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Comparison between Custodiol, del Nido and modified del Nido in the myocardial protection - Cardioplegia Trial: a study protocol for a randomised, double-blind clinical trial

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ABSTRACT

Introduction Myocardial protection is essential for successful cardiac surgery, and the search for an ideal cardioplegic solution has continued since its beginning. In this context, Custodiol, del Nido and modified del Nido are single-dose cardioplegic solutions with good safety profiles and great relevance in modern surgical practice. While these solutions have all been evaluated for their impact on patient outcomes independently, limited research exists comparing them directly. Thus, the present study aims to examine the effects of these cardioplegic solutions on myocardial protection and clinical outcomes in adult patients undergoing elective cardiac surgery. The assessment of the increase in myocardial injury biomarkers in patients submitted to all treatment methods may be considered a major strength of our study.

Methods and analysis This is a clinical trial study protocol that will compare myocardial protection and clinical outcomes among three patient groups based on which cardioplegic solution was used. Patients will be randomised to receive del Nido (n=30), modified del Nido (n=30) or Custodiol (n=30). Myocardial injury biomarkers will be measured at the baseline and 2 hours, 12 hours and 24 hours after the cardiopulmonary bypass. Clinical outcomes will be assessed during the trans operative period and the intensive care unit stay, in addition to other haematological parameters.

Ethics and dissemination This protocol and its related documents were approved by the Research Ethics Committee of the Hospital Nossa Senhora da Conceição, Brazil, registered under no. 4.029.545. The findings of this study will be published in a peer-reviewed journal in the related field.

Trial registration number RBR-7g5s66.

Strengths and limitations of this study

- This is one of the first prospective randomised clinical trials comparing myocardial damage and clinical outcomes between Custodiol, del Nido and modified del Nido cardioplegic solutions.
- The assessment of the increase in myocardial injury biomarkers in patients submitted to all treatment methods may be considered a major strength of our study.
- The broad inclusion criteria will increase generalisability and may also make it possible to evaluate subgroups of interest.
- This trial will be performed at a single centre.
- This is a study with an insufficient sample for rare events.

INTRODUCTION

Cardiac surgery procedures usually involve using cardiopulmonary bypass (CPB) and cardiac arrest, and, in consequence, myocardial protection is essential.[1] Failure to adequately protect the heart may lead to severe adverse consequences, including myocardial infarction (MI), ischaemia-reperfusion injury and low-output cardiac syndrome. Such complications are associated with more extended stays in the intensive care unit (ICU), congestive heart failure and increased perioperative mortality.[2]

Cardioplegia is a fundamental component in providing heart protection, limiting metabolic activity and increasing the myocardium's capacity to resist ischaemia for prolonged periods, thus being essential for good surgical outcomes. Seeking an ideal solution, long-acting cardioplegic solutions were introduced[3] with two primary benefits: (1) in more complex or minimally invasive cardiac surgeries, the application of cardioplegia in a single dose avoids procedure interruptions, reducing the aortic cross-clamping time[3 4] and (2) patients submitted to cardiac surgery

still suffer from postoperative cardiac dysfunction, with it being postulated that single-dose cardioplegia would protect the heart more effectively.[3]

The histidine-tryptophan-ketoglutarate solution or Custodiol (Essential Pharmaceuticals, Ewing, New Jersey, USA) was described by Bretschneider in the 1970s[5] and conceived as an alternative to hyperkalaemic crystalloid cardioplegic solutions[6 7] used by some centres for myocardial protection in complex cardiac surgery and for organ preservation in transplant surgery.[8] The del Nido cardioplegia was developed by Pedro del Nido and his team at the University of Pittsburgh in the 1990s,[1 9 10] having been used since 1994 for paediatric cardiac surgery at the Boston Children's Hospital and also used successfully in adults since 2003.[1 11–16] The base solution for del Nido cardioplegia is usually Plasma-Lyte A (Baxter Healthcare Corporation, Deerfield, Illinois, USA), which has an electrolyte composition similar to the extracellular fluid and is calcium-free. More recently, some authors have advocated[17] the use of traditional del Nido cardioplegia ingredients added to lactated Ringer's solution, as the base solution provided either similar or superior myocardial protection than the blood cardioplegia strategy. Both, Custodiol and del Nido, be it traditional or modified, are associated with safe single-dose administration and capable of proper myocardial protection for prolonged periods during ischaemia in CPB, allowing the performance of uninterrupted procedures.[3 8 10 18–21]

Thus far, there are no guidelines regarding using of a specific solution, and the literature does not confirm the superiority of one over the others.[1] The standardisation of the method or ideal type of cardioplegic solution remains controversial due to the scarcity of studies clearly outlining the advantages and disadvantages of the available solutions. While each of these solutions has been evaluated for their impact on patient outcomes independently, limited research is available comparing them directly. Thus, the present study aims to examine the effects of Custodiol and traditional or modified del Nido, cardioplegic solutions, all with good safety profiles and great relevance in modern surgical practice, on myocardial protection and clinical outcomes in patients undergoing cardiac surgery.

METHODS AND ANALYSIS

The study protocol was developed following the Standard Protocol Items: Recommendations for Interventional Trials checklist,[22] provided in online supplemental file 1. This study's approach will be based on the Consolidated Standards of Reporting Trials.[23]

Study design

A randomised, double-blinded, clinical trial study will be carried out at the Hospital Nossa Senhora da Conceição, a tertiary referral hospital in Cardiovascular Surgery in southern Brazil, to compare the effects of cardioplegic solutions—Custodiol, del Nido and modified del Nido—on myocardial protection and perioperative outcomes. The study design is shown in figure 1.

Patient and public involvement statement

The patients or the public will not be involved in the design, recruitment or conduction of the study.

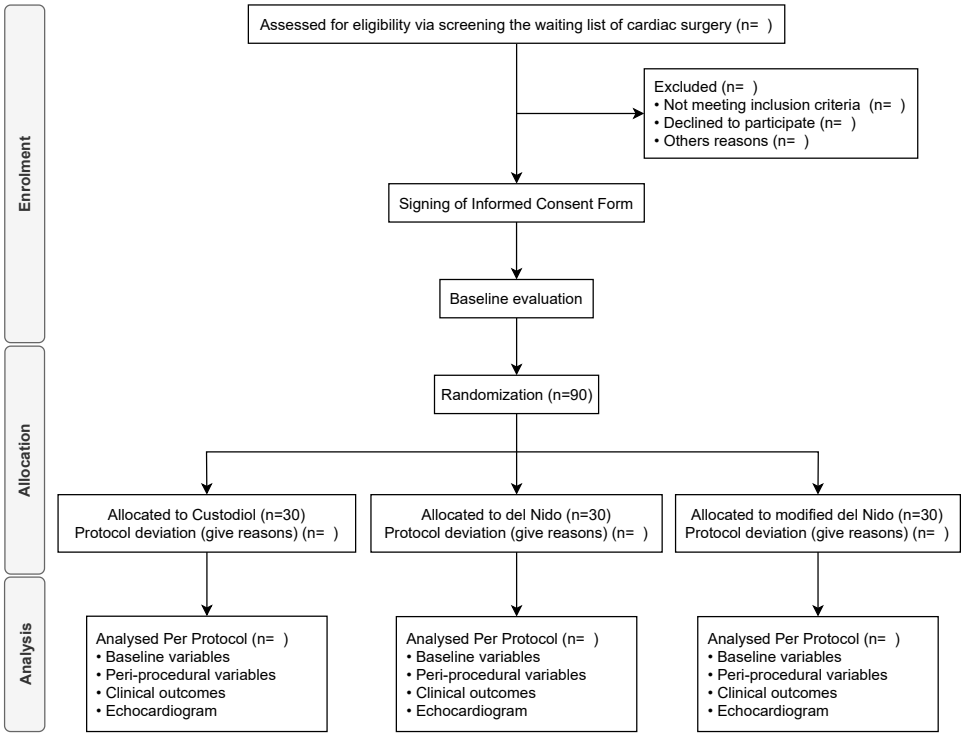

Figure 1 Consort diagram: flow of the participants throughout the study.

Eligibility criteria

Subject inclusion and exclusion criteria are defined as follows. The study centre was chosen by convenience, and the eligibility criteria were defined a priori by care providers.

Patients referred for elective valve replacement surgery or coronary artery bypass grafting surgery aged at least 18 years will be enrolled. Patients with chronic renal disease (previous medical diagnosis or serum creatinine greater than 1.5 mg/dL), previous cardiac surgery, severe psychiatric illness, or inability or unwillingness to give informed consent for participation will be excluded.

Interventions

Adult patients undergoing elective myocardial revascularisation surgery or valve replacement will be randomised to receive cardioplegic solutions del Nido (using Plasma-Lyte A as the base solution), modified del Nido (using lactated Ringer's as the base solution) or Custodiol during CPB. They will be followed up for evaluating the effectiveness of the treatments initially proposed.

Surgical technique

Conventional general anaesthesia will be used for all patients. The surgical approach will be via median sternotomy. The CPB will be established by an arterial cannula in the ascending aorta or femoral artery. Venous drainage will be obtained via a two-stage cannula in the right atrium or bicaval cannulation through the superior and inferior vena cavae or femoral vein. Under CPB and aortic cross-clamping, cardioplegic arrest will be induced.

Myocardial protection: preparation and handling of the solutions

The cardioplegic solutions will be administered anterogradely, at the root of the aorta or coronary ostia, as per specific indication.

All solutions will be prepared by the perfusionist, the professional responsible for conducting CPB, according to the standardised aseptic techniques routinised in the Cardiovascular Surgery Service, without any difference from what was habitually used before the beginning of the study since these solutions are already standardised and correctly employed at the institution.

Custodiol cardioplegia is a sterile prepackaged solution that does not require preparation since it comes ready for infusion. The composition of this solution may be observed in table 1.[8] This solution will be administered in a single dose of 25 mL/kg over 6–8 min at a temperature of 4°C–8°C with a perfusion pressure of 150–200 mm Hg and the possibility of an additional dose only after 3 hours of the first.

The del Nido and modified del Nido solutions will be manipulated at the Service moments before their administration, and either Plasma-Lyte A or the lactated Ringer's solution (modified del Nido) was used as the crystalloid base. The crystalloid:autologous blood ratio is 4:1. The composition made into a protocol at the Institution may also be observed in table 2. The solutions will be administered through a single dose of 20 mL/kg (maximum of 1000 mL for patients weighing over 50 kg), usually with a delivery temperature of 4°C, system pressure of 100–200 mm Hg, and an administration flow of 200–300 mL/min.[1] If necessary, additional doses will be infused after 90 min of the initial one.[1]

The nature of cardioplegic solutions del Nido and Custodiol is distinct in terms of their vehicles (blood and crystalloid, respectively) and electrolytic compositions (extracellular and intracellular, respectively), differing in the cardiac arrest mechanism (del Nido causes a depolarising arrest, while Custodiol causes a hyperpolarising arrest).

Table 1 Custodiol composition

Composition	
Sodium chloride	15.0 mmol/L
Potassium chloride	9.0 mmol/L
Magnesium chloride	4.0 mmol/L
Calcium chloride	0.015 mmol/L
Histidine	180.0 mmol/L
Tryptophan	2.0 mmol/L
Ketoglutarate	1.0 mmol/L
Mannitol	30.0 mmol/L
pH	7.02–7.20 at 25°C (77.0 °F) 7.4–7.45 at 4°C (39.2 °F) Osmolality: 310 mosmol/Kg

Outcomes

Primary outcome

The primary outcome will be to assess myocardial protection between cardioplegic solutions Custodiol, del Nido and modified del Nido using the serum levels of cardiac enzymes, including creatine kinase (CK), CK isoenzyme MB (CK-MB) and troponin in the immediate postoperative period as well as 12 hours and 24 hours after the CPB.

Secondary outcomes

The secondary outcomes include:

Table 2 Compositions of del Nido cardioplegia

del Nido cardioplegia (1:4)	
Composition	
Plasma-Lyte A or Lactated Ringer's solution	1000 mL
Sodium bicarbonate 1 mEq/mL	13 mL
Mannitol (20%)	16.3 mL
Magnesium sulfate (50%)	4 mL
Lidocaine (1%)	13 mL
Potassium chloride 2 mEq/mL	13 mL
Dose 20 mL/kg with a maximum dose of 1000 mL for patients weighing more than 50 Kg	

	Study Period					
	Enrolment	Allocation	Post-allocation			Close-out
Time point	Interviews	Following confirmation of eligibility to day of surgery	Day of surgery	0-24h Post op	Post op onwards until discharge	Discharge or 30 days after enrolment
Enrolment						
Eligibility screen	X					
Informed consent	X					
Demographic data	X					
Anthropometric data	X					
Clinical data	X					
Allocation (randomization)		X				
Interventions						
Custodiol			X			
del Nido			X			
del Nido modificado			X			
Assessments						
Baseline variables		X	X			
Peri-procedural variables			X	X	X	
Clinical outcomes			X	X	X	X
Echocardiogram	X					X

Figure 2 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrolment, interventions and assessments.

1. Assessments of additional myocardial protection measures: incidence of ventricular fibrillation requiring electrical defibrillation after aortic cross-clamp removal, postoperative changes in the left ventricular ejection fraction (LVEF) and in the ventricular septal function, blood gas analysis, duration of inotrope or vasopressor requirement and requirement for intra-aortic balloon pump (IABP) support.
2. Intraoperative outcomes: total volume of cardioplegia and number of doses, total aortic cross-clamp time and CPB.
3. Clinical outcomes: ICU stay, prolonged ventilation (over 24 hours), the incidence of postoperative atrial fibrillation (AF) or flutter, acute MI, mortality and blood products transfusion.
4. Comparisons among cardioplegic solutions regarding the prediction of major cardiovascular events in adult patients undergoing cardiac surgery.

Participant timeline

The schedule for enrolment, interventions and assessments is outlined in figure 2. The recruitment of study participants began in 15 July 2020.

Sample size

The sample size calculation was performed using the G-Power program V.3.1.9.4. Considering an effect f=0.466 on troponin levels based on the study by Talwar *et al*,[24] maintaining a 95% statistical power and a 5% significance, it would be necessary to investigate 75 patients. Thus, with an additional 20% to account for potential losses, 90 individuals will be selected for the study, with 30 randomised for each group.

Recruitment and allocation

Candidate patients for cardiac surgery will be identified at the point of referral or from the inpatient waiting list by the clinical team and approached by a research team member about participation in the study. After consent, the eligible patients will be randomised to receive Custodiol, del Nido or modified del Nido following confirmation of eligibility.

Randomisation

The patients will be randomised in blocks to receive the del Nido, modified del Nido or Custodiol solutions during CPB, with a sequence generated by website randomizer.org and the numbers being placed in opaque envelopes and sealed individually.

Blinding

On the same day of surgery and before anaesthetic induction, the perfusionist will receive the opaque and sealed envelope indicating the cardioplegic solution to be prepared and administered according to its particularities.

All the patients, anaesthetists, echocardiographers, nurses and laboratory staff will be blinded to the type of intervention.

Since the Custodiol infusion requires an administration time and interval between doses different from the del Nido solution, the surgical team will only be blinded to the intervention with del Nido or modified del Nido, besides not participating in the analysis of the results to avoid measurement biases. There is no possibility of standardising the volume of the solutions, administration times and interval between doses due to the potential increase in risk for the patients.

After surgery, all patients will be transferred to the ICU, intended for the recovery of patients submitted to cardiac surgery, and monitored by a team with postoperative expertise in the specialty, according to the standard institutional protocols, blinded to the type of cardioplegia administered during the surgery. After discharge from the ICU, these patients will be transferred to the postoperative cardiology unit, where they will be managed until hospital discharge by the team responsible, according to standard protocols, also blinded to the type of intervention.

Moreover, the lead investigator, who will identify the outcomes and perform the statistical analyses, will be blinded to the type of intervention used in each case.

All deaths or complications, be they cardiovascular or not, reported during the conduction of the study will be analysed. All researchers involved in the adjudication process will remain blind to the allocation of the patients regarding the type of intervention. The adjudicated data will be used in the final analysis of safety and efficacy.

Data collection methods

Baseline assessments

The baseline interviews pertaining to demographic, anthropometric and clinical data using a standardised questionnaire will be recorded during the enrolment process, following consent and before the randomisation. Demographic data include age, gender and education

level. Anthropometric data include weight, height and body mass index. Clinical data include diseases, treatment information, medical history and medications at the time, as well as preoperative laboratory work, an echocardiogram and coronary angiography. Venous blood samples will be collected to measure the lipid profile, blood count, serum electrolyte levels (Na+, K+), blood gas analysis, C reactive protein, creatinine, urea and glucose.

Diabetes mellitus will be defined as a patient's self-report of a physician's diagnosis or use of hypoglycaemic agents or insulin. Three blood pressure measurements will be taken using a validated automatic device according to guidelines.[25] Hypertension will be defined as the average of the last two among three blood pressure measurements greater than 140/90 mm Hg, or the use of blood pressure-lowering medication.

The estimated surgical risk will be calculated before the randomisation by the EuroSCORE (European System for Cardiac Operative Risk Evaluation), Society of Thoracic Surgery (STS) Score and Ambler, available online: http://www.euroscore.org; http://riskcalc.sts.org/stswebriskcalc/calculate and https://wwwthecalculatorco/health/Heart-Valve-Surgery-Risk-Calculator-1107html. Note: the STS Score allows calculating isolated surgeries for aortic and mitral valve replacement; combined surgery cannot be included in the STS, only in the Ambler.

Laboratory assessment

Arterial blood will be collected from patients to perform serum troponin and CK-MB tests, in addition to blood count, glucose, C reactive protein, lactate, and blood gas measurements, at four scheduled times: before anaesthesia induction, and 2 hours, 12 hours and 24 hours after the discontinuation of CPB.[9]

Laboratory measurements will be performed by the clinical diagnostic laboratory of the hospital, and the devices will be checked and calibrated as part of the daily laboratory practice. The laboratory staff will be unaware of the groups to which each patient is assigned.

Echocardiogram

The calculated LVEF and ventricular septal function will be assessed using transthoracic echocardiography at two different times: during enrolment and on the seventh postoperative day. The echocardiography exams will be performed by the hospital diagnostic service with standardised equipment and techniques for all patients.

Clinical outcomes

A predefined team of researchers will monitor clinical or surgical outcomes during the transoperative period and the ICU stay.

Other parameters of cross-clamp time, CPB time, the total volume of cardioplegia and number of doses, mechanical ventilation, haemodynamic parameters, transfusion of blood and blood products, the requirement for IABP support and the use of inotropes will be recorded.

Outcomes after surgical treatment defined before the analysis, including mortality, MI, stroke, the incidence of blood products transfusion, as well as prolonged ventilation (over 24 hours) and ICU stay, will be compared among groups. In addition, we will compare, among the groups, the proportion of patients experiencing postoperative new-onset AF or flutter requiring treatment, heart block and ventricular tachycardia or fibrillation requiring cardioversion or intravenous amiodarone.

MI will be diagnosed by increasing cardiac biomarkers in the presence of symptoms or ECG abnormalities suggestive of ischaemia.[26 27]

Strokes will be diagnosed by CT scanning and compatible clinical findings, besides medical record reviews.[28 29]

Deaths will be classified according to the Atherosclerosis Risk in Communities Study protocol.[26]

Data management

The data will be managed by study investigators using a predesigned data collection form and SPSS files V.26.0 (IBM) with double data entry.

Data checks will be performed regularly to ensure data quality. Patients will be identified by codes to ensure their anonymity, and only the authors involved in the trial will have access to their full identification details.

The total number of patients meeting the eligibility criteria of the study will be recorded, as well as the number of patients agreeing or not to participate in the study, the number of patients assigned to each branch of the study, the number of patients attending all sessions, the number of patients included in the final analysis and the number of withdrawals.

Statistical analysis

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

To compare means among groups, a one-way analysis of variance with Tukey's post hoc analysis will be applied. In case of asymmetry, the Kruskal-Wallis test complemented by the Dunn test shall be used. In order to compare proportions among groups, Pearson's χ^2 test complemented by the adjusted residual test shall be applied.

A generalised estimating equations model will be used to compare the parameters over the follow-up time among the groups, complemented by the Bonferroni test. A linear model will be used for variables with normal distribution and the gamma model for those with asymmetric distribution.

The significance level adopted will be 5%, and the data will be analysed using the SPSS V.26.0.

Safety and data monitoring

Although the natures of the del Nido and Custodiol cardioplegic solutions are different regarding their cardiac arrest mechanisms, both are associated with safe

single-dose administration and capable of preserving the myocardium for a prolonged period during ischaemia in CPB.[3 8 10]

The outcomes will be audited by the lead investigator every five interventions or earlier if serious adverse postoperative events are recorded.

Adverse events will be evaluated by the study investigators, who will decide to stop the study early if there is a clinically relevant increased risk.

All data will be evaluated by at least two authors independently, with quality control on data entry to verify amplitude and consistency. For quality control of the team's performance, 20% of the protocols will be randomly selected for review by the lead investigator.

ETHICS AND DISSEMINATION

Registered under no. 4.029.545, this study protocol and its related documents were approved by the Research Ethics Committee of the Hospital Nossa Senhora da Conceição, which is accredited by the Office of Human Research Protections as an institutional review board. This study will be conducted following the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All participants will provide informed consent (online supplemental file 2). During the preclinical assessment, investigators will explain all study details. When it is not possible to obtain consent for whatever reason, the patient cannot be involved. It will be ensured to the volunteer the right not to participate, without this representing any prejudice to their care within the institution.

Any modifications that could impact the conduction of the study, such as changes to the objective, design, sample or significant administrative aspects, will require a formal request for amendment with the institutional research ethics committee.

Regarding privacy and confidentiality, the preservation of patient anonymity and the use of data obtained in the research only for the purpose of the project are guaranteed.

The findings of this study will be submitted to a peer-reviewed journal for publication and presented at relevant medical conferences.

Data availability statement

The datasets generated and used during this study are available from the corresponding author on reasonable request.

The technical appendix, statistical code and dataset may be available on the completion of the trial from the Dryad or a similar repository.

DISCUSSION

Potential impact and significance of the clinical trial

This project was developed through extensive bibliographic research on a subject of great importance in daily surgical practice. The interpretation of the results published in several studies enabled the development of this well-structured protocol.

Optimal myocardial protection during cardiac surgery is one of the main components of a successful procedure. Since the 1950s,[30 31] many strategies have continuously been developed to improve myocardial protection and prevent further ischaemic injury. Over the past few decades, there have been no standardised guidelines for using cardioplegic solutions, and prolonged-action or single-dose solutions seem closer than expected to an ideal solution.

Talwar *et al*[24] randomised 100 paediatric patients submitted to elective surgical correction of Fallot's tetralogy to receive cardioplegic solutions del Nido or Custodiol. The first was associated with the better preservation of the cardiac index, shorter mechanical ventilation time, shorter stay at the ICU and the hospital, better cardiac output, lower inotropic scores and lower release of troponin-I. Electronic microscopy evinced less myocardium oedema and better preservation of the myofibrillar architecture and glycogen storage in the group that received del Nido. In another clinical trial, Mehrabanian *et al*[32] randomised 40 patients to receive one of these cardioplegic solutions, concluding that both offer effective and similar cardioprotective properties during CPB in adults. The authors did not show any significant differences in CPB time, cross-clamp duration, urine output, chest tube drainage, duration of mechanical ventilation, ICU stay, mean arterial pressure, LVEF, use of blood products and inotropic support. Blood chemistry parameters and blood gas analysis revealed a similar trend between the groups except for sodium levels after cardioplegia and the end of CPB, potassium levels after cardioplegia, and bicarbonate anions at the end of the bypass, with lower results in the Custodiol group compared with the del Nido group.

In several studies, patients who received del Nido had lower ventricular fibrillation rates after aortic cross-clamp removals than those who received conventional blood cardioplegia,[4 9 12 33–35] in addition to lower CK-MB values,[34] lower glucose levels during CPB[35–37] or less use of postoperative intravenous insulin,[34] less need for transoperative inotropic support and lower troponin levels,[9] suggesting better myocardial protection with this solution.

The base solution for the del Nido cardioplegia is Plasma-Lyte A, which is unfortunately unavailable in many countries, precluding many cardiac centres from using del Nido cardioplegia with their typical base solution. Kantathut *et al*[17] published an observational study that evaluated myocardial preservation and clinical outcomes when using the lactated Ringer's solution as the base solution for the del Nido cardioplegia compared with the standard blood cardioplegia strategy (St. Thomas cardioplegia). The group that received the modified del Nido stayed at the ICU and the hospital for a shorter time, showing a lower use of inotropic support and a lower incidence of postoperative fibrillation or flutter. These results

make the lactated Ringer's solution seem like an excellent alternative to Plasma-Lyte A in the del Nido formulation for adult patient surgeries.

Hence, the del Nido cardioplegic solution seems highly efficient both for myocardial protection and regarding the economic aspects. However, extensive literature comparing its use with that of Custodiol does not exist, especially with the addition of the lactated Ringer's solution to its formulation. Therefore, it is necessary to conduct prospective and randomised studies to prove the hypothesis of the superiority of this cardioplegia over the others in terms of myocardial protection in adult patients.[1 12]

Clinical applicability

The results obtained in the proposed clinical trial may provide subsidies via publication to implement and insert clinical protocols in many institutions, increasing safety and reducing expenses. In addition, despite being performed in a single centre, the clinical practice of our hospital reflects the standard of practice in our country and may contribute to the international assessment of the cardioplegic solution with the best profile for reducing myocardial injury.

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Contributors ASA, ROC, FA, LK, KBL, RSD, JR and RAWR contributed to the conceptualisation, study design, proposal development, methodology, validation, resources, writing-original draft, writing-review, editing and visualisation. ASA is also responsible for data curation and supervision. KBL and RSD are also involved in recruitment and data collection. EIW and ARR are involved in the clinical follow-up in the preoperative and postoperative period, as well as in requesting and reviewing tests necessary for research at this stage. All authors have read and approved the final version to be published and agreed to be accountable for all aspects of the work.

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