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Original research

Comparison between three single-dose cardioplegic solutions in myocardial protection: Cardioplegia Trial – a double-blind randomised clinical trial

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ABSTRACT

Objectives To compare myocardial protection afforded by three single-dose cardioplegic solutions — Custodiol (HTK), del Nido (DN) and modified del Nido (MDN) — in adult elective cardiac surgery.

Design Double-blind randomised controlled trial.

Setting Tertiary hospital in southern Brazil.

Participants 99 adults undergoing elective valve or coronary artery bypass surgery with cardiopulmonary bypass.

Interventions Administration of HTK, DN or MDN solution during surgery.

Main outcome measures High-sensitivity cardiac troponin T (hs-cTnT) at 0, 2, 12 and 24 hours postoperatively. Additionally, indirect measures of myocardial protection were compared, both laboratory and clinical, during intraoperative and postoperative periods.

Results All solutions provided effective myocardial protection, with similar clinical and laboratory outcomes. DN was associated with significantly lower hs-cTnT at 2 hours (p=0.023) and fewer intraoperative transfusions (p=0.008). HTK patients had lower postoperative sodium and potassium levels (p=0.049 and p=0.002, respectively). Survival and major postoperative outcomes, including vasoactive or mechanical support, were similar across groups.

Conclusions The three cardioplegic strategies showed comparable biochemical profiles of myocardial injury. DN was associated with lower early troponin release and reduced transfusion requirements, while HTK produced transient electrolyte shifts.

Trial registration number ReBEC; RBR-7g5s66.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Single-dose cardioplegia is increasingly used in adult cardiac surgery, particularly Custodiol and del Nido solutions, including their modified formulations. These strategies simplify operative management and provide prolonged myocardial arrest with satisfactory myocardial protection. However, direct comparative data among solutions remain limited and inconclusive, and no clear evidence supports the superiority of any specific formulation.

WHAT THIS STUDY ADDS

⇒ In this randomised controlled trial comparing Custodiol, del Nido and modified del Nido cardioplegia in adult valve and coronary surgery, all solutions provided equivalent myocardial protection. Del Nido cardioplegia was associated with lower early postoperative troponin release and fewer intraoperative transfusions, while Custodiol produced transient electrolyte changes without apparent clinical consequences. These findings support the safety and practical interchangeability of single-dose cardioplegic strategies in contemporary adult cardiac surgery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings may support the safe and effective use of different single-dose cardioplegic strategies in adult cardiac surgery, allowing selection according to institutional experience, availability and cost considerations. The lower early troponin release and reduced transfusion requirements observed with del Nido cardioplegia may support future optimisation of myocardial protection protocols. Further multicentre studies powered for clinical outcomes and cost-effectiveness are warranted.

INTRODUCTION

Myocardial protection remains fundamental to the success of cardiac surgery. Single-dose cardioplegic solutions such as Custodiol (HTK) and del Nido (DN) have gained widespread use because they simplify operative management and provide sustained myocardial arrest with reliable recovery.[1–3] However, evidence comparing their effectiveness in adult patients is limited, and the performance of

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modified formulations, such as the modified del Nido (MDN) solution, has not been clearly established.

The challenge lies in the absence of consensus on the optimal cardioplegic solution.[1 2] Although numerous formulations and techniques have been evaluated over several decades, postoperative myocardial injury remains frequent.[2–4] The continued need for inotropes, mechanical support or other circulatory assist devices indicates that current strategies, while generally effective, are not yet ideal.[5] Well-designed head-to-head clinical trials are therefore required to determine whether any single-dose solution can consistently prevent biochemical or clinical signs of myocardial injury and whether differences in composition translate into improved myocardial protection or perioperative outcomes.

To address this gap, we conducted a double-blind, randomised controlled trial comparing three single-dose cardioplegic solutions in adults undergoing elective valve surgery or coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB). The study focused on postoperative high-sensitivity cardiac troponin T (hs-cTnT) as a marker of myocardial injury, together with clinical outcomes, to answer a central question: in adults undergoing elective cardiac surgery, do single-dose HTK, DN and MDN cardioplegic solutions differ in their ability to prevent postoperative myocardial injury and influence clinical outcomes?

METHODS

Details of this clinical trial have been previously reported, including the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist, as described in the published study protocol.[6] Methods relevant to this report are described below. The approach of this study adhered to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT),[7] as illustrated in figure 1.

The study was undertaken in accordance with the Declaration of Helsinki (as revised in 2013).

Study design, participants and eligibility criteria

A double-blind, randomised clinical trial was conducted at Nossa Senhora da Conceição Hospital, a tertiary centre specialising in cardiothoracic surgery in southern Brazil. The study included all adult patients (aged ≥18 years) undergoing elective valve surgery or CABG with CPB. Patients were randomised to receive one of three cardioplegic solutions: HTK, DN or MDN, and were monitored to evaluate the effectiveness of each solution on myocardial protection and perioperative outcomes. All primary analyses followed a per-protocol approach, as prespecified in the study protocol[6]; however, because no participants were lost to follow-up and no post-randomisation exclusions occurred for the primary outcome measurements, the analysed cohort corresponded to the randomised population. Patients with prior cardiac surgery, chronic renal failure (serum creatinine >2.0 mg/dL),[8] severe psychiatric illness, emergency surgeries or multiple surgeries were excluded.

The sample size calculation for the Cardioplegia Trial was conducted using G*Power software (V.3.1.9.4), with an effect size of $f=0.466$ for troponin levels, based on the study by Talwar *et al*.[9] To achieve a significance level of $\alpha=0.05$ and a power of 95%, a sample of 75 patients was required. Allowing for a potential 20% loss and to preserve statistical power in the multivariable analysis, a minimum of 90 patients would be necessary for the study, with at least 30 randomised to each group.

Primary outcome

The primary outcome was the assessment of myocardial protection with the three cardioplegic solutions through serial serum measurement of hs-cTnT, which was selected for its greater

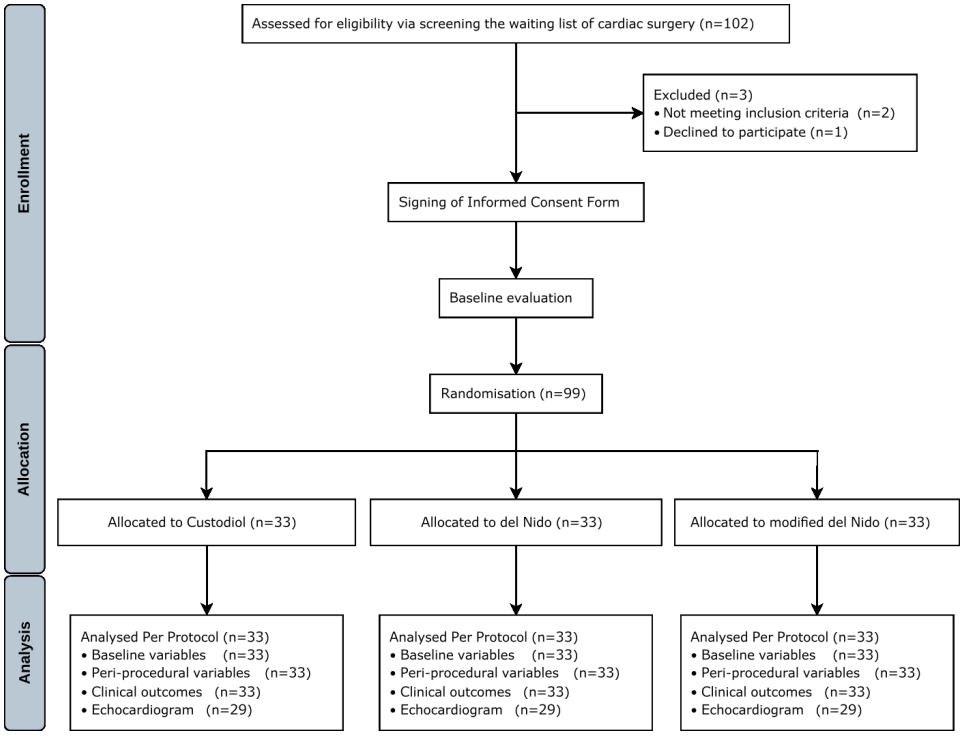


Figure 1 Flow of participants through the trial (CONSORT diagram). Adapted from the previously published study protocol.[6] CONSORT, Consolidated Standards of Reporting Trials.

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sensitivity, specificity and clinical relevance.[10 11] hs-cTnT levels were measured before cardioplegia infusion (baseline) and at 2, 12 and 24 hours postoperatively.

Secondary outcomes

Secondary outcomes included indirect clinical indicators of myocardial protection in the perioperative period. These comprised changes in left ventricular ejection fraction (LVEF), occurrence of arrhythmias and need for haemodynamic or mechanical (intra-aortic balloon pump, IABP) circulatory support. The Vasoactive-Inotropic Score (VIS), reflecting overall haemodynamic demand,[12] was calculated at the end of surgery, immediately before intensive care unit (ICU) transfer, using the Gaies[13] formula: dopamine dose (µg/kg/min) + dobutamine dose (µg/kg/min) + 100 × epinephrine dose (µg/kg/min) + 10 × milrinone dose (µg/kg/min) + 10 000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (µg/kg/min). Intraoperative times, including aortic cross-clamp and CPB, were assessed.

Other postoperative outcomes were blood products transfusion requirements, electrolyte changes, prolonged mechanical ventilation (>24 hour), acute myocardial infarction (AMI), stroke, acute kidney injury (AKI) requiring dialysis and mortality classified according to the Academic Research Consortium (ARC)−2 criteria.[14] Duration of ICU and total hospital stay were also recorded.

Randomisation and masking

Participants were randomly assigned in a 1:1:1 ratio using a computer-generated randomisation sequence with three fixed blocks of 33 participants to receive DN, MDN or HTK solutions during CPB. The sequence was generated by an independent statistician, using website randomizer.org, before study initiation and remained concealed from investigators responsible for patient enrolment until the moment of assignment. Each assignment was sealed in an opaque envelope and only revealed to the perfusionist immediately before preparation.

All the patients, anaesthesiologists, echocardiographers, nurses and laboratory staff were blinded to the type of intervention. The surgical team remained blinded to DN and MDN interventions but not to HTK, due to differing administration requirements. Standardisation of cardioplegic solution volumes, administration times and intervals between doses was avoided to mitigate patient risk.

Postoperatively, all patients were transferred to the ICU and later to the ward, with both the ICU and ward staff blinded to the cardioplegia type. The primary investigator, blinded to group allocation, conducted all outcome assessments and statistical analyses. All deaths or complications during the study were adjudicated by a blinded research team, and these data were incorporated into the final safety and efficacy analysis.

Surgical technique

The surgical approach followed the protocol previously published.[6]

Cardioplegic solutions: preparation and administration

All cardioplegic solutions were prepared by the perfusionist under standardised aseptic hospital procedures. The detailed composition and specific characteristics of each solution have been described in a previously published protocol.[6]

HTK cardioplegia was administered as a single dose of 20 mL/kg over 6–8 min at a temperature of 4–8°C and a perfusion pressure of 80–200 mm Hg. Even when the minimum infusion time was applied, the minimum volume required for induction in adults was 1500 mL, with a maximum of 2000 mL. Additional half-doses were infused only after 3 hours from the initial administration.[6]

Both DN (using Plasma-Lyte as the crystalloid solution) and MDN (Ringer's lactate was used as the crystalloid solution) cardioplegia were delivered as a single dose of 20 mL/kg (maximum of 1000 mL for patients weighing over 50 kg), typically at 4°C, with system pressure maintained between 80 and 200 mm Hg and flow rates of 150–300 mL/min. These variations in pressure and flow reflect the antegrade infusion technique, depending on whether the solution was administered through the coronary ostia or the aortic root. If required, supplementary doses of 10 mL/kg were infused after 90 min, providing an additional 45 min of myocardial protection.[1]

Following cardioplegia administration and before the first blood gas analysis, haemoconcentration and sodium bicarbonate were administered in proportions of 1.0 mL/kg and 0.5 mL/kg, respectively, in the HTK and DN groups (both original and modified formulations), to prevent metabolic acidosis. Subsequent adjustments were made as needed based on standard postoperative blood gas analysis results.

Protocol amendments

Details of protocol amendments are provided in online supplemental table S1. Changes were minor and aimed at improving feasibility and precision, with study team approval. The sample size was adjusted to 102 participants, with serum hs-cTnT levels as the primary outcome.[10 11] The creatinine exclusion threshold was revised (>2.0 mg/dL),[8] and creatine kinase myocardial band (CK-MB) was excluded due to laboratory discontinuation. The VIS was incorporated to assess haemodynamic support. Minor adjustments to HTK dosing and perfusion parameters for all solutions were made to align with institutional protocols.

Statistical analysis

Quantitative variables were described by means and SE in cases of symmetrical distributions or by medians and IQR in cases of asymmetric distributions. Qualitative variables will be described by the absolute and relative frequencies.

The Kolmogorov-Smirnov test was applied to assess the distribution type. The χ^2 test, in conjunction with adjusted residual analysis, was used to compare categorical variables. Analysis of variance, along with Tukey's test, was employed for comparing continuous variables with a normal distribution, while Kruskal-Wallis, in conjunction with Dunn's test, was used for comparing skewed continuous variables. A Generalised Estimating Equations model was employed to compare parameters over the follow-up period and between groups, supplemented by the Least Significant Difference test. The baseline measurement was included as the first time point in the model. A linear model was used for normally distributed variables, and a Gamma model was used for skewed variables. To assess survival among the three groups, the Kaplan-Meier method, along with the log-rank test, was used. Univariate Cox Proportional Hazards Regression was employed to assess the effect of the type of solution on the probability of death. For controlling confounding factors, a multivariable Cox Proportional Hazards Regression model was used to assess the effect of the type of solution on the probability of death. The significance level adopted was 5%, and the data were analysed using SPSS V.27.0.

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Table 1 Baseline clinical characteristics and surgical procedures of patients according to the study groups

Baseline characteristics*	HTK (n=33)	DN (n=33)	MDN (n=33)
Age (years)	63.4±2.0	64.3±2.2	62.4±1.8
Gender			
Female	12 (36.4)	11 (33.3)	13 (39.4)
Male	21 (63.6)	22 (66.7)	20 (60.6)
BMI (kg/m²)	27.5±1.0	27.7±0.8	28.1±0.8
Person who smoked previously	24 (72.7)	21 (63.6)	18 (54.5)
Person who smokes currently	7 (21.2)	4 (12.1)	6 (18.2)
Pacemaker	2 (6.1)	1 (3.0)	0 (0.0)
Atrial fibrillation	3 (9.1)	3 (9.1)	6 (18.2)
LVEF (%)	55.7±2.3	55.7±2.3	52.1±2.5
NYHA Classification			
I	11 (33.3)	6 (18.2)	6 (18.2)
II	7 (21.2)	13 (39.4)	11 (33.3)
III	11 (33.3)	10 (30.3)	9 (27.3)
IV	4 (12.1)	4 (12.1)	7 (21.2)
Diabetes mellitus	15 (45.5)	11 (33.3)	12 (36.4)
Peripheral vasculopathy	8 (24.2)	8 (24.2)	6 (18.2)
Hypertension	25 (75.8)	26 (78.8)	27 (81.8)
Cerebrovascular disease	3 (9.1)	3 (9.1)	4 (12.1)
Chronic pulmonary disease	3 (9.1)	3 (9.1)	4 (12.1)
STS risk score	1.7 (0.8–2.2)	1.7 (1.1–2.7)	1.8 (0.9–2.7)
EuroSCORE II	1.9 (1.0–3.4)	1.9 (1.1–3.5)	1.8 (1.2–2.7)
Surgery			
CABG surgery	21 (63.6)	20 (60.6)	20 (60.6)
Valve surgery	12 (36.4)	13 (39.4)	13 (39.4)

Valve surgery, aortic or mitral valve replacement.
*Variables were described by mean±SE, median (P25–P75) or as number (percentage).
BMI, body mass index; CABG, coronary artery bypass grafting; DN, del Nido; EuroSCORE II, European System for Cardiac Operative Risk Evaluation Score - II; HTK, histidine-tryptophan-ketoglutarate; LVEF, left ventricular fraction ejection; MDN, modified del Nido; NYHA, New York Heart Association; STS score, Society of Thoracic Surgeons score.

Patient and public involvement

The patients or the public were not involved in the design, recruitment or conduct of the study. This approach was chosen to ensure rigorous control of clinical variables and to maintain the study's scientific validity in a highly standardised surgical setting.

RESULTS

Between 15 July 2020 and 18 November 2022, 102 adult patients undergoing elective CABG or valve surgery at Nossa Senhora da Conceição Hospital, of whom 99 were randomised to receive HTK, DN or MDN cardioplegia and included in the analysis (figure 1). Baseline characteristics were comparable among groups (table 1). The mean age was 63±11 years, with a predominance of male patients, and CABG was the most common procedure.

Primary outcome and other laboratory findings

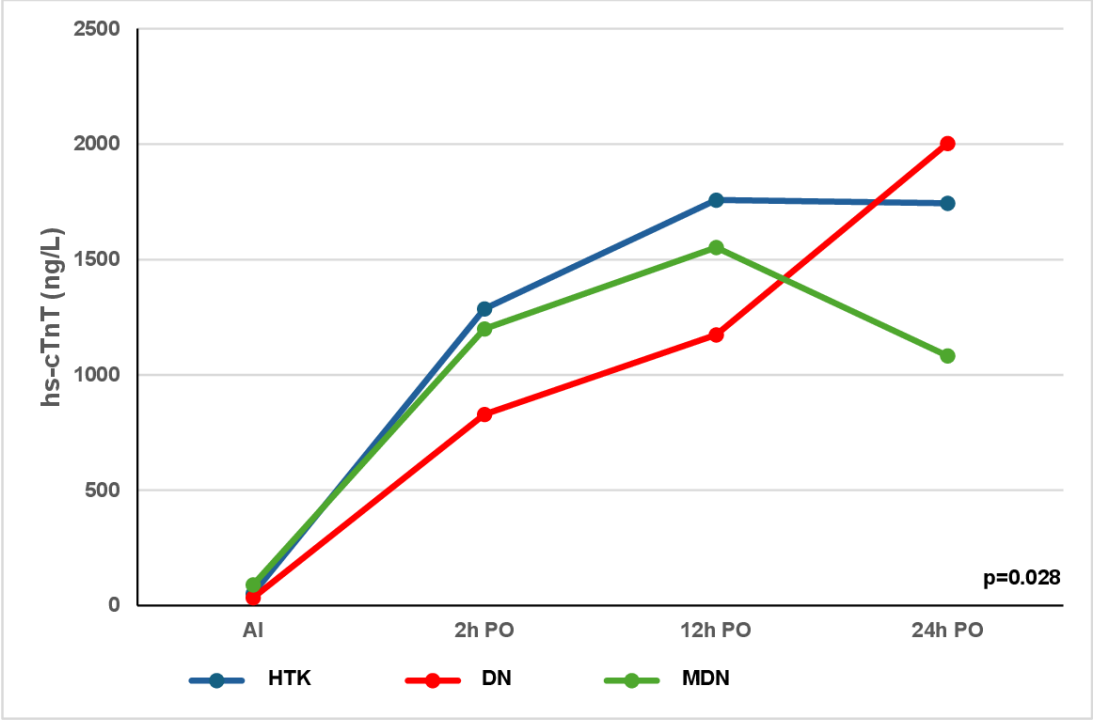
Serial laboratory analyses are summarised in table 2, while figure 2 illustrates the temporal behaviour of serum hs-cTnT. No missing values were observed for hs-cTnT at the predefined perioperative sampling time points; therefore, no imputation procedures were required. Baseline hs-cTnT concentrations were

Table 2 Comparison of blood parameters among the three cardioplegia groups at four postoperative time points

Variables*	HTK (n=33)	DN (n=33)	MDN (n=33)	P value
	Mean±SE	Mean±SE	Mean±SE	
hs-cTnT (ng/L)				
BI	52.3±27.5	33.8±7.3	90.0±66.6	1.00
2 hours PO	1286±216[b,f]	828±85.9[a,f]	1199±155[b,f]	**0.02**
12 hours PO	1758±344	1173±129	1552±216	0.11
24 hours PO	1744±534	2003±885	1083±165	0.20
CK (u/L)				
BI	59.9±6.1	71.7±10.6	64.8±5.5	0.60
2 hours PO	899±154	696±88.8	705±55.2	0.41
12 hours PO	1553±325	1083±202	1008±85.7	0.16
24 hours PO	1695±464	1445±291	1259±280	0.70
Lactate (mmol/L)				
BI	1.38±0.24	1.37±0.16	1.08±0.07	0.12
2 hours PO	3.66±0.62	3.01±0.45	3.17±0.40	0.68
12 hours PO	3.61±0.61	3.81±0.74	3.21±0.33	0.68
24 hours PO	2.94±0.38	2.56±0.42	2.38±0.37	0.55
pH				
BI	7.39±0.00	7.40±0.01	7.39±0.01	0.69
2 hours PO	7.34±0.01	7.38±0.01	7.36±0.01	0.15
12 hours PO	7.39±0.01	7.36±0.01	7.39±0.01	0.09
24 hours PO	7.41±0.01	7.40±0.01	7.40±0.01	0.44
Bicarbonate (mmol/L)				
BI	25.3±0.43	24.5±0.40	25.1±0.34	0.35
2 hours PO	23.1±0.49	22.2±0.47	22.9±0.41	0.31
12 hours PO	22.4±0.61	22.4±0.60	22.6±0.54	0.95
24 hours PO	23.3±0.45	24.2±0.50	23.5±0.39	0.37
Sodium (mEq/L)				
BI	136.1±0.73	136.6±0.42	135.9±0.60	0.69
2 hours PO	134.3±0.69[a,e]	136.1±0.58[b,e]	136.3±0.54[b,e]	**0.05**
12 hours PO	136.1±0.76	137.2±0.68	136.6±0.48	0.56
24 hours PO	134.9±0.63	136.3±0.62	135.3±0.86	0.28
Potassium (mEq/L)				
BI	4.15±0.06	4.31±0.09	4.39±0.09	0.07
2 hours PO	4.06±0.08[a,e]	4.47±0.10[b,ef]	4.39±0.10[b,e]	**<0.01**
12 hours PO	4.39±0.07[a,f]	4.71±0.10[b,f]	4.80±0.14[b,f]	**<0.01**
24 hours PO	4.10±0.06[a,e]	4.41±0.08[b,e]	4.34±0.09[b,e]	**0.01**
Calcium (mmol/L)				
BI	1.19±0.01	1.18±0.01	1.18±0.01	0.68
2 hours PO	1.13±0.02	1.15±0.01	1.16±0.01	0.42
12 hours PO	1.12±0.01	1.13±0.01	1.13±0.01	0.79
24 hours PO	1.10±0.01	1.11±0.01	1.11±0.01	0.83
Haematocrit (%)				
BI	37.6±4.0	35.5±6.4	36.3±5.4	0.28
2 hours PO	30.0±4.8	31.0±5.5	31.1±4.7	0.60
12 hours PO	29.5±4.5	30.4±5.2	30.2±3.7	0.71
24 hours PO	27.9±4.3	28.5±4.8	27.7±4.0	0.75

Equal letters indicate statistically similar results between groups (a, b) and within groups (e, f, g, h) by the Least Significant Difference test at a 5% significance level.
P values are presented with two decimal places.
Statistically significant values are highlighted in bold (p<0.05).
*Variables were described by mean±SE.
BI, before induction; CK, creatine kinase; DN, del Nido; hs-cTnT, high-sensitivity cardiac troponin T; HTK, histidine-tryptophan-ketoglutarate; MDN, modified del Nido; PO, postoperative.

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AI, anaesthetic induction; DN, del Nido; hs-cTnT, high-sensitivity cardiac troponin T; HTK, histidine-tryptophan-ketoglutarate; MDN, modified del Nido.

Figure 2 Interaction between cardioplegia type and time for high-sensitivity cardiac troponin T. Serial hs-cTnT concentrations (ng/L) at anaesthetic induction and 2, 12 and 24 hours postoperatively in patients undergoing elective cardiac surgery with single-dose cardioplegia (HTK, blue; DN, red; MDN, green). The DN group showed significantly lower hs-cTnT at 2 hours (p=0.028), suggesting reduced early myocardial injury. PO, postoperative.

similar across groups before cardioplegia infusion. All cardioplegic solutions produced a postoperative increase in hs-cTnT, peaking between 12 and 24 hours after CPB. A significant interaction between solution type and time was observed (p=0.028), mainly due to lower hs-cTnT levels at 2 hours in the DN group (828±86 ng/L) compared with HTK (1286±216 ng/L) and MDN (1199±155 ng/L; p=0.023). At later time points, troponin concentrations converged among the groups, with DN and HTK showing similar kinetics through 24 hours, while MDN demonstrated a gradual decline between 12 and 24 hours.

No significant intergroup differences were found in other biochemical or metabolic variables, including creatine kinase, glucose, lactate, pH, bicarbonate, calcium, haematocrit or inflammatory markers. In the immediate postoperative period, patients receiving HTK showed lower sodium and potassium concentrations (p=0.049 and p=0.002, respectively), consistent with the dilutional effect of its crystalloid composition. These transient changes normalised by 24 hours and were not clinically relevant. Additional haematological parameters are presented in online supplemental table S2.

Secondary perioperative outcomes

These outcomes are summarised in the text, with detailed data provided as online supplemental material.

Intraoperative variables are presented in online supplemental table S3. All three cardioplegic regimens achieved effective myocardial arrest, with similar CPB and aortic cross-clamp times. Patients who received DN, either in its original or modified formulation, had a greater tendency for spontaneous rhythm recovery without the need for defibrillation (30.3% vs 54.5% in HTK; p=0.065), supporting the biochemical findings of reduced reperfusion injury. No differences were observed between groups in the use of the IABP, VIS or temporary pacemaker during the intraoperative phase. Transfusion requirements differed significantly between groups: 78.8% of HTK patients required intraoperative blood transfusion compared with 42.4% for DN and 66.7% for MDN (p=0.008; online supplemental table S3). This finding is consistent with the smaller haematocrit reduction observed in DN patients (table 2), suggesting reduced haemodilution associated with lower infusion volumes. Detailed transfusion criteria are provided in online supplemental table S4.

Postoperative intensive-care outcomes are summarised in online supplemental table S5. Transfusion requirements, bleeding volumes, duration of mechanical ventilation, vasoactive-drug support, IABP use and major postoperative complications, including AMI, stroke, atrial fibrillation and flutter, tamponade and AKI requiring dialysis, were comparable across cardioplegia strategies, with none reaching statistical significance.

Overall postoperative outcomes were comparable across cardioplegia strategies (online supplemental table S6). ICU and hospital length of stay, 30-day mortality, changes in LVEF and major postoperative complications, including AMI, arrhythmia, dialysis and reoperation, were similar between groups. Kaplan-Meier analysis showed no significant difference in survival (log-rank p=0.753; online supplemental figure S1), with non-significant HRs in both unadjusted and adjusted models.

DISCUSSION

This randomised, double-blind clinical trial compared the myocardial protection afforded by three single-dose cardioplegic solutions — HTK, DN and MDN — in adults undergoing elective cardiac surgery. All regimens were safe and effective,

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yielding comparable biochemical and clinical outcomes. DN was associated with lower early postoperative troponin release and reduced transfusion requirements, whereas HTK produced transient electrolyte changes; however, these differences were modest and clinically insignificant.

The main strengths of this trial include its randomised, double-blind design, strict intraoperative standardisation and the use of hs-cTnT as the primary endpoint, allowing precise detection of myocardial injury.[10 11] The study directly compared three of the most widely used single-dose solutions within a single institutional protocol, thereby minimising performance bias. Limitations include its single-centre setting, a sample size powered for biochemical rather than clinical outcomes, and the absence of immediate postoperative echocardiography due to institutional logistical constraints; postoperative assessments were conducted within 7 days, potentially underestimating transient left ventricular dysfunction. In addition, the lack of formal adjustment for multiplicity despite the large number of outcomes and time points analysed may increase the risk of type I error; when stringent adjustment methods, such as the Holm-Bonferroni procedure are applied, some statistically significant findings ($p<0.05$) are not maintained. Therefore, the results, while highlighting clinically relevant trends, should be interpreted with caution and considered exploratory, serving as a basis for future studies incorporating appropriate multiplicity adjustments for secondary outcomes.[15]

The biochemical and clinical findings of this trial are consistent with previous evidence comparing single-dose cardioplegic solutions. Myocardial injury, assessed by postoperative hs-cTnT,[16] increased in all groups following CPB, peaking between 12 and 24 hours, in line with expected reperfusion patterns. The transiently lower levels observed with DN at 2 hours suggest reduced early injury but without apparent meaningful clinical impact, consistent with prior studies showing similar troponin kinetics between DN and HTK.[1 7 16–19]

All regimens ensured effective myocardial arrest with comparable cross-clamp and CPB times. The higher rate of spontaneous rhythm recovery observed with DN and MDN aligns with meta-analyses reporting improved electrical recovery and fewer defibrillation requirements compared with conventional solutions.[16] Similarly, in other recently published articles,[18 20] the use of HTK was also associated with an increased risk of reperfusion fibrillation. Although transfusion was not a prespecified primary outcome and should therefore be interpreted cautiously, transfusion needs were lower in the DN group, in line with earlier reports linking its smaller volume and reduced haemodilution[21] to fewer blood product requirements and shorter ICU stays.[22–24] The transient reductions in sodium and potassium observed with HTK reflect its low electrolyte content and high infusion volume, as reported previously,[25–29] but had no evident clinical consequences.

Overall postoperative outcomes were similar across groups, including arrhythmias, VIS, AMI, stroke and AKI, confirming the safety and equivalence of all three solutions.[25–27] The Kaplan-Meier analysis demonstrated no survival differences, even after adjustment for transfusion, aligning with recent meta-analyses showing equivalent mortality among DN, HTK and blood cardioplegia.[28]

These findings reinforce that myocardial protection in adult cardiac surgery can be safely and effectively achieved with any of the evaluated single-dose cardioplegic solutions when administered according to protocol. DN offers practical advantages, including simpler administration and reduced transfusion requirements, while the modified formulation using Ringer's lactate provides an equivalent, feasible alternative when Plasma-Lyte is unavailable.[4 30] HTK remains appropriate but should be used cautiously in patients prone to electrolyte imbalance. Overall, the comparable outcomes support a pragmatic approach, allowing institutions to select cardioplegia based on experience, logistics and patient characteristics, while favouring the interchangeability of single-dose strategies and offering flexibility in procurement and standardisation without appearing to compromise clinical performance or patient safety.

Future multicentre studies with long-term follow-up are warranted to confirm these results and assess their applicability to urgent, complex and redo procedures. Comparative cost-effectiveness analyses and histological correlates from myocardial tissue may provide further insight into mechanisms of protection and guide optimisation of cardioplegic formulations. Importantly, as Allen[5] has noted, future research should also address postoperative ventricular septal function, as the ultimate goal of myocardial protection is not merely to identify a superior solution but to eliminate any biochemical or functional evidence of myocardial injury.

CONCLUSIONS

In adults undergoing elective cardiac surgery, single-dose cardioplegic solutions (HTK, DN and MDN) were associated with similar postoperative hs-cTnT profiles, with no sustained differences in biochemical markers of myocardial injury across strategies. None of the approaches demonstrated clear superiority in preventing postoperative myocardial injury or preserving left ventricular function across the perioperative period. DN cardioplegia was associated with a transient reduction in troponin release 2 hours after CPB, but this difference was not maintained at later time points, and with fewer intraoperative transfusions, whereas HTK produced transient electrolyte changes without apparent adverse clinical consequences. Accordingly, perioperative clinical findings should be interpreted cautiously, regarded as exploratory and hypothesis-generating. Overall, these findings suggest that different single-dose cardioplegic approaches may achieve adequate myocardial protection when applied within a standardised surgical protocol, allowing selection based on institutional availability, cost and patient characteristics. Larger multicentre trials powered for clinical endpoints are needed to determine whether clinically meaningful differences exist between cardioplegic strategies.

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