Efficacy of Levosimendan vs. Dobutamine in the Treatment of Ventricular Dysfunction in Patients Subjected to Aortic Valve Replacement

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ABSTRACT

Introduction: The ischaemic lesion due to coarctation of the aorta, inadequate myocardial protection, cardioplegic solutions, hypothermia and other factors can contribute to alterations in the myocardial contractility in the postsurgical period of valve replacement.

Objective: To determine the efficacy of Levosimendan vs. Dobutamine in the treatment of ventricular dysfunction in patients subjected to aortic valve replacement.

Materials and Methods: Quasi-experimental research was carried out on 60 patients diagnosed with stenosis, insufficiency or double aortic lesion subjected to aortic valve replacement under general anaesthesia. Cohorts were randomly assigned, group I (n=30) Dobutamine at 7.5 µg/kg/min, and group II (n=30) Levosimendan infusion of 0.2 µg/kg/min. The following criteria were monitored in both groups arterial tension, heart rate, oxygen saturation, and the hemodynamic variables with central venous catheter 7 Fr Arrow and Swan Ganz catheter 7Fr Edwards via internal jugular. For the statistical analysis, the variables were analysed using the student’s t-test P<0.05.

Results: The average age was 57.02±13 years. The average dose was 3.5 gammas for Dobutamine and 0.1-0.2 gammas for Levosimendan. The left ventricular ejection fractions were 56.2±11% and 56.4±10%, respectively. In the postsurgical setting, significant differences were observed only in the capillary pressure (17.03±5.8 vs. 13.87±2.9 cmH2O, p<0.01). The Levosimendan group (64.1±13.6 vs. 57.6±12.9%, p=0.06).

Conclusion: The administration of Levosimendan during the perioperative aortic valve replacement was associated with a tendency of deterioration of the ejection fraction in the left ventricle compared to the use of Dobutamine.

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Introduction

Several factors can contribute to alterations in the myocardial contractility, including ischaemic lesion due to coarctation of the aorta, inadequate myocardial protection, cardioplegic solutions, hypothermia, surgical repair and repercussion lesions that occur in the hours after cardiac surgery [1, 2]. The treatment of ventricular dysfunction, derived from cardiac surgery and extracorporeal circulation, includes the administration of positive inotropic drugs and vasodilators. The most commonly used inotropic agents are beta-adrenergic agonists and phosphodiesterase inhibitors III/IV. However, the introduction of Levosimendan – a positive inotropic drug – that belongs to the group of agents can increase the sensitivity of calcium contractile proteins [3, 4]. Regarding the effects of calcium sensitizers over the function of myocardial relaxation and diastolic function in humans, in vitro studies have shown that calcium sensitizers can affect myocardial relaxation and increase diastolic pressure [5].

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Recently, it has been observed that Levosimendan enhances the echocardiographic variables of the diastolic function [6, 7]. Levosimendan sensitizes troponin C to calcium without impairing the diastolic relaxation. Furthermore, it has a vasodilator effect mediated by the opening of vascular potassium channels sensitive to ATP [8, 9]. These properties decrease both preload and afterload, increasing the left ventricular function and decreasing pulmonary resistance. The LIDO study, which includes centers in 11 European countries, compares the efficacy and safety of Levosimendan and Dobutamine in patients with heart failure and cardiac output severely diminished. This study found hemodynamic improvement, which was defined as an increase greater than 30% in the cardiac output and a decrease greater than 25% in the pulmonary artery pressure. After 30 days, 8% of patients in the Levosimendan group died, compared to 17% in the Dobutamine group. The most frequent hemodynamic side effect was arterial hypotension [10]. The survival of patients with acute heart failure requiring intravenous inotropic support was evaluated in the study SURVIVE. This was the first prospective, double-blinded, randomized study that took into consideration mortality as a primary variable in the assessment of the efficacy of Levosimendan in comparison to Dobutamine. At the end of the follow-up (final survival point at 180 days), 26% of the participants in the Levosimendan group died, while 28% died in the Dobutamine group [11, 12]. On the other hand, Dobutamine has shown an increase in atherogenicity and sudden cardiac death, probably, related to an increase in the concentrations of intracellular cAMP and myocardial ischaemia [13]. The goal of the current research is to compare Levosimendan against Dobutamine concerning the improvement of ventricular function, which is quantified by LVEF in patients subjected to aortic valve replacement.

Materials and Methods

Quasi-experimental research was carried out on 60 patients of UMAE#14 IMSS diagnosed with stenosis, insufficiency or double aortic lesion subjected to aortic valve replacement. The study was performed during the period June-September 2019, with prior authorization from the local Research Committee and informed consent. The age group was: 18 to 75 years old, both sexes. Patients with the following conditions were excluded from the experiment: Concomitant valvular injury and/or ischaemic heart disease, ejection fraction less than 30%, use of intravenous inotropic during hospitalization, patients with chronic renal failure, presence of complex ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation within the last 48 hours) and patient with a history of CVD events. Cohorts subjected to aortic valve replacement under general anaesthesia were randomly assigned. Group I (n=30) received Dobutamine at 7.5 µg/kg/min, and group II (n=30) Levosimendan infusion of 0.2 µg/kg/min. A central venous catheter 7 Fr Arrow and Swan Ganz catheter 7Fr Edwards via internal jugular was installed. The following criteria were monitored in both groups; heart rate, systolic blood pressure, mean pulmonary arterial pressure, pulmonary capillary pressure (PCP), central venous pressure, cardiac output, cardiac index, stroke volume, systemic vascular resistance, pulmonary vascular resistance. The anaesthesia technique varied between patients. The determination of the left ventricular ejection fraction, the stroke volume, the dimension of the cavities, the wall thickness of the left ventricle in systole and diastole was done by means of echocardiography in the preoperative and 48 hours after the surgical intervention that was carried out with Extracorporeal circulation and global myocardial ischaemia due to aortic clamping and electromechanical arrest of the heart by cold cardioplegia solution. For the statistical analysis, the variables were analysed using the student’s t-test P<0.05 to determine differences among groups. The statistical package used for this research was: SPSS 20.0.

Results

The following characteristics were considered: age group (Group I 55.2 ±14.5 and Group II 59.6 ± 11.7 years old), gender, weight, body mass index, cardiopulmonary bypass time and aortic clamping. The therapeutic dose for both groups was represented in 3-5 gammas for Dobutamine and 0.1-0.2 gammas for Levosimendan (Table 1).

Table 1: General characteristics of patients subjected to aortic valve replacement.

| PARAMETER          | DOBUTAMINE  | LEVOSIMEDAN | "P" value |
|--------------------|-------------|-------------|-----------|
| Age (years)        | 55.2 ± 14.5 | 59.6 ± 11.7 | 0.33 *    |
| Male               | 10 (33%)    | 7 (23%)     | 0.39      |
| Weight (Kg)        | 68.15 ± 12.7| 68.14 ± 11.7| 0.99      |
| BMI (Kg/m²)        | 1.73 ± 0.24 | 1.71 ± 0.18 | 0.64 *    |
| CEC Time (min)     | 105.6 ± 33.1| 118.9 ± 54.9| 0.54 *    |
| PAo Time (min)     | 73.9 ± 17.1 | 80.4 ± 25   | 0.59 *    |
| Dose (gammas)      | 4.05 ± 1.05 | 0.16 ± 0.05 | NA        |

*Student T-test of independent samples.

In order to analyse the hemodynamic and echocardiographic variables, the results were considered under two categories: preoperative and postoperative. Regarding the hemodynamic variables in the postoperative setting, there was a decrease in SAP, a slight increase in mean PAP, and a significant increase in CO and CI. There were no statistically significant differences in PCP, stroke volume, LVWI, and pulmonary resistance. There was an improvement in LVEF which in turn might positively affect the systolic volume, LVDD and LVSD. There was a significant decrease in the right ventricular diameter in the postoperative setting. No significant changes occurred in cohorts during the preoperative measurements, except in SAP from the Levosimendan group (p<0.05) and LVWI (p<0.05) (Table 2).

There were no significant changes in the hemodynamic and echocardiographic variables in the patients from both cohorts during the postoperative period. The PCP in the patients from the group of Levosimendan was low and there is a trend of lower values in the postoperative LVEF in the levosimendan group (Table 3).
Table 2: Preoperative Levosimendan vs. Dobutamine groups in ventricular dysfunction in patients subjected to aortic valve replacement.

| PARAMETER                        | DOBUTAMINE          | LEVOSIMEDAN        | 'P' value |
|----------------------------------|---------------------|--------------------|-----------|
| Cardiac frequency (lpm)          | 61.6 ± 11.8         | 61.5 ± 16          | 0.61 *    |
| Systolic arterial pressure (mmHg)| 108.5 ± 16.8        | 96.9 ± 20          | 0.02      |
| Mean pulmonary pressure (mmHg)   | 22.9 ± 7.2          | 24.4 ± 9.1         | 0.82 *    |
| Pulmonary capillary pressure (cmH2O) | 16.4 ± 5.7       | 16.5 ± 6.8         | 0.91      |
| Central venous pressure (cmH2O)  | 11.1 ± 3.9          | 11.3 ± 3.3         | 0.89      |
| Cardiac output (L/min)           | 3.2 ± 1.3           | 3.1 ± 1.1          | 0.83      |
| Cardiac Index (L/min/m²)         | 1.84 ± 0.7          | 1.77 ± 0.64        | 0.80 *    |
| Stroke volume (cc/min)           | 52.5 ± 17.2         | 50.1 ± 13.3        | 0.56      |
| Systolic index (cc/min/m²)       | 31.4 ± 10.1         | 30.6 ± 9.1         | 0.73      |
| Systematic resistance (dinas.cm-5) | 1877 ± 674       | 1743 ± 742         | 0.29 *    |
| LVWI (g.m/m²)                    | 40.9 ± 59           | 30.2 ± 29.7        | 0.03 *    |
| Pulmonary resistance (dinas.cm-5) | 205 ± 133          | 240 ± 168          | 0.37      |
| LVEF (%)                         | 56.2 ± 11           | 56.4 ± 10          | 0.94      |
| Systolic volume (cc)             | 72.2 ± 45.8         | 66.2 ± 43          | 0.32 *    |
| Right ventricle (mm)             | 155 ± 72.5          | 139 ± 82.2         | 0.15 *    |
| LVDD (mm)                        | 48.3 ± 8.4          | 47.4 ± 9.8         | 0.53 *    |
| LVSD (mm)                        | 33 ± 7.6            | 30.5 ± 9           | 0.92      |
| IVS (mm)                         | 13.6 ± 2.2          | 13.3 ± 1.8         | 0.61      |

*Student T-test of independent samples.

Table 3: Postoperative Levosimendan vs. Dobutamine groups in ventricular dysfunction in patients subjected to aortic valve replacement.

| PARAMETER                        | DOBUTAMINE          | LEVOSIMEDAN        | 'P' value |
|----------------------------------|---------------------|--------------------|-----------|
| Cardiac frequency (lpm)          | 92.03 ± 16.4        | 92.7 ± 20.2        | 0.89      |
| Systolic arterial pressure (mmHg)| 101.5 ± 13.7        | 102.3 ± 26         | 0.66 *    |
| Mean pulmonary pressure (mmHg)   | 26.5 ± 5.1          | 24.9 ± 5.8         | 0.24      |
| Pulmonary capillary pressure (cmH2O) | 17.03 ± 5.8       | 13.87 ± 2.9        | 0.01      |
| Central venous pressure (cmH2O)  | 13.87 ± 4.1         | 12.1 ± 2.9         | 0.06      |
| Cardiac output (L/min)           | 5.15 ± 1.5          | 5.5 ± 1.46         | 0.83      |
| Cardiac Index (L/min/m²)         | 3.0 ± 0.8           | 3.2 ± 0.9          | 0.32      |
| Stroke volume (cc/min)           | 58.5 ± 18.5         | 56.3 ± 18.4        | 0.65      |
| Systolic index (cc/min/m²)       | 36.1 ± 12.7         | 34.9 ± 19.7        | 0.56 *    |
| Systematic resistance (dinas.cm-5) | 969 ± 344          | 1018 ± 391         | 0.61      |
| LVWI (g.m/m²)                    | 34 ± 20             | 35 ± 45            | 0.34 *    |
| Pulmonary resistance (dinas.cm-5) | 152 ± 78           | 195 ± 137          | 0.23 *    |
| LVEF (%)                         | 64.1 ± 13.6         | 57.6 ± 12.9        | 0.05      |
| Systolic volume (cc)             | 52 ± 36             | 53 ± 36            | 0.87 *    |
| Right ventricle (mm)             | 88.7 ± 48.4         | 106.7 ± 52.2       | 0.17      |
| LVDD (mm)                        | 42.3 ± 6.9          | 42.5 ± 9.0         | 0.69 *    |
| LVSD (mm)                        | 28.8 ± 7.6          | 30.5 ± 9.0         | 0.67 *    |
| IVS (mm)                         | 13.2 ± 2.4          | 13.6 ± 2.5         | 0.56      |

*Student T-test of independent samples.

Discussion

In the current study, the studied population was homogenous, showing similar demographic and clinical characteristics. The dose of Levosimendan used in the subgroup was 0.1-0.2 gamma, which is the recommended dose that has been employed in other studies such as the LIDO and SURVIVE studies [7]. However, due to institutional methodological reasons, the loading bolus dose was not administered. It is noteworthy that the Dobutamine dose was 3 to 5 gamma, and no progressive increment was observed until 40 gamma, which is the level used in the SURVIVE study [12]. In contrast to the aforementioned studies, in our research, the female sex was predominant by approximately 70%. The time of aortic clamping and the time of extracorporeal circulation met the parameters established as safety ranges by the Society of Thoracic Surgeons in the United States. When comparing the values of the hemodynamic variables of both groups, an increase in the cardiac output and cardiac index, with a significant increase of CVP, mean PAP and PCP (the latter showing no statistical significance) was observed. This means that a hyperdynamic state might be produced by the inotropic in question. Furthermore, there was a
significant improvement in the LVEF measure through echography. A similar improvement in the cardiac output was observed in the levsimendan group, which is associated with an increase in CVP and PCP (not statistically significant). However, LVEF showed a decrease in the postoperative period of these patients. On comparing both drugs, it was found that LVEF tends to deteriorate when levsimendan was administered, which represents a negative result in this research. One possible explanation for this result might be the limited sample size [14, 15]. Overall, the administration of levsimendan in the preoperative setting of aortic valve replacement was associated with a deterioration of the left ventricular ejection fraction compared to the use of Dobutamine.

### Abbreviation

- **ATP**: Adenosine Triphosphate
- **cAMP**: Cyclic Adenosine Monophosphate
- **LVEF**: Left Ventricular Ejection Fraction
- **CVE**: Cerebrovascular Event
- **BMI**: Body Mass Index
- **LVWI**: Left Ventricular Work Index
- **LVDD**: Left Ventricular Diastolic Diameter
- **LVSD**: Left Ventricular Systolic Diameter
- **LVPW**: Left Ventricular Posterior Wall
- **IVS**: Interventricular Septum
- **SAP**: Systolic Arterial Pressure
- **PAP**: Pulmonary Artery Pressure
- **CVP**: Central Venous Pressure
- **CO**: Cardiac Output
- **CI**: Cardiac Index

### Tests of Normality of The Variables.

| CHARACTERISTIC | MEAN  | SD    | MEDIAN | MIN  | MAX  | SESGO | CURTOSIS | KS   | SW  |
|----------------|-------|-------|--------|------|------|-------|----------|------|-----|
| Age            | 57.38 | 13.38 | 61     | 22   | 77   | -1.017| 0.45     | .005 | .000|
| Weight         | 68.35 | 12.08 | 67     | 34   | 105  | 0.15  | 1.23     | .167 | .390|
| Dose           | 2.08  | 2.1   | 0.2    | 0    | 7    | 0.42  | -1.34    | .000 | .000|
| BMI            | 1.72  | 0.21  | 1.73   | 1    | 3    | 1.5   | 6.5      | .006 | .000|
| FC pre         | 61.73 | 14.02 | 59     | 37   | 101  | 1.02  | 1.33     | .011 | .002|
| FC post        | 92.51 | 18.37 | 90     | 22   | 122  | -0.49 | 0.14     | .200 | .006|
| SAP pre        | 102.97| 19.29 | 99     | 74   | 154  | 0.99  | 0.73     | .027 | .001|
| SAP post       | 102.15| 20.83 | 99     | 60   | 179  | 1.45  | 3.84     | .002 | .000|
| PAP pre        | 23.63 | 8.19  | 23     | 7    | 48   | 0.88  | 1.07     | .001 | .004|
| PAP post       | 25.78 | 5.53  | 25     | 11   | 39   | -0.19 | 1.12     | .007 | .011|
| PCP pre        | 16.59 | 6.17  | 16     | 6    | 30   | 0.49  | -0.20    | .006 | .013|
| PCP post       | 15.54 | 4.84  | 15     | 4    | 31   | 0.57  | 1.18     | .090 | .132|
| CVP pre        | 11.25 | 3.62  | 11     | 5    | 19   | 0.31  | -0.86    | .182 | .048|
| CVP post       | 12.95 | 3.67  | 13     | 7    | 22   | 0.41  | -0.45    | .068 | .091|
| CO pre         | 3.2   | 1.18  | 3      | 1.2  | 7.9  | 1.35  | 3.45     | .058 | .001|
| CO post        | 5.33  | 1.58  | 5.2    | 2.5  | 9.9  | 0.52  | 0.02     | .200 | .218|
| CI pre         | 1.82  | 0.68  | 1.7    | 0.7  | 4.4  | 1.55  | 3.67     | .009 | .004|
| CI post        | 3.12  | 0.89  | 3      | 1.6  | 5.7  | 0.42  | 0.14     | .069 | .234|
| VL pre         | 51.64 | 15.17 | 51.5   | 14   | 106  | 0.49  | 2.2      | .200 | .090|
| VL post        | 57.5  | 57.5  | 56     | 26   | 115  | 0.78  | 0.88     | .200 | .044|
| IS pre         | 31.21 | 9.52  | 31.8   | 8    | 59   | 0.53  | 1.32     | .166 | .050|
| IS post        | 35.57 | 16.59 | 34.2   | 4    | 117  | 2.21  | 9.12     | .000 | .000|
| RVS pre        | 1794.9| 702.64| 1662   | 634  | 4413 | 1.34  | 2.72     | .011 | .000|
| RVS post       | 991.95| 369.34| 894    | 89   | 1774| 0.31  | -0.40    | .015 | .046|
| LVWI pre       | 35.77 | 46.92 | 22.4   | 8    | 344  | 5.39  | 33.44    | .000 | .000|
| LVWI post      | 34.9  | 35.09 | 27.3   | 11   | 264  | 5.15  | 32.07    | .000 | .000|
| RVP pre        | 222.69| 152.83| 200    | 52   | 922  | 2.28  | 7.78     | .010 | .000|
| RVP post       | 173.17| 114.02| 149    | 19   | 711  | 2.1   | 7.59     | .000 | .000|
| Pao            | 77.61 | 21.43 | 74     | 48   | 146  | 1.37  | 2.03     | .018 | .000|
| CEC            | 112.99| 45.63 | 99     | 71   | 328  | 2.92  | 9.78     | .000 | .000|
| LVEF pre       | 56.07 | 10.49 | 58     | 30   | 75   | -0.97 | 0.63     | .000 | .000|
| LVEF post      | 60.86 | 13.66 | 62     | 23   | 91   | -0.46 | 0.28     | .200 | .269|
| VS pre         | 69.51 | 44.54 | 54     | 18   | 250  | 1.77  | 3.96     | .001 | .000|
| VS post        | 52.81 | 36.47 | 40     | 13   | 195  | 1.6   | 2.91     | .000 | .000|
| VD pre         | 146.25| 77.37 | 119    | 31   | 388  | 1.33  | 1.6      | .001 | .000|
| VD post        | 97.95 | 51.17 | 95     | 19   | 253  | 0.88  | 0.78     | .032 | .009|
LVDD pre  47.92  9.14  47
LVDD post  42.36  8.06  41
LVSD pre  32.9  8.82  32
LVSD post  29.58  8.4  27
Septum pre  13.42  1.97  13
Septum post  13.41  2.45  13
PP pre  12.97  1.76  13
PP post  13.27  2.59  13

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