COMPARISON OF LEVOSIMENDAN AND IABP IN PATIENTS WITH IMPAIRED LEFT VENTRICULAR FUNCTION SUBJECTED TO CORONARY ARTERY BYPASS GRAFT SURGERY (CABG)

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ABSTRACT

Objectives: This research aims to compare levosimendan to the intra-aortic balloon pump (IABP) in impaired left ventricular function patients undergoing on-pump coronary artery bypass grafting (CABG) with less than 35% ejection fraction.

Methods: From December 2015 and March 2020, a prospective randomized trial was conducted on 60 patients with less than 35% left ventricular ejection fraction who experienced elective CABG with or without mitral ring repair. These patients were separated into two categories based on their treatment: those who got intra-aortic balloon counter-pulsation (group B) and those who received levosimendan (group A).

Results: Mortality and morbidity showed significant differences between both groups in relation to the IABCP group. Higher mean arterial blood pressure (6 hours after cardiopulmonary bypass) and a significantly lower heart rate on postoperative Day 2 were reported in the IABP group. Complications were slightly less frequent in group A than in group B.

Conclusion: In contrast to IABP, we found that initiating levosimendan infusion after induction of anaesthesia is an appropriate choice. Levosimendan is equivalent to IABP in boosting hemodynamics before and after traditional on-pump CABG in high-risk cardiac patients where IABP is contraindicated or too risky to use.

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INTRODUCTION

The Intra aortic balloon pump (IABP) is a well-established adjunctive therapy for the failing heart after myocardial infarction, unstable angina, or cardiac surgery. IABP therapy improves the supply and demand balance of the myocardium, decreases afterload, and increases diastolic pressure, all of which result in improved cardiac activity. Increased diastolic pressure redirects coronary blood supply into the ischemic regions of the myocardium.

Gunstensen and colleagues hypothesize that preoperative administration of an IABP can result in a reduction of myocardial ischemia, potentially improving myocardial revascularization outcome in impaired preoperative left ventricular function patients. Meta-analyses, on the other hand, favour the use of an IABP preoperatively in high-risk patients, even those with LVEF less than 0.35. These findings showed that patients who receive preoperative IABP care have a considerably lower hospital mortality risk than those who receive it postoperatively. Although the best period to begin preoperative IABP is not identified yet, **Christenson and colleagues** recently demonstrated in a randomized trial that initiating IABP therapy 24 hours prior to aortic cross-clamping did not increase postoperative mortality or morbidity in high-risk patients as compared to a 6 to 48 hours IABP treatment prior to aortic cross-clamping. The aim of this study is to compare preoperative IABP care to levosimendan bolus and infusion on perioperative and postoperative cardiac output, morbidity, and mortality in a group of high-risk patients undergoing CABG. The majority of inotropic drugs work by increasing myocardial contractility through increasing intracellular calcium concentrations, resulting in an increase in myocardial oxygen intake (**Silva-Cardoso, 2009)**. Arrhythmias are less likely to occur when levosimendan is used. This is because overall intracellular calcium levels are not increased. Levosimendan has little effect on the length of diastole and hence does not impair ventricular relaxation, thus ensuring proper ventricular filling and maximum coronary perfusion. Vasodilation induced by potassium channel opening can predispose to hypotension **(Packer, 2013)**. Levosimendan use has been associated with long-term advantages, as the presence of a pharmacologically active metabolite with a long removal half-life (75–80 h) results in long-lasting hemodynamic effects lasting up to 7–9 days.

PATIENTS AND METHODS

This prospective and retrospective, controlled, non-randomized study, Between February 2015 and March 2020, was conducted on 60 consecutive patients with less than 35% left ventricular ejection fraction, who experienced elective CABG without concomitant procedures. Patients were separated into two groups; group A: using levosimendan, and group B: using IABP. **Key exclusion criteria;**

Unstable cases undergoing urgent CABG, recent acute myocardial infarction within two weeks before surgery. Also excluded from our study were patients with severe chronic obstructive pulmonary disease (COPD), renal failure requiring hemodialysis, and history of cerebrovascular stroke, those who had levosimendan administered within the preceding 30 days, patients with contraindications to IABP as severe peripheral vascular disease, aortic regurgitation, dissection, or aneurysm, patients with CABG reoperations, had chronic obstructive pulmonary disease, or liver and kidney diseases. **Key inclusion criteria**; patients presented with multiple coronary vessels disease indicated for CABG confirmed by coronary angiographic studies, and those with preoperative echocardiography that revealed poor left ventricular function with ejection fraction less than 35%.

After infusion of anesthesia, levosimendan was delivered intravenously via a central venous line in Group A. Over a 24-hour period, hemodynamics is closely tracked with a continuous infusion of 0.1 μg/kg/min diluted in 5% glucose at a concentration of 0.25 mg/mL(without boluses). In the IABP group (Group B), the device was inserted during general anesthesia induction. Under local anesthesia and sedation, the IABP was inserted into the femoral artery using the Seldinger procedure (Datascope, linear 6.5-7.5 F, 40 mL; Datascope Corp, Fairfield, NJ). Sheathless injection was favoured. After verifying the absence of substantial mediastinal bleeding, heparin infusion was initiated postoperatively in the ICU at a rate of 5 U/kg/h to sustain ACT within 150 sec or enoxaparin 1 mg/kg bid. The IABP was maintained for at least 48 hours postoperatively or until hemodynamics and parameters of the patient revealed no evidence of poor cardiac activity. Routine median sternotomy incision was performed in all cases. Cardiopulmonary bypass (CPB) was initiated in all patients via aorto-atrial cannulation after ensuring that the ACT was greater than 480 sec. The left internal mammary artery was nearly always grafted to the left anterior descending artery, while other targets were grafted using the great saphenous vein or radial artery. The myocardial defence was achieved using warm transient antegrade blood potassium cardioplegia. Since weaning from CPB, heparin was replaced with protamine sulphate. In the IABP group, epinephrine and/or norepinephrine infusions were initiated in the event of decreased cardiac output. Norepinephrine was nearly exclusively used in the levosimendan group to prevent extreme peripheral vasodilation. With nearly all patients in both groups, we used norepinephrine to avoid the peripheral vasodilatory effect of both levosimendan and IABP to maintain sufficient hemodynamics. When necessary, norepinephrine was added to maintain cardiac output.

The primary endpoint was mortality. The secondary endpoints were ICU and hospital stays, mechanical ventilation time, morbidities (arrhythmias, dialysis, reopening, and mediastinitis), and postoperative ejection fraction.

All patients signed informed consents, and the study was approved by the local ethics committee. Every patient included in this study was subjected to medical history on admission to the cardiology department, including analysis of demographics, risk factors, associated comorbidities, general and cardiac examination coronary atherosclerosis, routine laboratory investigations, and 12 leads ECG.

Two-dimensional echo, M- Mode, Doppler and Simpson's methods were performed using General Electric System Vivid-3 machine with (2.5-5) MHZ probe to obtain measurements of ejection fraction, LV volumes, segmental wall motion abnormality, and mitral regurgitation according to the recommendations of American society of echocardiography **(Zoghbi et al., 2017)**. The following measurements were obtained; LV end-diastolic volume (LVEDV): Normal value (95±18 mL), LV end-systolic volume (LVESV): Normal value (39±11 mL), LV end-diastolic volume index (LVEDVI): Normal Value (45±10ml/ m^2), LV end-systolic volume index (LVESVI): Normal value (21±9ml/ m^2), the severity of secondary MR by effective regurgitate orifice area (EROA) ≥0.2, regurgitate volume (RV)≥30 ml/beat, vena contracta (VC) ≥ 4mm and Regurgitant Fraction(RF) ≥50 ml, and anatomical suitability of mitral leaflets for clipping. All data were analyzed by an expert echocardiographer.

Statistical analysis: For continuous data summarization, mean ±SD was used. Numbers and percentages were used for categorical data. Mann–Whitney U test was used for between-groups comparisons of continuous data. Chi-square test (or Fischer's exact test) was used for comparing qualitative data. The level of evidence was P value < 0.05. Data analysis was conducted by SPSS (version 22, USA, IL).

RESULTS

There were no significant differences in demographic data or baseline clinical characteristics between the groups, as shown in the first table (Table 1).

TABLE 1; Comparing demographic data and risk factors between both group

Baseline characteristics	**LEVOSIMENDAN(30)**	**IABCP (30)**	P-value
Age (years) Mean ± SD	61.9 ± 13.4	53.3 ± 10.3	<0.001
BMI Mean ± SD	29.0 ± 3.3	28.3 ± 3.0	>0.05
Demographics and co-morbidities			
Male gender	20 (66%)	21 (67%)	>0.033

DM	15 (50%)	18 (60%)	>0.04
HTN	16 (51%)	14 (49%)	>0.06
Dyslipidemia	15 (50%)	18 (60%)	>0.08
CKD	9 (30%)	10 (32%)	>0.10
EF	33%	30%	>0.12
NYHA class			
Class II	20 (66%)	18(0%)	>0.05
Class III	8 (28%)	9 (30%)	
Class IV	2 (6%)	3 (10%)	

Regarding intraoperative data, the total bypass time was calculated for all patients. The mean bypass time in Group A ranged between 65-135 minutes with a mean of 79.22 ± 20.88 minutes. In Group B, it ranged between 69-140 minutes with a mean of 80.7 ± 19.8 minutes. The number of grafts ranged from 2 to 4 with a mean of 3.2 ± 0.48 in Group A, while Group B had a number of grafts ranging from 2 to 4 with a mean of 3.2 ± 0.48. Bypass time and the number of grafts showed no significant differences between both groups. In our study, we recorded the mean arterial pressure, central venous pressure and heart rate of patients in the two groups, as shown in the second table (Table 2). The most notable result after review of the hemodynamic parameters of the two groups was the significant difference in mean arterial pressure six hours after CPB. It was 81.8 ± 6.2 in Group A compared with 88.8 ±9.7 in Group B (P = .01). Also, the heart rate showed a statistically significant difference on postoperative day two, being 89.6 ± 8.4 in Group A compared with 76.3 ± 3.6 in Group B (P = .007). On day two, there is also a statistical difference in mean arterial pressure, 70.6 ± 5.5 in group A compared with 85 ± 9.7 in group B.

The postoperative data shown in (Table 3) revealed no significant differences regarding postoperative mechanical ventilation time, arrhythmias, reopening, need for hemodialysis, mediastinitis, or hospital stay between both groups.

We used norepinephrine with nearly all patients to avoid peripheral vasodilatory effects in both groups to maintain mean arterial pressure above 70 mmHg, and we added adrenaline when needed to maintain sufficient hemodynamics. No significant difference was reported between both groups regarding the use of inotropes; with both, we almost always used norepinephrine, and there was no difference in the use of epinephrine (0.71). The mean time of inotropic support showed no significant difference between

both groups, with three days in Group A and five days in Group B (0.06). Regarding mortality, eight patients died in Group A from multi-organ failure due to low cardiac output syndrome. In Group B, five patients died, two patients developed acute renal failure, and the remaining three patients died from multi-organ failure due to low cardiac output syndrome. Mortality showed a significant difference between both groups (0.02). The postoperative measured EF, In Group A, the patients had an ejection fraction, ranging from 28-38% with a mean of 33.0 ± 5.0, while in Group B, it ranged from 29-41 % with a mean of 34.6 ± 6.4%, with no significant difference between both groups.

The only postoperative parameter showing a statistical significance between the two groups was intensive care unit stay. In Group A, it ranged between 4 to 9 days with a mean of 6.5 ±2.5 days, while Group B ranged from 3 to 7 days with a mean of 4.6 ± 2.4 days (P = .03).

In Group B (IABP), four patients developed limb ischemia (13%). 2 of those patients had transient ischemia that resolved after removal of IABP, while the remaining patient required a vascular surgical intervention in the form of fasciotomy, embolectomy and removal of balloon and reinsertion in other limb. Bleeding with Hematoma occurred in 3 patients (10%) without the need for surgical intervention.

TABLE 2; comparison between both groups postoperative haemodynamics

BASELINE	LEVOSEMINDAN	IABCP	P.VALUE
Mean arterial pressure (mmHg)	75.8 ± 7.8	78 ± 8.8	P = .092 (NS)
Central venous pressure (mmHg)	11.1 ± 1.7	10.5 ± 1.4	P = .36 (NS)
Heart rate (beat/min)	70.5 ± 6.1	72.4 ± 9.4	P = .63 (NS)
6 HOUR POST OPERATIVE			
Mean arterial pressure (mmHg)	81.8 ± 6.2	88.8 ± 9.7	P = .01 (S)
Central venous pressure (mmHg)	11.4 ± 1.5	8.8 ± 1.3	P = .03 (S)
Heart rate (beat/min)	80.2 ± 8.5	82.4 ± 10.5	P = .33 (NS)
24 HOUR POST OPERATIVE			
Mean arterial pressure (mmHg)	72.8 ± 5.4	85.5 ± 9.7	P = .02 (S)
Central venous pressure (mmHg)	9.6 ± 2.1	9.9 ± 1.5	P = .36 (NS)
Heart rate (beat/min)	81.6 ± 9.1	78.3 ± 11.5	P = .33 (NS)

48 HOUR POST OPERATIVE			
Mean arterial pressure (mmHg)	70.6 ± 5.5	85.8 ± 9.2	P = .02 (S)
Central venous pressure (mmHg)	12.1 ± 1.2	8.6 ± 1.0	P = .022 (S)
Heart rate (beat/min)	89.6 ± 8.3	76.3 ± 3.6	P = .007 (S)

Table3; Postoperative data in the study groups

	LEVOSIMENDAN	**IABCP**	P VALUE
ICU stay (days)	6.5 ± 2.5	4.6 ± 0.4	0.03
MV time (hours)	18.1 ± 2.6	13.5 ± 5.3	0.012
Arrhythmia	16(53%)	14 (46.6%)	0.44
Dialysis (crrt)	5 (16%)	4 (13%)	0.33
Reopening	2 (6%)	3 (10%)	0.62
Mortality	8 (26.7%)	5 (16%)	0.02
Hospital stay (days)	11.2 ± 2.2	10 ± 1.2	0.23
Ejection fraction (%)	33.0 ± 5.0	34.6 ± 6.4	0.62
Inotropes (adrenaline,levoved, etc)	22 (73%)	26 (86%)	0.71
Mediastinitis	8 (26%)	6 (20%)	0.63

DISCUSSION

The available surgical patients categorized as high risk are characterized by multiple co-morbidities, older age, lower cardiac function, and worse clinical condition compared to before. Ischemic dilated cardiomyopathy is considered a big problem that surgeons today. This explains the increasing numbers of patients with (low cardiac output syndrome) both pre-and postoperatively with a very high mortality rate[5]. According to Dietl et al., CABG redo, NYHA class III or IV, left main coronary artery disease, immediate or emergent CABG, and left ventricular end-diastolic pressure (LVEDP) greater than 20 mmHg

are predictors for hospital mortality in patients experiencing CABG with a LVEF of less than 25%. IABP is a frequently used method in cardiac surgery that provides mechanical circulatory support by reducing myocardial oxygen consumption of the heart, decreasing afterload, and enhancing hemodynamic stability, improving the results of high-risk patients with coronary artery disease undergoing surgery.

According to the current study, preoperative IABP use is encouraged in high-risk patients treated with CABG in order to decrease mortality while maintaining a tolerable rate of IABP-related complications. When clinical trials and cohort studies are combined, the NNT is 17; this means that only 17 high-risk patients need preoperative IABP to prevent one hospital death. Vascular damage, swelling, and limb ischemia are also thought to be potentially problematic complications of IABP.

IABP prophylaxis prior to surgery increases outcome and decreases patient mortality. A retrospective analysis done by Lavana and colleagues showed a reduction in hospital mortality in high-risk CABG patients[6].

According to the STS national database and the benchmark registry, patient mortality significantly declined when IABP was introduced preoperatively (9.5% and 8.8%, respectively) than when initiated intraoperatively (28.2% and 23.6%, respectively, p 0.0001).[7]Levosimendan is a calcium sensitizer drug that's effective in the treatment of heart failure and also has protective properties on the heart as it facilitates the opening of the adenosine triphosphate dependent potassium channel. Also, it decreases afterload, leading to increased cardiac index[6]. In Group A, levosimendan was given for 24 hours through a central venous catheter as a continuous infusion of 0.1 micrograms/kg/min diluted in 5% glucose with a 0.25-mg/mL concentration, without boluses. Levosimendan considerably improved hemodynamics without an increase in myocardial oxygen demand. Di Molfetta and colleagues showed the superiority of levosimendan in comparison with other conventional inotropes.

The timing of its administration was important. Preoperative administration to patients with severely reduced ventricular contractility is recommended6. It was found that patients with a preoperative LVEF ≤ 30 % who received levosimendan were treated with a smaller amount of dobutamine and showed a lower mortality rate after surgery compared to those treated with milrinone[6]. Impaired LV function was a constant characteristic of all our patients who received levosimendan after anesthesia induction as a prophylactic measure against reduced cardiac output syndrome. Timing of levosimendan infusion is crucial. When analyzing outcome for many authors, patients with LOS received levosimendan either after induction of anesthesia or in the ICU, hemodynamic responses were not different but use it preoperatively, improve outcomes[6].

In patients undergoing high-risk CABG with total contraindications to IABP, such as aortic

regurgitation or extreme peripheral arterial disease, perioperative levosimendan infusion may help improve outcomes and decrease hospital stay. As regard mortality, there was a discrepancy between our result and Alaa omar and his colleague, 2020. While mortality in our study was significantlty decreased in the IABP arm, in the other study, mortality was less in the levosimendan arm. This is explained by the number of patients and surgical hand skills and experiences.

As comparing our study with Rajek study, 2003, It was found that using levosimendan in patients with massively jeopardized systolic function and symptoms of congestive heart failure undergoing heart surgery showed augmentation in CO and improvement in various hemodynamic parameters. Levosimendan facilitates weaning from CPB in high perioperative risk patients, decreased catecholamine needs, mechanical circulatory support, and ICU stay. In our study, the most commonly used inotropic support were norepinephrine in almost always all patients to avoid peripheral vasodilatory effects in both groups to maintain a mean arterial pressure above 70 mmHg. We added adrenaline, dobutamine and sometimes milrinone when needed to maintain sufficient hemodynamics without statistically significant difference in both groups.

In our study, we noticed a significantly higher heart rate at postoperative Day 2 in the levosimendan group. This is in line with the previous studies concluding the potent levosimendan inotropic and vasodilator effect. In the levosimendan group compared with the IABP group, mean arterial blood pressure significantly was stable at 6 hours post CPB with more significance in the IABP group as it will increase coronary supply during diastole and decrease afterload in systole leading to improve contractility and haemodynamics. However, mortality and the rate of other major complications showed no significant differences between both groups. As regard arrhythmia, we did not find any significance in discrepancy to Ayman et al. 2018[4], who stated that there is increasing A-fib with levosimendan, and this can be explained by co-administrate inotropic support. We are in concordance with **Kevin et al. 2016** [4] who reported that; preoperative aortic counterpulsation was related to a significant decrease in low cardiac output syndrome in both the total population (95% CI 0.214-0.508, P 0.001) and the CAGB subgroup (95% CI 0.056-0.226, P 0.001), but not in the off-pump population (95% CI 0.209-1.474, P = 0.238). In all investigated populations, preoperative IABP implantation was related to a decrease in ICU stay, with a greater impact on the total population.

Our findings corrporated with **Yann 2016** [2]; analyses of RCTs indicated that preoperative IABP was associated with a substantial decrease in hospital mortality (95% CI 0.09-0.44; P = 0.0001) and 30-day mortality (95% CI 0.25-0.76; P = 0.003) compared to no preoperative IABP. IABP prior to CABG was also associated with a shorter period of stay in the intensive care unit (weighted mean difference -1.47 day; 95% CI -1.82 to -1.12 day;

P < 0.00001) and a shorter length of stay in the hospital (-3.25 days; 95% CI -5.18 to -1.33 days; P = 0.0009). Our results were in line with **M.pompeu 2012** [6], who stated that the overall relative risk of hospital mortality in patients treated prophylactically with IABP was (95% CI 0.122-0.533; P < 0.001). The risk ratio for postoperative low cardiac output syndrome was (95% CI 0.109-0.389; P < 0.001). Overall, patients treated with prophylactic IABP had a shorter intensive care unit or hospital stay than the control group (P < 0.001). About 7.4% of patients who received prophylactic IABP had complications at the injection site, and no patient died as a result of IABP.

Our findings contradict **Gutfinger et al.** [7], who documented a trend toward increased hospital mortality associated with preoperative IABP use. However, in the preoperative IABP group, this study recruited slightly more patients with acute MI, congestive heart failure, and a lower LVEF.

Antje Depp and colleagues, 2017 [1] confirmed that current data from RCTs and OT indicate that IABP has beneficial effects in high-risk patients prior to CABG surgery. **Yann Poirier and colleagues 2016** [2] concluded that; in contemporary practice, the evidence supporting preoperative IABP therapeutic benefit in high-risk patients is limited and requires confirmation in a fairly large multicenter randomized trial.

Conclusion: In patients undergoing high-risk CABG (EF less than 35%) who have complete contraindications to the IABP, such as aortic regurgitation or extreme peripheral arterial disease, perioperative levosimendan infusion can also help improve outcomes, reduce ICU and hospital stay.

Limitations of the study; Small sample size. Short follow up period. Lack of randomization, multiple surgeons.

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