptions and offering particular advantages in complex cardiac procedures.

In this study, patients who received Custodiol-HTK cardioplegia demonstrated a shorter duration of hospital stay compared to those in the blood cardioplegia group; however, the difference did not reach statistical significance. Postoperative complications, including arrhythmias, renal dysfunction, pulmonary complications such as prolonged mechanical ventilation and extended oxygen dependency, postoperative transaminitis, and new-onset heart failure, were observed more frequently in the Custodiol group, although these differences were not statistically significant. The underlying cause for the increased incidence of postoperative arrhythmias associated with Custodiol-HTK cardioplegia remains uncertain. Our findings are consistent with those reported by Saber et al., who also observed a higher incidence of postoperative ventricular fibrillation in patients receiving Custodiol HTK compared with blood cardioplegia.[9]

Other perioperative outcomes, such as the duration of ICU stay, were no significance difference between the two groups. However, the total length of hospital stay and 30-day mortality were shorter in the Custodiol-HTK group, although these differences did not reach statistical significance. Similar findings were reported by Ihab Ali et al., who observed shorter ICU and hospital stays in patients undergoing various cardiac surgical procedures using Custodiol HTK compared to blood cardioplegia.[10]

Our findings indicate that Custodial-HTK is a viable myocardial protection strategy, even in high-risk patients with impaired LV function or requiring IABP support. Despite longer operative times and more complex surgeries, outcomes were no significant difference to the standard blood cardioplegia group. This study has several limitations. The sample size of the Custodiol-HTK group was relatively small, which may limit the statistical power to detect significant differences between groups. Furthermore, the retrospective study design inherently restricts the ability to establish causal relationships.

Another important limitation is that propensity score matching could not be performed due to the very low number of patients in the Custodial group and the substantial imbalance in baseline characteristics between the two cohorts. Attempting to match these groups would have further reduced the sample size, resulting in inadequate statistical validity. Additionally, the cost of Custodiol-HTK represents a practical limitation in its wider adoption, as it is considerably more expensive compared to conventional blood cardioplegia. Future randomized controlled trials with larger sample sizes are warranted to better evaluate and optimize the clinical outcomes associated with Custodiol-HTK compared with blood cardioplegia.

CONCLUSION

In this retrospective experience from UiTM, Custodial-HTK cardioplegia was used predominantly in patients with more complex cardiac pathology and higher preoperative risk profiles, including reduced ventricular function and greater need for mechanical or inotropic support. Despite these higher-risk characteristics and longer operative durations typically associated with complex procedures, postoperative outcomes including 30-day mortality, ICU stay, hospital stay, and major postoperative complications, remained within clinically acceptable range to expected standards of care.

These findings suggest that Custodial-HTK can be used safely and effectively as a myocardial preservation strategy in selected higher-risk or complex surgical cases. Further prospective studies with larger cohorts are warranted to strengthen these observations and better define the optimal role of Custodial-HTK in contemporary cardiac surgery practice.

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