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Analysis of the Effects of Different Forms of Cardioplegia on the Degree of Myocardial Damage and Systemic Inflammation in Patients Undergoing Valvular Heart Disease Surgery

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Abstract

Introduction: Myocardial protection plays a fundamental role in obtaining good results in cardiac surgery. Among the several solutions proposed for myocardial protection, the balanced Del Nido's solution has gained much attention. Recently, a proposal was launched to modify the crystalloid media routinely used in such solutions with the replacement of Plasma-Lyte® by Ringer with lactate. **Methods:** This is a controlled, interventional, clinical trial, including patients submitted to valvular heart surgeries, performed at two centers in Rio de Janeiro, Brazil. Forty-three patients were stratified into two groups at random. Group A (n = 22) was composed of patients undergoing on-pump heart surgery using the cardioplegic solution modified with Ringer-lactate, while Group B (n = 21) represented the control group (standard Plasma-Lyte® cardioplegic solution). Serum levels of inflammatory (TNF-alpha and interleukin-6) and cardiac damage biomarkers (troponin and lactate) were measured immediately before (T0) and after (between 6 and 24 hours—T1) the surgical procedure, and then remeasured on the third postoperative day (T3). **Results:** Both groups were homogenous at baseline. There were no significant differences between groups in any of the biomarker measurements at any time, except for TNF-alpha at T0 (p = 0.005). The deltas of the dosages of lactate, troponin, TNF-alpha, and interleukin-6 along the period of analysis also were similar between groups. **Discussion:** The inflammatory response induced by exposure to the modified Del Nido's cardioplegic solution, by comparing IL-6 and TNF-alpha levels, showed no significant difference in relation to the standard solution. Also, the degree of myocardial injury and necrosis compared through lactate and troponin measurements showed no significant differences between groups. **Conclusion:** Both Del Nido's cardioplegic solution modified with Ringer-lactate and the standard Plasmalyte® cardioplegic solution proved to be effective in cardioprotection of adult patients undergoing valvular heart surgery.

Keywords

Cardiac Arrest, Induced, Cardioplegia, Solutions, Heart Surgery

1. Introduction

Cardiac surgery under cardiac arrest is associated with myocardial ischemia, leading to anaerobic metabolism that generates lactate accumulation and consequent intracellular acidosis. Also, cardiopulmonary bypass is closely related to some degree of inflammatory response in the postoperative period. In such patients, serum levels of inflammatory biomarkers (TNF-alpha and interleukin-6), troponin, and lactate can reflect the related degree of inflammatory response, myocardial injury, and acidosis, respectively [1] [2].

Myocardial protection plays a fundamental role in obtaining good results in such surgical procedures. Indeed, it has enabled a huge advance in modern cardiac surgery since the introduction of cardiopulmonary bypass. Over the years, there has been a race to find a method that allows better tolerance to perioperative ischemia and cardiopulmonary bypass. Among the several solutions proposed for myocardial protection, the balanced Del Nido's solution has gained much attention.

Recently, however, a proposal was launched to modify the crystalloid media routinely used in such solution with the replacement of Plasma-Lyte® by Ringer with lactate. This solution has been tested with promising results. Considering its lower cost, this change in crystalloid solution turns routine use of Del Nido solution more accessible without any drop in quality of myocardial protection [3].

This study compares the degree of myocardial injury, anaerobic metabolism, and inflammatory response related to the use of two kinds of Del Nido's cardioplegic solution (standard and modified) in valvular patients undergoing cardiac surgery with cardiopulmonary bypass.

2. Methods

This is a controlled, interventional, clinical trial, including patients submitted to valvular heart surgeries, performed at two centers, the cardiac surgery services of Hospital Universitario Pedro Ernesto (HUPE/UERJ) and Hospital Naval Marcilio Dias, between January 2020 and October 2022.

Initially, 48 patients were selected. Later, five cases were excluded from the study due to the need for combined surgery (valvular and myocardial reperfusion strategies), leaving 43 patients to be studied. Patients were stratified into two groups at random by drawing by an external person to the study. Group A (n = 22) was composed of patients undergoing on-pump heart surgery using the cardioplegic solution modified with Ringer-lactate, while Group B (n = 21) represented the control group (on-pump heart surgery using the standard Plasma-Lyte® cardioplegic solution).

2.1. Investigation Procedures

All cases were submitted to surgery by the same surgical team, receiving the same anesthesia protocol and monitorization in the operating room. Cardioplegia solutions (**Table 1**) were placed in the ascending aorta. The volume of cardioplegia solution was 20 ml/kg (maximum of 1000 ml, even in patients heavier than 50 kg), repeated every 90 minutes as needed.

Table 1. Composition of standard and modified Del Nido cardioplegia solutions.

Standard solution	Volume	Modified solution
Plasma Lyte®	1000 mL	Ringer lactate
Sodium bicarbonate (1mEq/mL)	13 mL	Sodium bicarbonate (1mEq/ml)
Mannitol (20%)	16.3 mL	Mannitol (20%)
Magnesium sulfate (50%)	4 mL	Magnesium sulfate (50%)
Lidocaine (1%)	13 mL	Lidocaine (1%)
Potassium chloride (2mEq/mL)	13 mL	Potassium chloride (2 mEq/mL)

Serum levels of inflammatory and cardiac damage biomarkers were measured immediately before and after (between 6 and 24 hours) the surgical procedure, and then remeasured in the third postoperative day.

The choice of dosage on the third day, is explained by the fact that the peak of inflammatory response to trauma occurs 72 hours after the surgical procedure.

Dosages of interleukin-6 and TNF-alpha were performed through the enzyme-linked immunosorbent assay (ELISA) method with the reagent kit ReD *System ELISA Duo Set* and the spectrophotometer EspectraMax. Lactate was measured in arterial blood gases in a GEM premier 3500 device. The blood sample for troponin dosage was promptly centrifuged, and then stored in a *freezer* at −5˚C anda measured by immunochromatography technique.

The troponin dosage was listed separately from the pH level, given that the PH can be compensated, even if the patient has elevation in lactate levels.

2.2. Safety Procedures

Since the cardioplegic solutions evaluated in this study are already routinely used in different cardiac surgery centers, the application of the modified solution posed no additional risks to the research subjects. Also, the confidentiality of the data was preserved, so that the participants can not be identified by any product resulting from its realization. The study protocol was approved by Medical Ethics Committees of both centers.

2.3. Statistical Analysis

Results were expressed as means ± standard-deviations for continuous variables and in percentages for categorical variables. To evaluate the results regarding the occurrence of parametric distribution, the Shapiro-Wilks test ($n < 50$) was used. Results were compared before and after the procedure.

The main analysis performed consisted in comparing the groups (cardioplegic solution used) for the parameters: lactate, troponin, TNF-alpha, and IL-6. This comparison was performed at three moments: T0 (preoperative), T1 (immediate postoperative) and T2 (third postoperative day). We also compared the deltas, the simple mathematical differences in values (increases or reductions) between times of analysis, in which delta 1 (D1) means T1 minus T0, D2 means T2 minus T0, and D3 means T2 minus T1.

All quantitative variables were analyzed using non-parametric tests since there was no guaranteed normality distribution. Friedman test was applied to check whether the treatments applied to the individuals had an effect, analyzing the evolution of the measurements of lactate, troponin, TNF-alpha, and IL-6 in each group. Mann-Whitney was used to compare the groups in each of the three moments of time and calculated deltas. To carry out a *post-hoc* analysis of the moments per group of lactate, troponin, TNF, and interleukin-6 measurements, we used the Wilcoxon test to accurately determine the moments in which differences could occur. Distribution of qualitative variables was evaluated through Chi-Square test. A p-value less than 0.05 was considered to be statistically significant.

For biomarker changes over time (lactate,troponin,TNF-alpha and IL-6), repeated measures ANOVA was applied to asses intra –group diferences across the three time points (T0-preoperative,T1-immediate postoperative anda T2 postoperative day 3). When sphericity was not assumed , the Greenhouse-Geisser correction was applied.

In this statistical analysis, the following softwares were used: SPSS V26 (2019), Minitab 21.2 (2022), and Excel Office (2010). Graphs were created using the GraphPad Prism 8.0.1 software (GraphPad Software, San Diego, California, USA).

3. Results

Forty-three patients were studied: 22 underwent surgery with Del Nido's solution composed of ringer-lactate (Group A) and 21 (Group B) with Plasma-Lyte® solution (standard group). Procedures performed were 22 aortic valve replacements, 20 mitral valve replacements and 1 combined mitral and aortic valve replacement.

The mean age of the study population was 54 ± 15.76 years; in group A it was 54.2 ± 17.1 years, and in group B it was 53.8 ± 14.6 years ($p = 0.874$). The qualitative variables studied are shown in **Table 2**, while quantitative variables related to times (age, duration of extracorporeal circulation, duration of clamp and length of stay) are shown in **Table 3**.

Table 2. Distribution of qualitative variables.

N		Group A		Group B		Total		p-value
		N	%	N	%	N	%	
Gender	Male	15	68.2	10	47.6	25	58.1	0.172
	Female	7	31.8	11	52.4	18	41.9	
Death	No	20	90.9	20	95.2	40	93.0	0.578
	Yes	2	9.1	1	4.8	3	7.0	
Valve replaced	Aortic	12	54.5	10	47.6	22	51.2	0.507
	Mitral	9	40.9	11	52.4	20	46.5	
	Both	1	4.5	0	0.0	1	2.3	

Table 3. Distribution of quantitative variables related to times.

		Mean	Median	Standard-Deviation	Q1	Q3	CI	p-Value
Age (years)	Group A	54.2	55.5	17.1	42.0	67.8	7.1	0.874
	Group B	53.8	53.0	14.6	44.0	66.0	6.3	
ECC time (minutes)	Group A	109.3	97.0	47.1	79.3	133.3	19.7	0.865
	Group B	105.9	100.0	31.6	88.0	111.0	13.5	
Clamp time (minutes)	Group A	93.6	84.5	39.6	69.0	126.8	16.5	0.923
	Group B	86.9	93.0	20.3	73.0	100.0	8.7	
Length of stay (days)	Group A	6.39	5.0	6.39	3.3	6.0	2.95	0.975
	Group B	5.32	4.0	2.40	4.0	6.5	1.08	

Group A—modified group; Group B—standard group; CI—confidence interval; Q1—quartile 1 value; Q3—quartile 3 value; ECC time—duration of extracorporeal circulation; clamp time—duration of clamp.

There were no differences in extracorporeal circulation times between groups (mean ± SD – Group A: 109.3 ± 47.1 versus Group B: 105.9 ± 31.6 – p = 0.865). Similarly, no differences were observed regarding aortic clamp times (Group A: 93.6 ± 39.6 versus Group B: 86.9 ± 20.3 – p = 0.923). Lengths of stay were also similar (p = 0.975).

Table 4 depicts the results of lactate, troponin, TNF-alpha, and interleukin 6 measurements (shown as means ± standard-deviations, medians, quartiles, and confidence intervals) along the analyses.

Table 4. Biomarkers measurements in both groups at the 3 times of analysis.

Time/group		Mean	Median	Standard-deviation	Q1	Q3	CI	p-Value
Lactate								
T0	Group A	0.836	0.700	0.416	0.600	1.000	0.174	0.472
	Group B	0.924	0.900	0.462	0.600	1.100	0.198	
T1	Group A	2.786	2.450	1.626	1.800	3,375	0.679	0.158
	Group B	2.067	2.000	0.842	1.600	2.300	0.360	
T2	Group A	1.414	1.100	0.857	0.725	1.775	0.358	0.471
	Group B	1.205	1.000	0.732	0.800	1.100	0.313	
Troponin								
T0	Group A	14.8	5.6	28.0	2.0	15.2	11.7	0.789
	Group B	10.3	6.0	15.5	1.8	7.9	6.6	

Continued

T1	Group A	2348.0	295.3	5418.4	43.9	779.4	2264.2	0.285
	Group B	2811.3	470.5	5271.6	209.0	3076.0	2254.7	
T2	Group A	746.9	267.0	1266.9	2.9	846.5	529.4	0.308
	Group B	1123.5	342.0	1697.5	90.0	888.2	726.0	
TNF-alpha								
T0	Group A	87.5	87.5	39.8	64.0	101.8	16.6	0.005
	Group B	242.2	45.0	882.2	28.0	81.0	377.3	
T1	Group A	183.7	120.0	175.8	91.0	178.5	73.5	0.349
	Group B	238.5	184.0	202.0	86.0	270.0	86.4	
T2	Group A	122.5	89.5	107.1	59.0	131,0	44.8	0.827
	Group B	125.3	91.0	107.1	52.0	138.0	45.8	
IL6								
T0	Group A	30.5	29.5	18.2	13.6	38.0	7.6	0.971
	Group B	98.8	26.0	321.5	22.0	41.0	137.5	
T1	Group A	680.0	679.0	282.5	472.5	858.5	118.1	0.808
	Group B	816.8	650.0	791.2	398.0	830.0	338.4	
T2	Group A	308.0	290.0	223.2	110.0	402.3	93.3	0.343
	Group B	300.1	190.0	317.1	98.0	360.0	135.6	

Group A—modified group; Group B—standard group; CI—confidence interval; Q1—quartile 1 value; Q3—quartile 3 value.

Using the Friedman test to compare the temporal evolution of measurements of each biomarker in each of the two groups, we observed that there were statistically significant differences at all times ($p < 0.001$ – except for TNF-alpha [$p = 0.048$]).

Mann-Whitney test showed that there were no significant differences between groups in any of the biomarker measurements at any time, except for TNF-alpha at T0 ($p = 0.005$). **Tables 5-8** show the deltas of the dosages of lactate, troponin, TNF-alpha, and interleukin-6 along the period of analysis; no differences were observed between groups.

Table 5. Deltas of the dosages of TNF-alpha in both groups.

	Group	Mean	Median	Standard-deviation	Q1	Q3	IC	p-Value
D1	Group A	96.1	41.5	166.4	6.5	120.8	69.5	0.138
	Group B	−3.7	115.0	839.7	26.0	229.3	359.2	
D2	Group A	34.9	5.0	115.8	−18.0	50.3	48.4	0.072
	Group B	−116.9	58.3	883.1	2.0	81.0	377.7	
D3	Group A	−61.2	−21.5	153.3	−106.8	2.0	64.1	0.159
	Group B	−113.2	−83.0	120.0	−171.0	−20.0	51.3	

Group A—modified group; Group B—standard group; CI—confidence interval; Q1—quartile 1 value; Q3—quartile 3 value.

Table 6. Deltas of the dosages of IL-6 in both groups.

	Group	Mean	Median	Standard-deviation	Q1	Q3	IC	p-Value
D1	Grouo A	649.5	633.0	282.2	439.3	824.5	117.9	0.865
	Group B	718.0	628.0	900.1	374.0	807.0	385.0	
D2	Group A	277.4	253.0	229.2	53.3	386.9	95.8	0.496
	Group B	201.3	164.0	468.3	61.0	337.0	200.3	
D3	Group A	−372.1	−466.5	393.8	−609.3	−90.0	164.6	0.865
	Group B	−516.8	−470.0	511.8	−540.0	−186.0	218.9	

Group A—modified group; Group B—standard group; CI—confidence interval; Q1—quartile 1 value; Q3 – quartile 3 value.

Table 7. Deltas of the dosages of lactate in both groups.

	Group	Mean	Median	Standard-deviation	Q1	Q3	CI	p-Value
D1	Group A	1.950	1.300	1.626	0.925	2.800	0.679	0.210
	Group B	1.143	1.100	0.947	0.700	1.600	0.405	
D2	Group A	0.577	0.200	0.902	<0.001	1.375	0.377	0.550
	Group B	0.281	0.200	0.768	0.100	0.400	0.328	
D3	Group A	−1.373	−1.050	1.785	−2.400	−0.250	0.746	0.415
	Group B	−0.862	−0.800	1.016	−1.200	−0.200	0.434	

Group A—modified group; Group B—standard group; CI—confidence interval; Q1—quartile 1 value; Q3—quartile 3 value.

Table 8. Deltas of dosages of troponin in both groups.

	Group	Mean	Median	Standard-deviation	Q1	Q3	CI	p-Value
D1	Group A	2333.2	281.3	5414.4	36.1	771.1	2262.5	0.259
	Group B	2801.0	468.7	5270.7	201.7	3073.8	2254.3	
D2	Group A	732.2	257.3	1262.2	0.2	842.0	527.4	0.244
	Group B	1113.2	334.1	1689.5	74.5	888.1	722.6	
D3	Group A	−1601.1	−3.2	4528.7	−546.9	59.0	1,892.4	0.319
	Group B	−1687.8	−152.0	4424.8	−1691.1	0.6	1,892.5	

Group A—modified group; Group B—standard group; CI—confidence interval; Q1—quartile 1 value; Q3—quartile 3 value.

4. Discussion

Homogeneity between groups A and B was observed, with no significant differences observed in terms of demographic and procedural features (Table 2 and Table 3).

We highlight the similarities in the times of cardiopulmonary bypass and length of stay (Figure 1) between the two groups studied. Clamp and ischemia times were also similar (not shown).

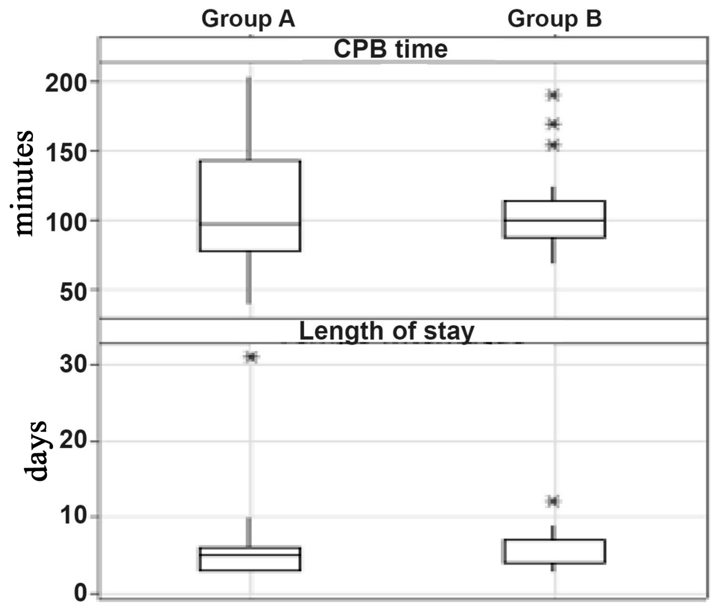

Figure 1. Box-plot of CPB and hospitalization times in both groups. Legend: Group (A) modified group; Group (B) standard group; CPB—cardiopulmonary bypass.

Figure 2 shows the temporal evolution of biomarkers of inflammatory response and myocardial necrosis between the preoperative period and the third postoperative day. The analysis by Mann-Whitney test showed that there were no statistically significant differences between groups for all markers.

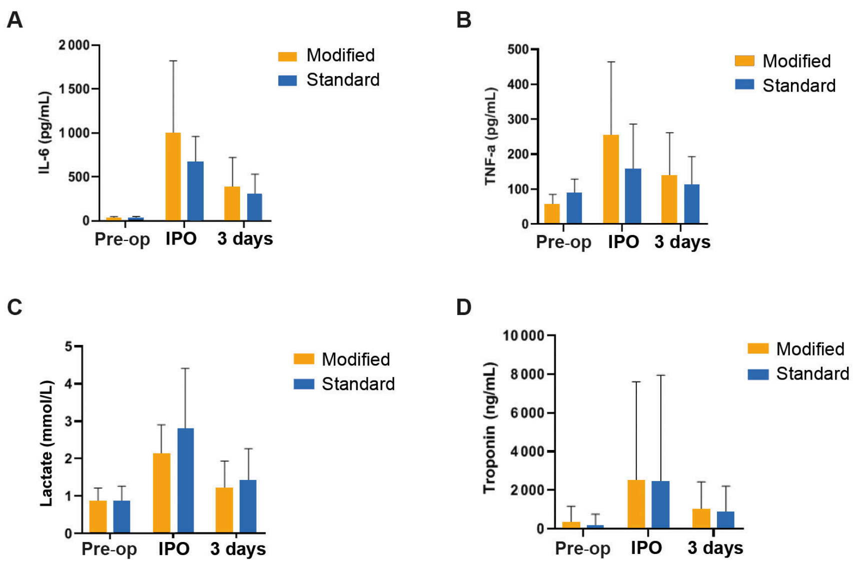

Figure 2. Time evolution of inflammatory and necrosis markers along the perioperative period. (A): IL-6 dosage preoperatively and in the first 72 hours postoperatively in the groups studied; (B): TNF-alpha dosage preoperatively and in the first 72 hours postoperatively in the groups studied; (C): lactate dosage preoperatively and in the first 72 hours postoperatively in the groups studied; (D): troponin dosage preoperatively and in the first 72 hours postoperatively in the groups studied. Pre-op—pre-operative; IPO—immediate post-operative.

As presented, using the Friedman test we concluded that there were statistically significant differences over time in all four parameters in both groups. Since there were three moments of analysis, we had to use the wilcoxon test to compare the moments in pairs (*post-hoc* analysis) and thus determine precisely in which moments there was a difference. We show such analysis in **Table 9**, where just cross the line with the column to find the related p-value.

In fact, the differences in lactate and interleukin-6 measurements were statistically significant in both groups at all times. Although such differences were also found in troponin and TNF-alpha measurements in group B, that was not the case for group A. In such group, there were no significant differences between troponin T1 and T2 means (respectively 14.8 vs. 746.9; p-value = 0.263). Regarding the measurements of TNF-alpha, we concluded that the difference relies only in T0 and T1 means (respectively 87.5 vs. 183.7; p-value = 0.005).

Table 9. *Post-hoc* analysis of the differences in all biomarkes between both groups.

			T0	**T1**
Lactate	Group A	T1	<0.001	
		T2	0.006	0.002
	Group B	T1	<0.001	
		T2	0.040	0.001
Troponin	Group A	T1	<0.001	
		T2	0.001	0.263*
	Group B	T1	<0.001	
		T2	<0.001	0.021
TNF-alpha	Group A	T1	0.005	
		T2	0.314*	0.074
	Group B	T1	0.001	
		T2	0.007	0.001
IL6	Group A	T1	<0.001	
		T2	<0.001	0.002
	Group B	T1	0.001	
		T2	0.001	<0.001

* Not statistically significant (Wilcoxon test).

We could not find an effective explanation for the differences between TNF-alpha measurements in both groups at T0. However, we did not observe significant differences in any one of the deltas (D1, D2, and D3) of the four biomarkers along the study, although there was a trend toward significance in D2 related to TNF-dosages (p = 0.072, **Table 5**). It is noteworthy that a positive delta means an increase in results along the time, while a negative delta means a reduction in values. So, taken together, such data may lead us to conclude that the disproportionately low value of TNF-alpha at T0 in group A had some impact on the variations observed over time.

An important study by Giacinto *et al*, at the University of Rome, made a comprehensive analysis, addressing the endothelial dysfunction and inflammatory response caused by cardiac surgery [4]. Such study is similar to the present work in an important aspect: there was a correlation between serum levels of TNF-alpha and the inflammatory reaction seen after surgery with cardiopulmonary bypass (CPB), highlighting the direct relationship between CPB and the elevation of TNF-alpha. However, the population studied here differs from the sample of the other study, since only patients undergoing surgery for valve diseases were evaluated. Giacinto *et al* evaluated as a single block patients undergoing cardiac surgery, not singling out a specific group.

As published, the Del Nido's solution is a reality for adult cardiac surgery. In a study conducted by Sevuk *et al.*, such cardioplegic solution proved to be a good alternative, especially when CPB times were prolonged [5]. Outcomes in troponin dosages were similar when compared Del Nido's solution with blood cardioplegia, the usual solution used in the Turkish hospital where the research was performed. However, unlike the present analysis, the authors evaluated the impacts in several surgical techniques, predominantly mitral valve replacement.

One of the pioneer studies in the use of Ringer-lactate as the basis of Del Nido solution was performed in Thailand, at Bangkok University, by Kantathut *et al.* [6]. In this study, the use of Ringer-lactate in the solution was considered because it was easier to obtain, thus increasing the range of possibilities for cardioplegic solutions. Outcomes were similar to that observed in this study: there was no difference in clinical outcomes, as well as in the degree of myocardial injury, as measured by troponin levels postoperatively.

The cardioplegic solutions used in this study are already routinely performed in different cardiac surgery centers. It is noteworthy that the application of the modified solution posed no additional risks to the research subjects.

The considerable variability observed in postoperative troponin levels, as indicated by the large standard deviations, underscores the heterogeneous nature of myocardial injury in patients undergoing valve surgery with cardiopulmonary bypass. Factors such as differing degrees of ischemia-reperfusion injury, baseline cardiac function, and intraoperative events may contribute to this wide range of responses. Recognizing this skewness in the data distribution, we applied non-parametric statistical tests to ensure accurate comparisons between the groups and to mitigate potential biases associated with parametric analyses in non-normally distributed datasets.

We highlight that no analysis of myocardial function (e.g. echocardiography) was done along the study because such analysis was beyond the scope of its protocol. Indeed, as there were no significant effects of either cardioplegic solutions on inflammatory or myocardial damage parameters in postoperative times, we would not expect that any effect could be related to the intervention under analysis. However, we do think that such evaluation could help in obtaining additional information, ideally in another prospective multicenter study with a larger N. Our N was limited by being a study in only two institutions.

5. Conclusions

The comparative analysis of the standard and modified groups showed that the dosages of interleukin-6, TNF-alpha, lactate, and troponin showed no significant differences. Both Del Nido's cardioplegic solution modified with Ringer-lactate and the standard Plasmalyte® cardioplegic solution proved to be effective in cardioprotection of adult patients undergoing valvular heart surgery.

The inflammatory response induced by exposure to the modified Del Nido's cardioplegic solution, by comparing IL-6 and TNF-alpha levels, showed no significant difference in relation to the standard solution. Also, the degree of myocardial injury and necrosis compared through lactate and troponin dosages showed no significant differences between the groups that used the Del Nido's cardioplegic solution modified with Ringer-lactate and the standard Plasmalyte® cardioplegic solution.

However, the cost of producing the modified solution is 90% lower than the standard solution. Therefore, in services with a large number of surgeries, it becomes a saving of financial resources.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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