A COMPARATIVE STUDY BETWEEN LEVOSIMENDAN AND EPHEDRINE-CALCIUM IN PATIENTS UNDERGOING OFF-PUMP CORONARY ARTERY BYPASS GRAFTING

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Abstract:
Background: Many adult patients require temporary inotropic support after cardiac surgery. However, cardiac displacement & manipulation during OPCAB may cause some hemodynamic alterations. So, prophylactic usage of inotropic agents would be mandatory even in patients with normal left ventricular function. The aim of our study is to compare between levosimendan & ephedrine-calcium as inotropic agents during OPCAB in patients with normal left ventricular function.

Methods: 24 patients with normal ventricular function included in this randomized controlled trial, were divided into 2 groups: Group A (n=12) received ephedrine-calcium boluses immediately prior to revascularization. Group B (n=12), received 12ug/kg of levosimendan over a period of 15 minutes, immediately after induction of anesthesia. The heart rate, cardiac index, stroke volume index, and left ventricular ejection fraction were measured before and 10 and 60 minutes after the drugs administration as well as 2 hours postoperatively.

Results: Heart rate was significantly higher in the calcium-ephedrine group than in the levosimendan one after 10 & 60 minutes from the beginning of revascularization (P<0.05). Compared with ephedrine-calcium group, cardiac index was significantly higher 10, 60minutes & 2 hours postoperative (p< 0.05) after administration of levosimendan. Stroke volume index was significantly higher 10 minutes after levosimendan administration (p< 0.05). Left ventricular ejection fraction increased significantly after 60 minutes, and 2 hours postoperative in the levosimendan group (P<0.05).

Conclusion: Levosimendan in a dose of 12 ug/kg over a period of 15 minutes enhances the left ventricular performance during off-pump coronary artery bypass grafting in patients with normal preoperative left ventricular function, better than calcium-ephedrine with neutral effect on myocardial energy.

Key words: Levosimendan- Calcium- Ephedrine- OPCAB
Introduction:
During conventional coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB), the development of systemic inflammatory response syndrome, hypothermia, formation of microemboli, and desensitization of beta adrenoceptors could extend postoperative recovery (1, 2). On the other side, off-pump coronary artery bypass grafting (OPCAB) achieves better inhospital outcomes, similar completeness of revascularization, and shorter lengths of stay compared with conventional CABG (3, 4). Heart displacement during OPCAB is necessary to expose target coronary arteries. This manipulation of the beating heart, especially on the lateral and posterior left ventricular wall, may cause significant fluctuation in the patient’s hemodynamic state (5, 6). The major cause of hemodynamic changes is transitory biventricular systolic and diastolic dysfunction, and disturbance of diastolic filling of the right ventricle, primarily by direct ventricular compression (7). Inotropic support and use of vasoconstrictors are frequently essential for the myocardial dysfunction after episodes of ischemia (stunning) during coronary occlusion. The myocardial stunning is related with decreased myofibril calcium sensitivity (8). Prophylactic usage of inotropic agents seems to be reasonable in this setting for patients undergoing OPCAB with normal left ventricular (LV) function (9, 10). Levosimendan is a new calcium sensitizer, which induces contractility by binding to troponin C without increasing intracellular calcium concentration. It has vasodilatatory and antiischemic properties attributable to its effects on adenosine triphosphate-dependent potassium channels. It also lowers the possibility of stunning and arrhythmias, and has neutral effect on myocardial energy (11, 12). Some studies proved a positive effect of levosimendan on myocardial function following cardiopulmonary bypass in patients undergoing elective heart surgery (13, 14). Many studies have shown that low doses of ephedrine in combination with calcium boluses are commonly administered to restore cardiac output and mean arterial pressure during manipulation of the heart, particularly if positional changes like the Trendelenburg position, are not effective (15, 16). The aim of our study is to compare between levosimendan and calcium-ephedrine on left ventricular systolic function during OPCAB in patients with normal LV function.

Patients and Methods:
24 patients were scheduled for OPCAB operation at the Cardiothoracic Department, Cairo University Hospitals. These 30 patients were divided into 2 groups, each one containing 12 patients. The 1st group was the ephedrine-calcium, where patients received a combination of ephedrine & calcium boluses, while the 2nd one was the levosimendan, where patients received this drug over a period of 15 minutes. The inclusion criteria were as follows: primary OPCAB, angiographically verified coronary artery disease, and left ventricular ejection fraction (EF) ≥50%. All patients were male and younger than 70 years of age (Table 1). Patients were excluded from the study if they had any kind of heart disease except coronary artery disease, congenital heart disease, atrioventricular conduction disturbances, evidence of previously ventricular arrhythmias requiring antiarrhythmic treatment, atrial fibrillation with rapid ventricular response, significant valvular stenosis or regurgitation, or pulmonary hypertension. Patients with myocardial infarction or stroke within 6 months, diabetes mellitus, end-stage of obstructive or restrictive pulmonary disease, severe kidney (serum creatinine >1.5 mg/dl) or hepatic disease (bilirubin 1.5 times above the upper limit of normal), or sepsis were also excluded. Patients taking antiarrhythmic or digoxin therapy and requiring inotropic support before surgery were also excluded from the study. Exclusion criteria during surgery were myocardial ischemia (depression or elevation of the ST-segment for more than 1 mm on 6-lead electrocardiography) and hemodynamic instability (heart rate>120 beats/min, reduction of mean blood pressure more than 30% from the baseline reading taken prior to induction, need for use of cardiopulmonary bypass or need for cardiac pacing).

Anesthesia technique:
All patients received standard anesthetic technique. Patients were premedicated with 10 mg morphine intramuscularly injected an hour prior to surgery and 0.05 mg/kg midazolam intravenously administered 20 minutes pre-induction. Anesthesia was induced by 5 microgram/kg body weight
fentanyl and 2.5 mg/kg body weight thiopentone sodium. 0.1 mg/kg pancuronium was given to facilitate tracheal intubation. Maintenance of anesthesia was achieved with isoflurane 0.4 to 0.8% in FIO₂ 0.6 oxygen/air mixture. Mechanical ventilation was maintained at tidal volume of 6-8ml/kg and frequency of 10-12 breaths/minute, facilitated by 1mg boluses of pancuronium every hour. Fentanyl infusion at rate of 2 microgram/kg/hr was used with additional boluses of 50 microgram given when needed to maintain adequate analgesia.

**Hemodynamic Monitoring:**
Arterial catheter was inserted into the left radial artery, to measure direct arterial blood pressure. Seldinger’s technique was used for the central venous catheter placing and for the placing of a 5-lumen, 7.5 French pulmonary artery catheter (PAC) into the right internal jugular vein to be settled in a pulmonary artery branch. Central venous, radial and pulmonary arterial pressure transducers were zeroed at the level of the left atrium. Electrocardiographic leads II and V5 to monitor the heart rate & rhythm were also used. Thermodilution method was used for measuring cardiac output in our clinical setting. By this method, multiple cardiac output measurements can be obtained at intervals by using an inert indicator. A 10mL bolus of 5% glucose was injected into the right atrium as the indicator of the room temperature; the following temperature changes were detected by the thermistor on the top of pulmonary catheter. During the patient’s exhalation, an indicator was injected over 4 seconds throughout the proximal port of the catheter. The thermodilution curve was monitored on the thermodilution monitor (Cardiac Output Computer). Three repeated measurements were done & the mean value was calculated. The transesophageal echo probe was inserted and positioned in the stomach. Superior angulation (flexing the scope) in the O₂ imaging plane yielded the transgastric mid short-axis view. At this level, we determined both the left ventricular end-systolic dimension and left ventricular end-diastolic dimension. By recording the left ventricle cross-sectional view, we measured the percent fractional shortening and calculated the Ejection Fraction.

**Study Design:**
Patients were randomized into two groups. One group received ephedrine 30mg divided into 3 doses, each 10mg, the 1st one started with the beginning of revascularization, the 2nd after 20 minutes & the last one after another 20 minutes. Additonally, this group received 10 ml of calcium chloride (10%) containing 272 mg of calcium, this was given by slowly Intravenous injection with the 1st dose of ephedrine. The other group received 12 ug/kg of levosimendan (Simdax 2.5 mg/ml, under license by Orion corp Espoo Finland, Abbott, USA), during a period of 15 minutes, immediately after induction of anesthesia. Infusion of 500 mL hydroxyethylstarch 6% solution (HAES-sterile 6% in saline 0.9 %,) was administered in all patients to optimize preload. Heart rate, cardiac index (CI), stroke volume index (SVI), and left ventricular EF were measured before and 10, 60 minutes & 2 hours postoperatively after ephedrine-calcium as well as levosimendan administration. Any major change in the hemodynamic parameters (Heart rate, mean blood pressure, pulmonary artery pressure or cardiac index) throughout the procedure was recorded.

**Statistical Analysis:**
Data were statistically described in terms of mean ± standard deviation (± SD), median and interquartile range, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the 2 study groups was done using Mann Whitney U test for independent samples. Within group comparison was done using Friedman’s test. For comparing categorical data, Chi square (χ²) test was performed. Yates correction was used in stead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program.

**Results:**
Concerning the patients demographics, there was no statistically significant difference between the the calcium-ephedrine group as well as the levosimendan one (Table 1).
Concerning the hemodynamic parameters, there was no statistically significant difference between the 2 groups in the baseline values (cardiac index, stroke volume index & heart rate). This was also the case for the left ventricular ejection fraction. (Table 2)

Within the ephedrine-calcium group, there was no difference in the cardiac index, stroke volume index at different time points. However, there was an improvement in the Left ventricular ejection fraction (%) after 10, 60 minutes as well as 2 hours postoperative (P= 0.023). As regards the heart rate, there was a significant increase both intraoperatively & 2 hours postoperative (P= 0.018). (Table 2)

For the levosimendan group, there was a significant improvement in the cardiac index, stroke volume index & left ventricular ejection fraction  (P=0.009, 0.022 & 0.008 respectively). However, there was no difference in the levosimendan group concerning the heart rate. (Table 2)

Table 2: Hemodynamic parameters (median, interquartile range) of myocardial contractility after 15-minute infusion of either calcium ephedrine or 12 ug/kg levosimendan in off-pump coronary artery bypass
the heart. In this type of surgery immediate postoperative left ventricular dysfunction often occurred (17). Transient ischemia from the direct coronary occlusion often resulted in myocardial stunning followed by hemodynamic instability (18). Animal studies, which investigated the hemodynamic changes during heart displacement, have indicated that such displacement has its primary deleterious effects on the right heart (19). The main cause of hemodynamic instability (decreases of cardiac output and arterial pressure; increases of left and right atrial pressures; and left and right ventricular end-diastolic pressures) is the disturbance of ventricular diastolic filling by direct ventricular compression (7). Although exposure of the posterior and lateral vessels caused a decrease in left ventricular contractile state, these cardiovascular disturbances could be easily corrected by anesthetic intervention, such as fluid loading, low doses of inotropic agents, or boluses of vasoconstrictors (7, 20-22).

There is still not uniform established opinion about vasoactive drug support in OPCAB. Catecholamines are not recommended in this setting because they could cause significant hemodynamic disturbances (primarily tachycardia) and increase in myocardial oxygen consumption. Vasoconstrictors are the medications mostly used in these situations, but they could have an effect on cardiac output and on the patency of arterial grafts due to increasing systemic vascular resistance. Because of the unfavorable effects of the previously mentioned medications, levosimendan could be an alternative agent for the maintenance of hemodynamic stability in OPCAB.

Myocardial dysfunction during this procedure is characterized by impaired postischemic systolic function, which is related to decreased myofibril calcium sensitivity (23). Calcium sensitization has been proposed as a novel therapeutic approach by which cardiac performance may be enhanced without predisposition to calcium-induced arrhythmias or an increase in myocardial oxygen demand (24). Clinical data indicate that levosimendan produces hemodynamic improvement in patients with normal preoperative left ventricular function undergoing heart surgery, but the role of myofilament calcium sensitizers has not been described until now in OPCAB (13, 14). Our results were in contrast to the findings of Lilleberg et al (13), who proved that a single intravenous loading dose of levosimendan produces hemodynamic changes that are characteristic of the agents with inodilation effect. In this study, after administering levosimendan, heart rate increased, which was a reflection of baroreceptor activation caused by lessening of left ventricular afterload. However, concerning the hemodynamic changes, our study confirms with that of Lilleberg et al (13), which could mean that levosimendan has a favorable effect on stroke volume index, cardiac index & LVEF. In some studies of patients undergoing CABG, higher doses of levosimendan might have a slight reduction in left ventricular afterload, however, not accompanied with a fall in systemic arterial pressure (25).

In the ephedrine-calcium group, there was a significant increase in the heart rate in comparison to the levosimendan one. Concerning the left ventricular ejection fraction, there was a remarkable improvement after 60 minutes & 2 hours postoperative among the patients receiving this combination. However, there was a significant difference between the 2 groups concerning improvement of LV function. This was also the case for the stroke volume index as well as the cardiac index where there was a significant improvement in the levosimendan group rather than the ephedrine-calcium one.

The limitations of this study were a small number of patients and specific surgery procedure (cardiopulmonary bypass was not performed). A possible shortcoming of levosimendan usage in cardiosurgery patients could be the fall of blood pressure due to the decrease in the right ventricular filling pressure. The same mechanism, based on the baroreceptors activation, could aggravate reflex tachycardia. However, reflex tachycardia was not registered in our study, because we used a lower dose of levosimendan, which could additionally limit the results of this study. Favorable hemodynamic effect of levosimendan, as shown in our study, could hasten the healing and decrease the patients’ length of stay in intensive care units. However, these results have to be interpreted with caution in patients with preoperative left-sided heart failure and hemodynamic criteria for low cardiac output syndrome.

In conclusion, levosimendan offers a promising therapeutic choice for the management of patients...
with optimal hemodynamic stability. It also enhances left ventricular performance during OPCAB in patients with good preoperative left ventricular function. Further clinical investigations should include patients with low cardiac output syndrome in early postoperative period and those with diastolic myocardial dysfunction, and should provide answers to questions about oxygen balance in the myocardium and potential unfavorable effects of levosimendan on intrapulmonary shunt.

References:
