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Effect of Levosimendan Infusion 24 Hours Before CABG Surgery in Patients with Impaired Left Ventricular Function on the Need for Postoperative IABP

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Abstract: Background: Due to their unfavorable outcome, patients with impaired left ventricular function undergoing CABG surgery (LVEF ≤ 35%) are in a real need for optimization of their preoperative status in order to achieve the best possible results. In this retrospective comparative study we analysis our results in patients with impaired LV function after using Levosimendan as a continuous infusion 24 hours prior to CABG surgery regarding the need for postoperative IABP. Patients and methods: We included in this study 103 patients with LVEF ≤ 35% that underwent coronary artery bypass grafting with or without repair of ischemic mitral regurgitation and received Levosimendan infusion 24 hours before surgery in the period between January 2016 and January 2019 in 2 hospitals (Group A). These data were compared to another matched control group of 98 patients with similar conditions that were operated in the same hospitals over a previous period of 3 years but received no Levosimendan infusion preoperatively (Group B). Results: There was a statistically significant difference in the postoperative results in favor of group A regarding the need for IABP application (P-value = 0.013). However there were no statistically significant differences between both groups in concern of duration of inotropic support (P-value = 0.40), duration of mechanical ventilation (P-value = 0.30), total ICU (P-value = 0.20) and hospital stays (P-value = 0.40), incidence of postoperative atrial fibrillation (P-value = 0.50), incidence of major adverse effects, and in-hospital mortality (P-value = 0.20). There was only one in-hospital mortality in each group. Conclusion: According to our study, infusion of Levosimendan 24 hours prior to CABG surgery in patients with impaired left ventricular contractility is safe and effective in reducing the need of IABP application. However Levosimendan infusion did not affect significantly postoperative coarse, incidence of major adverse effects, and in-hospital mortality.

Keywords: CABG Surgery, Levosimendan Infusion, Intra-aortic Balloon Counter-pulsation Pump

1. Introduction

With advances in health care services whether in diagnostic tools or therapeutic options, more risky patients especially those with impaired left ventricular (LV) function are referred to surgery. Unfortunately these patients represent a problematic population due to their unfavorable outcome especially for the fact that there is a 19% increase in the odds of death with each 10-unit decrease in preoperative LV ejection fraction (LVEF) according to the Society of Thoracic Surgeons National Adult Cardiac Surgery Database. [1] Therefore such patients are in a real need for optimization of their preoperative status in order to achieve the best possible results. Hence the prophylactic use of inotropic agents especially Levosimendan has been suggested as a pharmacological preparation to improve postoperative outcomes in those patients. [2-3] In this retrospective

comparative study we analysis our results in patients with impaired LV function after using Levosimendan as a continuous infusion 24 hours prior to CABG surgery regarding the need for postoperative IABP.

2. Patients and Methods

We included in this study 103 patients with LVEF ≤ 35% that underwent coronary artery bypass grafting with or without repair of ischemic mitral regurgitation and received Levosimendan infusion 24 hours before surgery in the period between January 2016 and January 2019 in 2 hospitals (Group A). These data were compared to another matched control group of 98 patients with similar conditions that were operated in the same hospitals over a previous period of 3 years but received no Levosimendan infusion preoperatively (Group B). An informed consent was obtained from all patients and an institutional review board was obtained.

Patients with recent myocardial infarction (MI) within 2 weeks, valve lesions other than the mitral valve, chronic renal failure (serum creatinine > 2 mg/dl) and prior cardiac surgery were not included in the study. A myocardial viability study using Thalium perfusion scan or Dobutamine stress echocardiography was performed for all patients preoperatively to ensure the presence of viable myocardium for revascularization.

Group A patients were admitted one day before surgery to the ICU where invasive monitoring of arterial blood pressure and central venous pressure was established together with monitoring of urine output, pulse oximetry and electro-cardiograpy (ECG). Levosimendan (Simdax, Orion Pharma, Espoo, Finland) was administered as a continuous infusion at a dose of 0.1 μg/kg/min for 24 hours without a loading dose.

All patients received the same anaesthetic protocol and were operated through full median sternotomy. Patients without concomitant mitral valve repair were operated without the help of heart lung machine (Offpump) which is routine at our hospitals. All CABG procedures were performed by the same surgeons with the use of the left internal mammary artery (LIMA) as a conduit for the left anterior descending artery (LAD) and saphenous vein grafts (SVGs) for the other coronary vessels. Mitral valve repair was done in all cases with a remodeling annuloplasty ring (Edwards Lifesciences Physio 1 ring). In the ICU the haemodynamic parameters, duration of inotropic support, need for IABP, duration of mechanical ventilation, and length of stay were recorded in both groups. In addition other data of the postoperative course were collected including total hospital stay, occurrence of major adverse events and operative mortality (death within 30 days postoperatively or during the same hospitalization). Major adverse events were defined by postoperative myocardial infarction (CK-MB levels > 125 IU/l during the first 72 hours with development of a new Q wave or left bundle branch block in the ECG), new renal impairment (serum creatinine levels > 2 mg/dl or twice the preoperative creatinine) and postoperative stroke (new neurological deficit persisting more than 24 hours).

3. Statistical Analysis

Data were coded and then analyzed using the SPSS statistical software (IBM SPSS Statistics, version 19). Continuous variables were expressed as mean ± standard deviation while categorical variables were expressed as numbers and percentages. The Mann–Whitney U-test was used to compare the continuous variables and the $\chi 2$ test or Fisher's exact test was used to compare the categorical data. Paired analysis and ANOVA for repeated measurements were used to detect differences between-groups. A P-value < 0.05 was considered statistically significant.

4. Results

There were no statistically significant differences in both groups regarding preoperative patient characteristics including; age, gender, risk factors, EuroSCORE II, LVEF, percentage of scar tissue to viable myocardium and significant mitral regurgitation necessitating repair (Grade III-IV). Table 1.

Table 1. *Preoperative patient characteristics (LVEF; left ventricular ejection fraction).*

Preoperative patient characteristics	Group A (n = 103)	Group B (n = 98)	P-value
Age	57 ± 11.3	55 ± 12.6	0.51
Gender			
Males	95 (92.3%)	93 (94.9%)	0.65
Risk factors			
Dyslipidemia	55 (53.4%)	48 (49%)	0.42
Systemic hypertension	70 (68%)	62 (63%)	0.53
Diabetes Mellitus	67 (65%)	58 (59%)	0.60
Smoking history	83 (80.6%)	71 (72%)	0.35
EuroSCORE II	2.8 ± 1.1	2.5 ± 1.3	0.62
LVEF (%)	30 ± 4.6	31 ± 3.5	0.70
Scar tissue/ viable myocardium (%)	25 ± 7	28 ± 5.8	0.32
Mitral regurgitation (III-IV)	29 (28.1%)	22 (22.5%)	0.27
Left main disease	11 (10.68%)	13 (13.26%	0.40

Levosimendan infusion could be completed in all patients of group A without the occurrence of hemodynamic

instabilities or need for vasopressors.

Similarly operative data were statistically similar in both groups in concern of the total operative time, cardiopulmonary bypass (CPB) and cross clamp (CC) times in cases with concomitant mitral valve repair, average number of grafts, occurrence of arrhythmia whether atrial or ventricular, and conversion to on-pump bypass. Table 2.

Table 2. *Operative data (CPB; cardiopulmonary bypass, CC; cross-clamp).*

Operative data	Group A (n = 103)	Group B (n = 98)	P-value
Total operative time (hours)	3.1 ± 1.2	3.6 ± 1.1	0.50
CPB time (in cases with mitral repair) (min)	82 ± 13	78 ± 8	0.45
CC time (in cases with mitral repair) (min)	70 ± 11	68 ± 12	0.70
Average number of grafts	3.2 ± 0.4	3.1 ± 0.6	0.20
Occurrence of arrhythmia			
Atrial	26 (25.2%)	32 (32.6%)	0.35
Ventricular	8 (7.76%)	10 (10.2%)	0.21
Conversion to on-pump bypass	2 (1.9%)	3 (3.06%)	0.15

On the other hand there was a statistically significant difference in the postoperative results in favor of group A regarding the need for IABP application (P-value = 0.013). However there were no statistically significant differences between both groups in concern of duration of inotropic support, duration of mechanical ventilation, total ICU and hospital stays, incidence of postoperative atrial fibrillation (AF), incidence of major adverse effects, and in-hospital mortality. Table 3.

Table 3. *Postoperative results (MI; myocardial infarction, AF; atrial fibrillation; IABP, intra-aortic counter-pulsations pump).*

Postoperative results	Group A (n = 103)	Group B (n = 98)	P-value
Need for IABP application	1 (0.97%)	9 (9.2%)	0.013
Duration of inotropic support (days)	3.5 ± 1.5	4.3 ± 1.2	0.40
Duration of mechanical ventilation (hours)	28 ± 9	32 ± 12	0.30
Adverse events			
MI	1 (0.97%)	1 (1.02%)	0.20
Stroke	0	1 (1.02%)	0.35
Renal failure	2 (1.94%)	3 (3.06%)	0.40
Postoperative Arrhythmia (AF)	33 (32%)	25 (25.5%)	0.50
Total ICU stay (days)	4.8 ± 1.7	5.3 ± 1.3	0.20
Total hospital stay (days)	9.1 ± 2.5	10 ± 2.1	0.40
In-hospital mortality	1 (0.97%)	1 (1.02%)	0.20

The total health care service coasts of all patients in both groups were similar with no statistically significant difference. There was only one in-hospital mortality in each group. In group A, one patient developed malignant intractable ventricular fibrillation on the second postoperative day and died suddenly despite normal serum electrolytes and without postoperative ECG changes. In group B, one patient developed severe low cardiac output syndrome immediately after CABG surgery and mitral valve repair which did not respond to maximum inotropic support and IABP application.

5. Discussion

Levosimendan (pyridazinone-dinitrite) is a member of a new group of inotropic agents known as the calcium sensitizers that are recently used in cardiac surgery to increase myocardial contractility especially in patients with impaired LV function. [4] Levosimendan has 3 unique vasoactive inotropic actions; it reduces the calcium-binding coefficient of troponin C enhancing myocardial contraction but with lower intracellular calcium concentration requirements in contrast to traditional inotropic agents (catecholamines and phosphodiesterase inhibitors) that increase cAMP resulting in increased calcium current into myocytes during systole. In addition Levosimendan opens adenosine triphosphate-sensitive potassium channels on vascular smooth muscle cells and in cardiac mitochondria. This results in arterial, coronary and venous vasodilatation decreasing preload and afterload in the systemic and pulmonary circulations as well as in mitochondrial activation acting in synergism with calcium sensitization to improve myocardial performance. [5] These actions are shown in some studies to be superior to those of traditional inotropic agents in improving surgical outcome especially in patients with impaired LV contractility since they are not associated with increased myocardial oxygen demand or decreased diastolic function. [6] However controversies do exist till now regarding the efficacy of prophylactic use of Levosimendan in cardiac surgery even in meta-analysis studies. [7-9] But when reviewing most of studies showing no benefits of the preoperative use of Levosimendan before cardiac surgeries we notice that most of the patients included in these studies received Levosimendan either shortly before

surgery or in the operating room and with a loading dose. Also some of these studies included patients with normal ventricular function leaving no real action for Levosimendan in improving myocardial contractility and thus surgical outcome. [10]

Our study included a larger sample size of patients with impaired LV function needing CABG surgery with or without concomitant ischemic mitral repair and receiving preoperative Levosimendan than previous similar studies which were underpowered by small patient cohort. [11] In addition, in our series we have chosen the strategy of giving Levosimandan as a continuous infusion at a rate of 0.1μg/kg/min without loading 24 hours before surgery to avoid the adverse effects of Levosimendan; namely hypotension and arrhythmias noted when giving the drug as an intravenous bolus or infusion at higher rates. [12] At that infusion rate the drug itself reaches a linear concentration in blood after 4 hours while its active metabolite, OR-1896, continues in blood to a peak level about 48 hours and achieves a half-life of about 80 hours after the end of the infusion, covering the most critical postoperative period after CABG surgery until complete recovery of the ischemic myocardium. [13] This strategy appears successful in avoiding the adverse effects of the drug since none of group A patients experienced these effects.

In our study we have focused on surgical outcome especially in-hospital mortality, ICU and hospital stays as well as the need for IABP insertion which is the main goal and what really matters for cardiac surgeons in high risk patients with low EF undergoing CABG surgery. According to our results administration of Levosimendan as a continuous infusion 24 hours before surgery was significantly associated with the reduction in the need for IABP but was not significantly associated with reduction in other postoperative parameters that appear to be more related to the expected course of such high risk patients after CABG surgery.

Although the use of IABP prior to CABG surgery in high-risk patients especially those with low LVEF has been shown in many studies to improve surgical outcomes in terms of in-hospital mortality, postoperative hemodynamic parameters and ICU stay. Yet IABP application is in general an invasive procedure that might be associated with some adverse effects like limb ischemia and arterial dissection. [14] On the other hand the coasts of Levosimendan infusion and insertion of an IABP set are similar and the increased coasts of preoperative admission to ICU for one day to receive the infusion are compensated postoperatively if the patient needed IABP which will remain for at least 48 hours before being removed.

Lastly our study included a large number of CABG cases that were operated upon without the heart lung machine (74 out of 103 patients). In all these cases we did not experience any complications related to Levosimendan infusion like hypotension and arrhythmia. Actually Levosimendan was shown in some studies to improve hemodynamics when given in small doses in patients undergoing Offpump CABG surgery. [15-16]

6. Conclusion

According to our study, infusion of Levosimendan 24 hours prior to CABG surgery in patients with impaired left ventricular contractility is safe and effective in reducing the need of IABP application. However Levosimendan infusion did not affect significantly postoperative coarse, incidence of major adverse effects, and in-hospital mortality.

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