



Del Nido cardioplegia is a cost-effective alternative to custodiol for myocardial protection in aortic valve surgery: A real-world study

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Abstract

Introduction: Myocardial protection is crucial in heart surgery to minimize ischemia-reperfusion injury. Del Nido cardioplegia has demonstrated clinical advantages; however, cost-effectiveness data over Custodiol remain scarce. We aimed to assess whether Del Nido could achieve comparable clinical outcomes at lower costs.

Methods: A retrospective single-center study was conducted on patients ≥ 18 years undergoing isolated surgical aortic valve replacement between 2009–2023. Patients received either Custodiol or Del Nido cardioplegia at the discretion of the surgical team. 30-day major adverse cardiac events (MACE) outcomes were extracted from medical records. Cost data was collected from hospital records. Inverse probability of treatment weighting (IPTW) was applied to balance baseline characteristics and mitigate indication bias. Incremental cost-effectiveness ratios (ICERs) were calculated, and probabilistic sensitivity analyses were performed using Monte Carlo simulations.

Results: 179 patients were included (58 Custodiol, 121 Del Nido). While both alternatives had similar 30-day survival (98.3%) and MACE-free survival (88.4% vs. 89.7%), the cost for Del Nido was lower (41,761 USD vs. 47,599 USD). Using the IPTW-weighted sample, an ICER of 123,363 USD for Custodiol favored Del Nido, particularly under local willingness-to-pay thresholds of 6,947–20,841 USD. Probabilistic sensitivity analyses confirmed the robustness of these findings, with Del Nido being cost-effective in up to 75.5% simulations.

Conclusions: Del Nido cardioplegia offers a cost-effective alternative to Custodiol, providing similar clinical outcomes at lower costs. These findings support the adoption of Del Nido in resource-limited settings, emphasizing value-based care in cardiac surgery.

Keywords

cardioplegia, cost-effectiveness, custodiol, del nido, histidine-tryptophan-ketoglutarate, latin America

Introduction

Aortic valve surgery is a cornerstone treatment for patients with severe aortic valve disease, improving survival and quality of life. Effective myocardial protection is crucial during these procedures to minimize ischemia-reperfusion injury and optimize postoperative recovery.¹ Custodiol cardioplegia (histidine-tryptophan-ketoglutarate (HTK) solution) has been the preferred solution for myocardial protection in many surgical centers worldwide for decades due to its simplicity and prolonged single-dose application.² Del Nido cardioplegia, originally developed for pediatric cardiac surgery, has gained traction as an alternative cardioplegia solution in adult cardiac procedures

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due to its low viscosity, reduced calcium load, and prolonged myocardial protection.³

In clinical practice, the choice between Custodioli and Del Nido often depends less on evidence-based recommendations and more on institutional preference, surgeon familiarity, and solution availability. Despite its lower costs and accumulating evidence suggesting that Del Nido provides comparable myocardial protection and postoperative outcomes to Custodioli in adult cardiac surgery,^{4,5,6,7} many centers continue to routinely use Custodioli. Current guidelines or expert consensus statements do not specifically favor one solution over the other.⁸

While several studies have compared the clinical and biochemical outcomes of these two solutions, the economic implications of selecting one over the other have not been explored.⁹ To date, there are no published cost-effectiveness analyses directly comparing both solutions, which is particularly relevant in resource-limited settings.¹⁰ Additionally, the generalizability of existing studies is hampered by methodological variability and a lack of robust statistical techniques to address confounding factors such as differences in patient characteristics, surgical practices, and healthcare costs.^{5,6,7,11,12} These gaps hinder evidence-based decision-making on the optimal cardioplegia strategy in adult aortic valve surgery.

To address these issues, this study investigates whether Del Nido cardioplegia is a cost-effective alternative to Custodioli for myocardial protection during aortic valve surgery in a Colombian healthcare setting. Using inverse probability of treatment weighting (IPTW)¹³ to balance baseline differences, our primary research questions addressed whether Del Nido achieves comparable or superior clinical real-world outcomes at a lower cost and meets cost-effectiveness thresholds under varying willingness-to-pay (WTP) scenarios. This analysis provides evidence on the real-world relative cost-effectiveness of these strategies, guiding policymakers and clinicians in optimizing resource allocation for cardiac surgery in Colombia and similar sociodemographic contexts.

Materials and methods

Study design and population

This is a single-center, retrospective cost-effectiveness analysis from the healthcare system perspective. All adult patients (≥ 18 years) who underwent isolated surgical aortic valve replacement with cardiopulmonary bypass using either Del Nido or Custodioli cardioplegia at Clínica Universitaria Colombia, a referral hospital in Bogotá, Colombia, between 2009 and 2023 were included. All surgeries were performed by a team of four surgeons, with two surgeons participating in each procedure (one as the primary surgeon and the other as an assistant). Those

patients with a history of prior cardiac surgery, use of Plegisol, a minimally invasive technique, moderate to high surgical risk (EuroSCORE $>5\%$), or a follow-up period of less than 1 year were excluded.

Cost-effectiveness analysis

Costs. The cost-effective analysis was conducted from the healthcare system perspective, specifically the payer's viewpoint, to reflect the direct medical costs of inpatient care. Cost data were obtained from the hospital's Diagnosis-Related Groups division, containing resources consumed during 2023, the most recent year with available data. As the cost data were collected within 1 year, no discount rate was applied. Costs were calculated at the patient level, capturing the total cost of the surgical episode, including operating room resources, prosthetic valves, medications, ICU and ward stay, and management of postoperative complications. The cost of the implanted prosthetic valve was inherently incorporated into the patient-level total hospitalization cost used in the cost analysis.

Particularly for Custodioli, costs included the HTK solution and cannulas, while for Del Nido, costs included solution components (Plasma-Lyte, lidocaine, potassium chloride, sodium bicarbonate, magnesium sulfate, and mannitol) and cannulas (see [Supplementary Table S1](#)). Costs are expressed in Colombian pesos and converted to USD using purchasing power parity (PPP) for 2023 (conversion factor = 1.401).¹⁴

Although this approach implies that 2009 patients were assigned present-day costs, it reflects a standard practice in cost-effectiveness analyses using retrospective data. The underlying assumption is that, if those patients were treated under current price conditions, their resource use patterns would be comparable, allowing for meaningful evaluation of the relative economic performance of both cardioplegia strategies.

Outcomes. The primary outcome assessed was MACE-free survival, defined as a composite of all-cause mortality, myocardial infarction, stroke, reoperation for bleeding, or low cardiac output syndrome requiring mechanical support within 30 days after surgery or during admission. Outcomes were extracted from patients' medical records.

Comparators. We compared two cardioplegia solutions: Del Nido and Custodioli. While Custodioli was the standard for many years, Del Nido was introduced at our institution in 2021. Since then, Del Nido has been the standard of care, except for patients undergoing emergency surgery, those with a lidocaine allergy, a previous diagnosis of cold agglutinin disease, heart or renal failure, or under specific conditions at the discretion of the surgical team.

Decision model and statistical analysis. To correct for a likely risk of confounding by indication, we followed an IPTW approach seeking a balanced comparison between the two cardioplegia methods. IPTW is a statistical technique used to adjust for potential confounding in observational studies by assigning weights to individuals based on the inverse of their probability of receiving a particular treatment.¹³ This method creates a synthetic sample in which the distribution of baseline covariates is balanced between treatment groups, mimicking a randomized controlled trial to reduce bias in estimating treatment effects. This study applied IPTW using sex, age, BMI, comorbidities (arterial hypertension, dyslipidemia, diabetes, peripheral artery disease, COPD), left ventricular ejection fraction (LVEF), and EuroSCORE II as adjustment variables. Pre-existing heart failure was not included in the IPTW model due to limited overlap between treatment groups, as Del Nido

cardioplegia was rarely used in patients with heart failure at our institution, which could violate the positivity assumption required for stable weighting. The effectiveness of each intervention was measured using the IPTW-weighted data.

A simple decision tree model was used to estimate the costs associated with a defined set of clinical outcomes and to assess the relationship between incremental costs and clinical benefits. Each possible outcome (or terminal branch) was identified, along with its associated probability (derived from the IPTW-weighted data), cost, and benefit. Each strategy's expected costs and benefits were calculated by summing the products of probabilities and their corresponding costs and benefits. Finally, the incremental cost-effectiveness ratio (ICER) was calculated by comparing the expected costs and benefits of Del Nido cardioplegia to those of Custodiol cardioplegia.¹⁵

Table 1. Baseline characteristics of the custodiol and Del Nido patient groups.

Variable	Custodiol (n = 58)	Del Nido (n = 121)	Total (n = 179)	p-value
Age (years)				0.159
Mean (SD)	60.6 (13.7)	63.1 (10.1)	62.3 (11.4)	
Range	24.5 - 83.2	20.1 - 82.0	20.1 - 83.2	
Female sex	23 (39.7%)	52 (43.0%)	75 (41.9%)	0.674
EuroSCORE II				0.006
Mean (SD)	2.5 (1.1)	2.0 (0.9)	2.2 (1.0)	
Range	0.5 - 5.0	0.6 - 4.5	0.5 - 5.0	
Preoperative LVEF (%)				0.599
Mean (SD)	56.6 (9.5)	57.4 (9.1)	57.2 (9.2)	
Range	23.0 - 72.0	25.0 - 77.0	23.0 - 77.0	
Body Mass index (kg/m ²)				0.065
Mean (SD)	25.9 (3.6)	24.9 (3.0)	25.2 (3.2)	
Comorbidities				
Hypertension	39 (67.2%)	86 (71.1%)	125 (69.8%)	0.601
Myocardial infarction	3 (5.2%)	6 (5.0%)	9 (5.0%)	0.951
Atrial fibrillation	1 (1.7%)	1 (0.8%)	2 (1.1%)	0.593
Heart failure	25 (43.1%)	1 (0.8%)	26 (14.5%)	<0.001
Infective endocarditis	1 (1.7%)	1 (0.8%)	2 (1.1%)	0.593
Peripheral arterial disease	1 (1.7%)	0 (0.0%)	1 (0.6%)	0.147
Dyslipidemia	24 (41.4%)	29 (24.0%)	53 (29.6%)	0.017
Diabetes mellitus	11 (19.0%)	26 (21.5%)	37 (20.7%)	0.697
Stroke	1 (1.7%)	1 (0.8%)	2 (1.1%)	0.593
COPD				0.050
Mild	7 (12.1%)	5 (4.1%)	12 (6.7%)	
Moderate	3 (5.2%)	2 (1.7%)	5 (2.8%)	
None	48 (82.8%)	114 (94.2%)	162 (90.5%)	
Hypothyroidism	11 (19.0%)	19 (15.7%)	30 (16.8%)	0.584
Renal failure	6 (10.3%)	2 (1.7%)	8 (4.5%)	0.008
Smoking	11 (19.0%)	13 (10.7%)	24 (13.4%)	0.131
Preoperative hematocrit (%)				0.005
Mean (SD)	40.1 (6.8)	37.0 (6.1)	37.9 (6.4)	
Preoperative creatinine (mg/dL)				0.392
Mean (SD)	1.0 (0.8)	0.9 (0.5)	1.0 (0.6)	

SD: Standard deviation; COPD: Chronic Obstructive Pulmonary Disease; LVEF: Left Ventricular Ejection Fraction.

Sensitivity analysis. The probabilistic sensitivity analysis addressed uncertainty by capturing variations in cost and effectiveness across different distributions. A Monte Carlo simulation with 10,000 iterations was conducted: cost estimates followed a log-normal distribution, where μ equaled the natural logarithm of the average cost and σ equaled 0.125. Effectiveness data were modeled using a beta distribution, with a mean derived from IPTW-weighted data and a standard deviation of 0.05.

Cost-effectiveness acceptability curves (CEACs) were then developed using the net benefit approach. These curves represent the proportion of ICERs that fall below specific willingness to pay (WTP) thresholds per additional unit of effect. Since Colombia has no established WTP threshold, the analysis included thresholds ranging from 1 to 3 times the per capita gross domestic product (GDP), following local guidelines for cost-effectiveness evaluations.¹⁶

All figures and analyses were performed using the statistical language R (version 4.0.3; R Core Team, 2020) (RRID:SCR_001905)¹⁷ and packages: *arsenal*, *tidyverse*, *MatchIt*, *DescTools*, *survival*, *tableone*, *scales*, *dampack*, *DiagrammeR*, *ggplot2*, and *ggpubr*.

Results

Population and outcomes

We included 179 patients who underwent isolated surgical aortic valve replacement, 58 of whom received Custodiol and 121 of whom received Del Nido cardioplegia. Baseline characteristics revealed significant differences in EuroSCORE II, renal failure, and heart failure, aligning with institutional preferences for Custodiol in patients at higher risk (Table 1). No differences were observed in distributions of age, sex, preoperative LVEF or BMI, other comorbidities or medical history, nor preoperative creatinine levels. Although the study period spans 14 years, since half of the surgical team joined in 2009 and the other half in 2019, only 21 cases correspond to procedures performed before 2019.

As shown in Table 2, the distribution of aortic valve prosthesis types differed between groups, with the majority of Del Nido patients having bioprosthetic prostheses. Operative mortality was 0% for both groups. 30-day mortality was low and comparable between groups (1/58 (1.7%) in the Custodiol group vs. 2/121 (1.7%) in the Del Nido group). Similarly, the incidence of MACE was comparable (5/58 (10.3%) in the Custodiol group vs. 14/121 (11.6%) in the Del Nido group, $p = 0.808$).

Cost-effective analysis

Inverse probability of treatment weighting. Standardized mean differences (SMDs) of $\geq 10\%$ were observed in the

unweighted sample for EuroSCORE II (42.4%), history of dyslipidemia (37.8%), renal failure (37.2%), and COPD (36.5%), as well as BMI (28.8%) and age (21.4%). The regression model for calculating the propensity scores reports a c-statistic of 0.75.

Unrestricted weights were calculated (75th percentile: 2.07; min: 1.09; max: 15.85), and a synthetic IPTW-weighted sample was obtained with a representation of 189.6 Custodiol and 175.9 Del Nido patients, respectively. As shown in Figure 1, no SMDs were above 10%, indicating minimal imbalance.

Base case results. In the weighted sample, the Del Nido group had higher MACE rates than the Custodiol group; however, the difference was not statistically significant (11.3% vs. 6.6%; $p = 0.098$). The average cost of the cardioplegia solution itself was 2,566 USD for Custodiol compared with 657 USD for Del Nido, corresponding to a difference of 1,909 USD per procedure (Supplementary Table S1). The average total cost of care was 47,599 USD in the Custodiol group and 41,761 USD in the Del Nido group.

The results of the base-case analysis are presented in Table 3. While Custodiol is more effective for MACE-free survival, it is 12.3% more expensive than Del Nido. When considering a WTP threshold of 6,947 USD to 20,842 USD (i.e., 1 to 3 GDPs per capita), with an ICER of 123,363 USD, Del Nido is the cost-effective strategy, offering lower costs with only marginal reductions in effectiveness.

Sensitivity analysis. The uncertainty in our results is assessed through a probabilistic sensitivity analysis incorporating parameter uncertainty into 10,000 Monte Carlo simulations (Figures 2 and 3). The Cost-Effectiveness plane shows that most points fall above the WTP threshold line, indicating that Custodiol is not cost-effective in most simulated scenarios. Additionally, the CEAC indicates that with a WTP threshold of 6,947 USD (1 GDP per capita) and 20,841 USD (3 GDP per capita), Del Nido was the cost-effective alternative in 75.5 and 72.35% of simulations, respectively.

Discussion

We found that Del Nido is a cost-effective strategy for myocardial protection in aortic valve surgery. With significantly lower costs, Del Nido consistently meets the cost-effectiveness criteria under WTP thresholds for the Colombian healthcare system. Specifically, Del Nido achieved comparable 30-day survival and MACE-free survival on both the crude and IPTW-weighted samples, with a cost of 41,761 USD, compared to 47,599 USD for Custodiol. Probabilistic sensitivity analysis reinforced these results, with Del Nido being the cost-effective

Table 2. Surgery, outcomes, and complications per cardioplegia solution.

Variable	Custodiol (n = 58)	Del Nido (n = 121)	Total (n = 179)	p-value
Setting				0.959
Elective (%)	29 (50.0%)	60 (49.6%)	89 (49.7%)	
Urgent/emergent (%)	29 (50.0%)	61 (50.4%)	90 (50.3%)	
Type of aortic valve prosthesis				0.024
Bioprosthetic (%)	45 (77.6%)	109 (90.1%)	154 (86.0%)	
Mechanical (%)	13 (22.4%)	12 (9.9%)	25 (14.0%)	
Cross-clamp time, min	72.4 (26.8)	71.4 (25.3)	71.7 (25.7)	0.818
CPB time, min	81.1 (29.9)	85.5 (33.7)	84.1 (32.5)	0.393
Red blood cell transfusions, units	0.4 (0.9)	0.5 (1.1)	0.5 (1.0)	0.771
Cryoprecipitate transfusions, units	0.2 (0.9)	0.7 (1.8)	0.5 (1.6)	0.065
Platelet transfusions, units	0.7 (2.1)	0.6 (1.7)	0.7 (1.8)	0.879
Fresh frozen plasma transfusions, units	0.2 (1.1)	0.6 (1.7)	0.5 (1.5)	0.157
Extubation in operating room (%)	6 (10.3%)	25 (20.7%)	31 (17.3%)	0.088
Outcomes and complications				
ICU LOS, days	3.6 (2.5)	3.5 (2.5)	3.5 (2.5)	0.683
Total postoperative LOS, days	7.3 (3.9)	7.8 (3.9)	7.7 (3.9)	0.442
Operative mortality (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
30-day mortality (%)	1 (1.7%)	2 (1.7%)	3 (1.7%)	0.972
MACE**	6 (10.3%)	14 (11.6%)	20 (11.2%)	0.808
Cardiogenic shock (%)	1 (1.7%)	3 (2.5%)	4 (2.2%)	
Reoperation for bleeding (%)	5 (8.6%)	11 (9.1%)	16 (8.9%)	
One-year mortality (%)	1 (1.7%)	5 (4.1%)	6 (3.4%)	0.402
Renal failure (%)	1 (1.7%)	0 (0.0%)	1 (0.6%)	0.147
Creatinine at 24 h, mg/dL	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)	0.220
Stroke, >24 h	0 (0.0%)	1 (0.8%)	1 (0.6%)	0.488

*Total postoperative stay, including ICU. ** MACE includes 30-day mortality; MACE components may sum up more than the absolute value, considering that one patient might have more than one type of event; LOS: length of stay. Percentages are calculated based on the number of patients for each group. All variables are described using means and standard deviations unless otherwise specified.

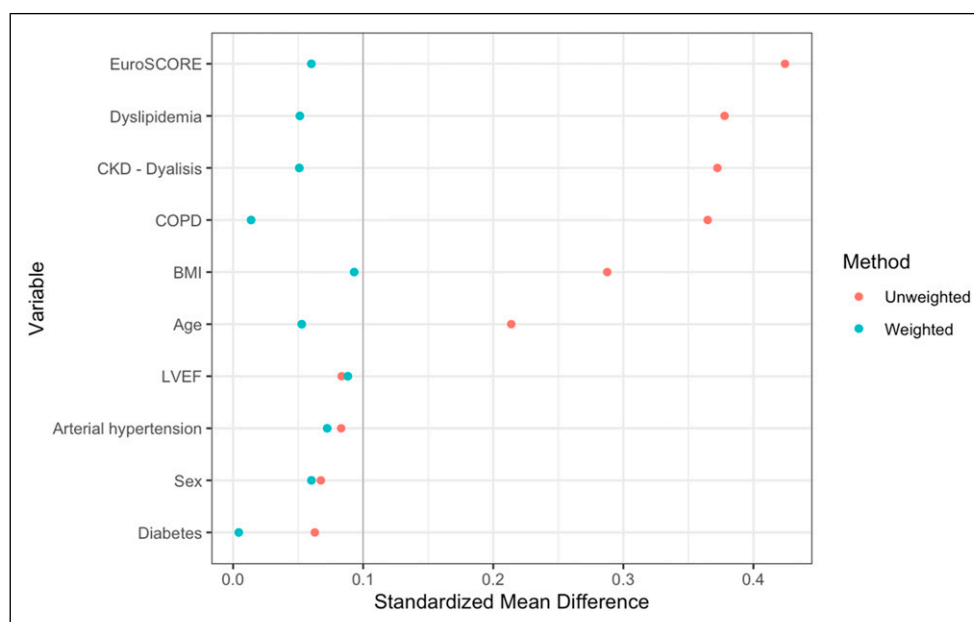


Figure 1. Key covariates before and after the inverse probability of treatment weighting. CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; LVEF: Left Ventricular Ejection Fraction – preoperative.

Table 3. Base case results of the comparison between Custodiol and Del Nido cardioplegia.

Strategy	Cost	Effect	Incremental Cost	Incremental Effect	ICER
Del Nido	41,761 USD	0.89	NA	NA	NA
Custodiol	47,599 USD	0.93	5,838 USD	0.047	123,363 USD

alternative in more than two-thirds of simulations under the Colombian WTP thresholds for MACE-free survival. These findings provide real-world evidence to support Del Nido as the preferred strategy, offering optimal value without jeopardizing clinical outcomes.

The baseline characteristics of our study cohort were largely comparable to those reported in similar analyses comparing Custodiol and Del Nido cardioplegia in aortic valve replacement. Our study population had a mean age of 62.3 years, similar to the ranges reported by Kantathut et al.⁴ and Sanetra et al.,⁷ yet slightly higher than that reported by Duan et al.⁵ Other variables, such as preoperative LEVF, preoperative risk, sex distribution, and selection criteria, were comparable to ours.^{4,5,6,7,9,11,12,18,19,20} On the other hand, while most previous studies focused on patients undergoing minimally invasive cardiac surgery (MICS),^{6,9,18,19,20} our cohort provides insights into the efficacy of these cardioplegia solutions in a more generalized surgical context. These nuances enhance the generalizability of our findings across diverse cardiac surgical populations.

Our findings reinforce the evidence that Del Nido cardioplegia achieves comparable clinical outcomes to Custodiol, consistent with prior studies.^{4,5,6,7,20} For instance, a 2024 retrospective single-center study in China reports, for CABG patients, in-hospital mortality rates of 1.4% for Custodiol vs. 1.9% for Del Nido ($p = 0.861$).¹¹ Similarly, a single-center Korean study reports 30-day

mortality rates for MICS patients from 2015 to 2019 of 0.5% for Custodiol vs. 0.9% for Del Nido ($p = 0.754$).¹⁹ Considering complications, such as postoperative bleeding, a single-center German study in patients undergoing non-emergent isolated MICS from 2018 to 2021 reports a higher cumulative incidence for Del Nido (5.7% vs. 1.5%, $p = 0.06$), yet without reaching statistical significance.²¹ The absence of significant differences in the total duration of hospital stay in our study aligns with findings from previous retrospective studies, which hypothesized that Del Nido cardioplegia adds to lower perioperative costs due to reduced cross-clamp times, ICU stays, and platelet transfusion requirements.^{5,6,7,9,11,12}

Although no prior cost-effectiveness evaluations have directly compared Custodiol and Del Nido, the costs observed in our cohort (41,761 USD and 47,599 USD) are broadly consistent with those reported in the literature for surgical aortic valve replacement (SAVR). These values are in line with those reported in a large 2003–2012 United States STS multi-centric study of 2,530 isolated SAVR procedures, which found mean costs of 35,021 USD for low-risk patients, 46,101 USD for intermediate-risk patients, and 51,145 USD for high-risk patients.²² Our cost estimates also fall within the 2014–2016 range observed in a large retrospective analysis of U.S. hospitals using the Premier Database, which reported mean in-hospital costs for SAVR of approximately 60,319 USD (SD 42,144).²³ The somewhat lower figures in our study likely reflect

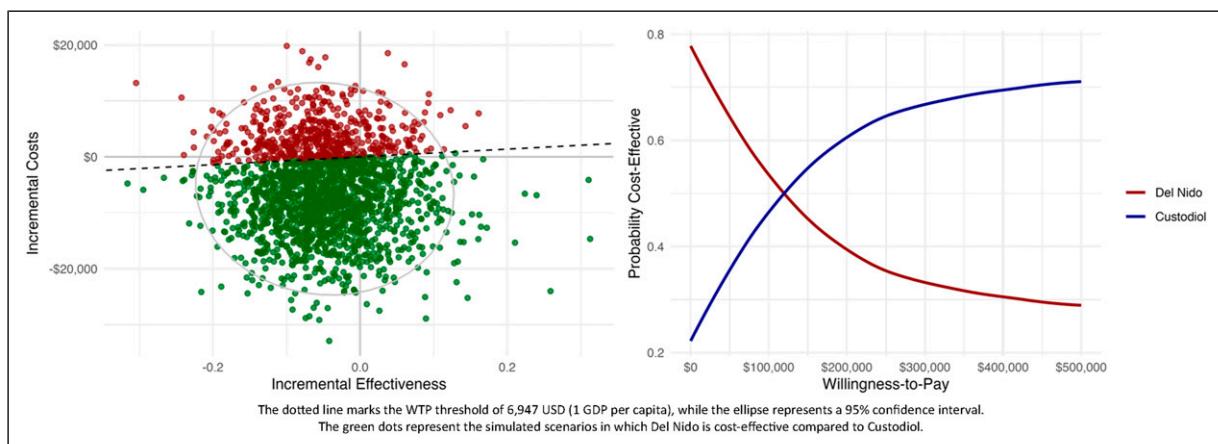


Figure 2. Cost-effectiveness planes (left) and Cost-effectiveness acceptability curves (right) for MACE-free survival. The dotted line marks the WTP threshold of 6,947 USD (1 GDP per capita), while the ellipse represents a 95% confidence interval. The green dots represent the simulated scenarios in which Del Nido is cost-effective compared to Custodiol.

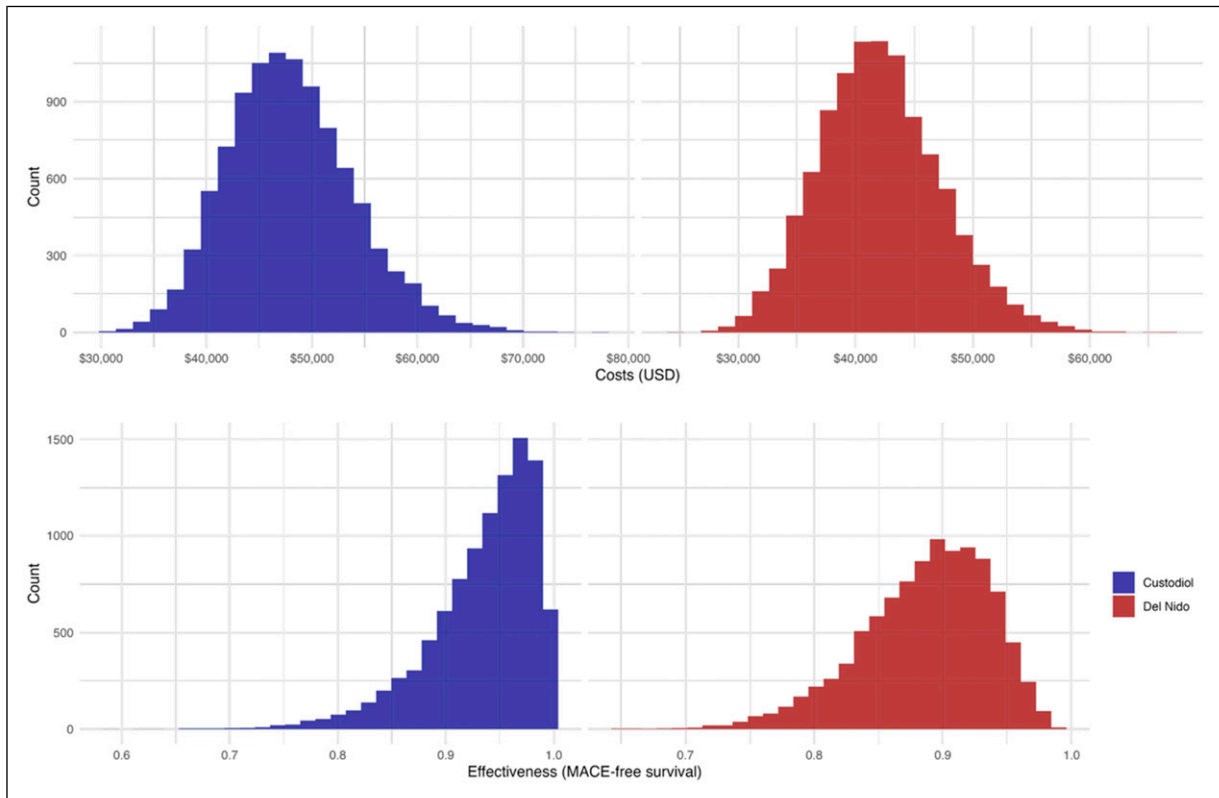


Figure 3. Costs and effectiveness distribution from the 10,000 Monte Carlo simulations.

differences in health care costs in Colombia versus the USA, geographical settings, hospital practices, and health systems, yet the magnitude is consistent with real-world SAVR benchmarks.

Our study, while robust, is not without limitations. First, cost-effectiveness models inherently rely on certain assumptions, such as the generalizability of clinical data and the exclusion of long-term outcomes. For example, our study focused on MACE-free survival as a composite endpoint to capture a broader number of events, but this may still represent a limitation, as the low event count could reflect limited power; furthermore, MACE events may not fully capture the long-term benefits of these strategies. Second, in our center, Del Nido was generally avoided in patients with pre-existing heart failure, resulting in limited covariate overlap between treatment groups. Consequently, heart failure could not be incorporated into the IPTW model without violating the positivity assumption. Although this reflects a degree of clinical selection bias, the IPTW approach allowed balancing of other baseline characteristics. While costs were mainly driven by operative and perioperative care components rather than comorbidity-related management, this situation represents a form of structural confounding by indication, which can be difficult to fully address in single-center retrospective analyses when treatment allocation follows strong clinical preferences.

Additionally, specific high-risk patient populations, such as those with combined, prolonged surgeries or severe comorbidities, may derive greater benefits from Custodiol that are not fully reflected in this analysis. Further, hospital care costs can vary considerably across institutions, which may limit the generalizability of our cost-effectiveness conclusions to other settings. Finally, although the distribution of valve types differed between cardioplegia groups, prosthetic valve costs were included within the patient-level hospitalization costs derived from administrative records. Therefore, any variation in valve price was inherently reflected in the total cost estimates used in the cost analysis. Consequently, the cost comparison reflects the overall resource utilization associated with each cardioplegia strategy, rather than isolated differences in device pricing.

Notwithstanding these limitations, a key methodological strength is the use of IPTW, which achieved baseline balance with an acceptable discriminative capacity (c -statistic = 0.75) and thereby minimized bias by indication, adding to the study's internal validity. Another strength is the assessment of uncertainty through 10,000 Monte Carlo simulations, reinforcing the consistency of our findings. However, the probabilistic sensitivity analysis incorporated parameter effectiveness uncertainty and consistently favored Del Nido across a wide range of scenarios.

We also acknowledge that Del Nido and Custodiol were not used in parallel but during partially distinct time periods. Although the study covers 14 years, only 21 procedures were performed before 2019, when half of the surgical team had already been part of the institution since 2009, and the remaining members joined in 2019. All surgeries before 2021 used Custodiol, whereas most—but not all—after 2021 used Del Nido, leading to a predominance of Del Nido cases. This temporal separation may have introduced factors related to institutional evolution or cumulative surgical experience. Nevertheless, surgical techniques, perioperative management, and patient selection criteria remained consistent throughout the study period. Although the IPTW method balances clinical covariates, it cannot fully account for unmeasured time-related factors; this limitation should therefore be considered when interpreting the results.

Taken together, these findings highlight the need for more comprehensive research on the cost-effectiveness of cardioplegia solutions across diverse surgical contexts. Future multicenter studies with broader treatment allocation patterns should explore the long-term clinical and economic outcomes of Del Nido and Custodiol cardioplegia, particularly in high-risk populations or complex surgical cases. Additionally, head-to-head trials incorporating patient-centered outcomes, such as quality of life and functional recovery, would provide valuable data to guide decision-making.^{9,10} On a policy level, our results advocate for including cost-effectiveness criteria in guidelines for cardioplegia selection. This approach could ensure that healthcare systems prioritize solutions that deliver the highest value to patients while optimizing resource utilization, thereby improving the sustainability of cardiac surgery programs.

Conclusion

Our study establishes Del Nido as a cost-effective strategy for myocardial protection in aortic valve surgery, providing high value at significantly lower costs than Custodiol. We underscore the importance of incorporating cost-effectiveness considerations into clinical decision-making, particularly in resource-constrained healthcare systems, and recommend Del Nido as the preferred strategy, given its ability to deliver comparable clinical outcomes at reduced costs. However, this should be interpreted with caution in certain patient subgroups—such as those with complex reoperations, prolonged ischemic times, or specific comorbidities—where evidence remains limited and the relative advantages of Del Nido have not yet been explored.⁸ Overall, this work highlights the need for ongoing evaluation of healthcare interventions to ensure they deliver value that aligns with their cost and clinical benefit. It also offers a scalable model for adopting value-based practices in cardiac surgery globally.

Acknowledgements

The main author would like to thank the professor and fellow classmates of the elective course “Escribir artículos en inglés,” offered by the Department of Clinical Epidemiology and Biostatistics at Pontificia Universidad Javeriana, for their valuable support and feedback throughout the preparation of this manuscript.

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Ethical considerations

This study was approved by the IRB of the Fundación Universitaria Sanitas [CEIFUS 2082-24]. In our institution, every patient scheduled for heart surgery signs a consent form authorizing the use of their anonymized clinical data for research purposes. Given this standard practice and the retrospective nature of the study, no additional informed consent was obtained. Findings were shared with clinicians and institutional stakeholders upon study completion to contextualize results and inform practice improvements.

Author contributions

KM-C - writing and editing of protocol and manuscript, study design, data acquisition, interpretation, statistical, and cost analyses. SAPL- protocol writing and coordination, writing and editing of manuscript, and data acquisition. VP-A, AFB, JAS, AM, CPR, NF, and SN - writing and editing of protocol and manuscript, and data acquisition. HO - clinical insights and interpretation of data. JM-E - project coordination and supervision, clinical insights, manuscript editing, study design, interpretation of data. All authors read and approved the final manuscript.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Vice Presidency of Innovation and Scientific Development of Clínica Colsanitas.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplemental material

Supplemental material for this article is available online.

References

1. Lalu MM, Pasini E, Schulze CJ, et al. Ischaemia–reperfusion injury activates matrix metalloproteinases in the human heart. *Eur Heart J* 2005; 26(1): 27–35. <https://doi.org/10.1093/eurheartj/ehi007>
2. Bretschneider HJ, Hübner G, Knoll D, et al. Myocardial resistance and tolerance to ischemia: physiological and biochemical basis. *J Cardiovasc Surg* 1975; 16(3): 241–260.
3. Matte GS and del Nido PJ. History and use of del Nido cardioplegia solution at Boston Children’s Hospital. *J Extra Corpor Technol* 2012; 44(3): 98–103.
4. Kantathut N, Luangpatom-Aram K, Khajareern S, et al. Comparison of Single-Dose Cardioplegia in Valvular Heart Surgery: lactated Ringer’s-Based del Nido vs. Histidine-Tryptophan-Ketoglutarate Cardioplegia Solution. *Braz J Cardiovasc Surg* 2023; 38(6): e20220447. <https://doi.org/10.21470/1678-9741-2022-0447>
5. Duan L, Hu GH, Wang E, et al. Del Nido versus HTK cardioplegia for myocardial protection during adult complex valve surgery: a retrospective study. *BMC Cardiovasc Disord* 2021; 21(1): 604. <https://doi.org/10.1186/s12872-021-02411-w>
6. Gerber W, Sanetra K, Gerber AD, et al. One-shot cardioplegia for minimally invasive mitral valve repair—a comparison of del Nido and Bretschneider Histidine-Tryptophan-Ketoglutarate solutions. *Perfusion* 2023; 38(4): 763–770. <https://doi.org/10.1177/02676591221080653>
7. Sanetra K, Domaradzki W, Białek K, et al. Del Nido versus Bretschneider cardioplegic solution in valve replacement for severe aortic stenosis - a case-control pilot study. *Kardiochir Torakochirurgia Pol* 2022; 19(2): 81–85. <https://doi.org/10.5114/kitp.2022.117496>
8. Whittaker A, Aboughdir M, Mahbub S, et al. Myocardial protection in cardiac surgery: how limited are the options? A comprehensive literature review. *Perfusion* 2021; 36(4): 338–351.
9. Hummel BW, Buss RW, DiGiorgi PL, et al. Myocardial protection and financial considerations of custodiol cardioplegia in minimally invasive and open valve surgery. *Innovat Tech Tech CardioThorac Vasc Surg* 2016; 11(6): 420–424. <https://doi.org/10.1097/IMI.0000000000000314>
10. Vervoort D, Swain JD, Pezzella AT, et al. Cardiac surgery in low- and middle-income countries: a state-of-the-art review. *Ann Thorac Surg* 2021; 111(4): 1394–1400.
11. Wang L, Dai Q, Hu L, et al. Influence of cardioplegic solution on incidence of acute kidney injury after coronary artery bypass surgery procedure: del Nido cardioplegia versus Histidine-Tryptophan-Ketoglutarate solution: insight of kidney disease improving global outcomes criteria. *Perfusion*. 2024; 2676591241244983. <https://doi.org/10.1177/02676591241244983>
12. Talwar S, Chatterjee S, Sreenivas V, et al. Comparison of del Nido and histidine-tryptophan-ketoglutarate cardioplegia solutions in pediatric patients undergoing open heart surgery: a prospective randomized clinical trial. *J Thorac Cardiovasc Surg* 2019; 157(3): 1182–1192. <https://doi.org/10.1016/j.jtcvs.2018.09.140>
13. Austin PC and Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015; 34(28):3661–3679. <https://doi.org/10.1002/sim.6607>
14. World Bank Group. *PPP conversion factor, GDP (LCU per international \$) international comparison program, world bank | world development indicators database*. World Bank | Eurostat-OECD PPP Programme. <https://data.worldbank.org/indicator/PA.NUS.PPP>
15. Mutubuki EN, El Alili M, Bosmans JE, et al. The statistical approach in trial-based economic evaluations matters: get your statistics together. *BMC Health Serv Res* 2021; 21(1): 475. <https://doi.org/10.1186/s12913-021-06513-1>
16. Díaz M, Peña E, Mejía A, et al. *Manual metodológico para la elaboración de evaluaciones de efectividad, seguridad y validez diagnóstica de tecnologías en salud*. : Instituto de Evaluación Tecnológica en Salud-IETS, 2014.
17. Dessau RB and Pipper CB. “R”--project for statistical computing. *Ugeskr Laeger* 2008; 170(5): 328–330.
18. Chan J, Oo S, Butt S, et al. Network meta-analysis comparing blood cardioplegia, Del Nido cardioplegia and custodiol cardioplegia in minimally invasive cardiac surgery. *Perfusion* 2023; 38(3): 464–472. <https://doi.org/10.1177/02676591221075522>
19. Lee CH, Kwon Y, Park SJ, et al. Comparison of del Nido and histidine-tryptophan-ketoglutarate cardioplegic solutions in minimally invasive cardiac surgery. *J Thorac Cardiovasc Surg* 2022; 164(4): e161–e171. <https://doi.org/10.1016/j.jtcvs.2020.11.163>
20. Gunaydin S, Akbay E, Gunertem OE, et al. Comparative effects of single-dose cardioplegic solutions especially in repeated doses during minimally invasive aortic valve surgery. *Innovations* 2021; 16(1): 80–89.
21. Kang J, Hoyer A, Dieterlen MT, et al. Comparison of modified Del Nido and Custodiol® cardioplegia in minimally invasive mitral valve surgery. *Eur J Cardio Thorac Surg* 2024; 65(4): ezae161. <https://doi.org/10.1093/ejcts/ezae161>
22. Osnabrugge RLJ, Speir AM, Head SJ, et al. Costs for surgical aortic valve replacement according to preoperative risk categories. *Ann Thorac Surg* 2013; 96(2): 500–506. <https://doi.org/10.1016/j.athoracsurg.2013.04.038>
23. Meduri C, Chung J, Gaffney J, et al. Comparison of U.S. hospital costs between transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR). *Value Health* 2017; 20(9): A579–A580. <https://doi.org/10.1016/j.jval.2017.08.1027>