ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/cardiosci.2021-83584

Prophylactic Use of Levosimendan in High-Risk Coronary Artery Disease: Retrospective Clinical Research

Yüksek Riskli Koroner Arter Hastalarında Profilaktik Levosimendan Kullanımı: Retrospektif Klinik Araştırma

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ABSTRACT Objective: To investigate the perioperative and postoperative effects of preoperative levosimendan use in coronary artery patients with low ejection fraction (EF) (<40%). **Material and Methods:** A total of 6,571 coronary bypass patients who were treated at Kartal Koşuyolu High Specialization Training and Research Hospital between 2016 and 2019 were scanned, and 132 patients with preoperative EF below 40% were retrospectively analyzed. The patients were divided into 2 groups as those who received preoperative levosimendan (Group 1: 90 patients) and the control group, who did not receive it at all (Group 2: 42 patients). All of the patients included in the study were on-pump coronary bypass patients and excluded off-pump bypass, emergency bypass, and other concomitant procedures. **Results:** In terms of EF values, improvements over time were significantly different in favor of Group 1 (p<0.043). The duration of the intensive care unit stay in Group 1 was longer (p<0.047). The changes in patients in terms of postoperative venous oxygen saturation over time were found to be statistically positive in favor of Group 1 (p<0.042). Mortality was observed in 5 patients in the postoperative early period (first 30 days), all of whom were from Group 1. However, no statistical difference was observed. **Conclusion:** Preoperative use of levosimendan in coronary artery patients with low EF improved some hemodynamic parameters; however, it did not make a significant hemodynamic and clinical contribution to surgery success in high-risk patients.

Keywords: Levosimendan; coronary bypass; ejection fraction

ÖZET Amaç: Ejeksiyon fraksiyonu (EF) düşük (<%40) olan koroner arter hastalarında preoperatif levosimendan kullanımının perioperatif ve postoperatif etkilerinin incelenmesi. **Gereç ve Yöntemler:** Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesinde 2016 ile 2019 arasında koroner baypas yapılmış olan toplam 6.571 hasta tarandı ve preoperatif EF'si %40'ın altında olan 132 hasta geriye dönük olarak incelendi. Hastalar preoperatif levosimendan alanlar (Grup 1:90 hasta) ve hiç almayan kontroller (Grup 2: 42 hasta) olmak üzere 2 gruba ayrıldı. Çalışmaya On-pump bypass hastaları dahil edildi ve Off-pump baypas, acil baypas ve diğer eşzamanlı işlemler yapılan hastalar alınmadı. **Bulgular:** EF değerleri açısından, zaman içindeki düzelmeler Grup 1 lehine anlamlı olarak farklıydı (p<0,043). Grup 1'de yoğun bakımda kalış süresi daha uzundu (p<0,047). Hastalarda zaman içinde postoperatif venöz oksijen saturasyonundaki değişmeler Grup 1 lehine istatistiksel olarak pozitifti (p<0,042). Postoperatif erken dönemde (ilk 30 gün) tamamı Grup 1'de olan 5 hastada mortalite gerçekleşti. Fakat istatistiksel anlam bulunmadı. **Sonuç:** Ejeksiyon fraksiyonu düşük koroner arter hastalarında preoperatif levosimendan kullanımı bazı hemodinamik parametreleri düzeltti fakat yüksek riskli hastalarda cerrahi başarısına anlamlı hemodinamik ve klinik katkısı olmadı.

Anahtar Kelimeler: Levosimendan; koroner baypas; ejeksiyon fraksiyonu

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Peer review under responsibility of Turkiye Klinikleri Cardiovascular Sciences.

Received: 04 Apr 2021 ***Received in revised form:*** 27 Dec 2021 ***Accepted:*** 05 Jan 2022 ***Available online:*** 12 Jan 2022

In isolated coronary artery patients, low ventricular function is the most important cause of perioperative mortality and morbidity.[1,2] Levosimendan is a calcium sensitizing agent. It has been reported that levosimendan decreases the symptoms of low cardiac output syndrome and it is associated with surgical mortality, as in heart failure and cardiogenic shock.[3,4] The use of inotropes increases the oxygen consumption of myocardium due to tachycardia. Levosimendan binds cardiac troponin-c and prolongs the contraction time of actin-myosin without increasing intracellular calcium. In addition, cardioprotective, immunomodulatory, antiarrhythmic, anti-inflammatory, and antioxidant properties of levosimendan make it an ideal inotropic drug by providing protection against ischemic stress.[5]

MATERIAL AND METHODS

Data belonging to 6,571 coronary bypass surgeries performed at Kartal Koşuyolu High Specialization Training and Research Hospital between 2016 and 2019 were retrospectively reviewed. We included 132 patients with preoperative low ejection fraction (EF) and their records were examined. The patients were evaluated in 2 groups. Group 1 included 90 patients who received preoperative levosimendan and Group 2 (control group) included 42 patients who did not receive it at all. All patients were those who underwent on-pump bypass surgery. Those who underwent off-pump bypass surgery and other concomitant procedures, those who required emergency coronary bypass surgery, and those with a history of cardiac surgery were not included in the study to ensure homogeneity between groups. In the selection of patients, based on the preoperative transthoracic echocardiography results, any value less than 40% was considered as low EF. All patients were isolated coronary bypass patients with no history of inotropic drug use. Not the same surgical team performed all the operations. The groups were compared in terms of perioperative and postoperative data, as well as in terms of myocardial infarction (MI). The drug protocol showed that patients were transferred to the intensive care unit (ICU) approximately 12 hours before the surgery and then levosimendan infusion was started. The infusion was continued during the peri- and postoperative period for a total of 24 hours with a 0.1 mg/kg per min using the routine treatment dose of 12.5 mg levosimendan/500 mL 5% Dx. Preoperative, perioperative, and postoperative data were recorded in detail. Anesthesia and surgical procedures were performed with routine techniques. While maintaining cardiac arrest with intermittent blood cardioplegia by antegrade and retrograde routes, it was ensured that the arterial pressure did not fall below 60 mmHg. All of the patients were routinely transferred to the ICU intubated. Ethics committee approval was obtained from Kartal Koşuyolu High Specialization Training and Research Hospital Non-interventional Procedures Council (12.12.2019, 2019.7/11-229). The study was carried out in accordance with the principles of the Helsinki Declaration.

STATISTICAL ANALYSIS

Descriptive statistics are presented as mean±standard deviation for variables with a normal distribution, median (minimum-maximum) for variables with non-normal distribution, and the number of cases (%) for nominal variables. The significance of the difference between the groups in terms of averages was evaluated with the t test, and the significance of the difference in terms of median values was evaluated with the Mann-Whitney U test. Nominal variables were evaluated with the Pearson chi-square or Fisher's exact test. Data analysis was performed using IBM SPSS 15.0 (SPSS Inc., Chicago, IL, USA) package program. Any p value less than 0.05 was considered statistically significant. The changes of the preoperative and postoperative measurements of the patients between the groups were evaluated by the two-way mixed ANOVA analysis.

RESULTS

A total of 132 patients, 116 (87.9%) male and 16 (12.1%) female, with a mean age of 61.423 (±9.160) years, were included in the study. There was no statistical difference between the 2 groups in terms of diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular event, and kidney failure (Table 1). There was no statistical difference between groups in terms of cross clamping time and cardiopulmonary bypass (CPB) time (Table 2). Postoperative intra-aor-

TABLE 1: Patients' preoperative parameters.

	Group 1	Group 2
Number of patients	90	42
BMI (kg/m^2)	26.6±3.6	27.6 ±3.5
DM (n, %)	51 (56.7%)	23 (54.8%)
COPD (n, %)	19 (21.1%)	6 (14.3%)
CVE (n, %)	4 (4.4%)	1 (2.4%)
Recent MI (n, %)	46 (51.1%)	14 (33.3%)
Kidney failure	6 (6.7%)	4 (9.5%)
Echocardiography		
EF (%)	33.8±4.3	35.9±5.2
LVEDD (cm)	5.4±0.6	5.5±0.6
LVESD (cm)	4.06±0.7	4.2±0.8
PAPs (mmHg)	33.3±2.3	32.6±2.5
TAPSE (cm)	1.1±0.08	1.08±0.01

BMI: Body mass index; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; MI: Myocardial infarction; CVE: Cerebrovascular event; EF: Ejection fraction; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; PAPs: Pulmonary artery pressure systolic; TAPSE: Tricuspid annular plane systolic excursion.

TABLE 2: Patients' intraoperative parameters.

	Group 1	Group 2
Cross clamping time (min)	72±23.7	80.5±24.9
CPB time (min)	118.8±39.6	128.3±30
2 X CABG (n)	22	2
3 X CABG (n)	27	2
4 X CABG (n)	26	22
5 X CABG (n)	27	14

CPB: Cardiopulmonary bypass; CABG: Coronary artery bypass graft.

tic balloon pump (IABP) was needed in 17 (12.9%) patients, 15 of whom were from Group 1, which was close to the statistical significance limit (p<0.057). For postoperative MI, the ECG and blood values of these patients were examined, and perioperative MI findings were observed only in 5 patients. It is noteworthy that 60 (45.5%) patients had recent MI, 46 of whom were from Group 1, which was close to the statistical limit (p<0.056). Mortality was observed in 5 patients in the postoperative early period (first 30 days) and these patients were from Group 1 (Table 3). However, there was no statistical difference. Changes in EF values over time were significantly different in favor of Group 1 (p<0.043) (Figure 1). Postoperative EF values in Group 2 increased compared to preoperative values, which was not significant. For both groups, no significant difference was observed between pre-operative and post-operative values in terms of left ventricular end-diastolic diameter, left ventricular end-systolic diameter, pulmonary artery pressure systolic, and tricuspid annular plane systolic excursion.

Extracorporeal membrane oxygenator (ECMO) was needed postoperatively in 2 patients in Group 1 (Table 3). There was no significant difference between the 2 groups in terms of the need for postoperative inotrope use. The changes in postoperative venous oxygen saturation with respect to time were statistically positive in favor of Group 1 (p<0.042) (Figure 2). The duration of ICU stay in Group 1 was longer (p<0.047). The average follow-up time was found to be 24.70 (±29.62) days in both groups.

DISCUSSION

Due to the development of percutaneous interventional techniques, coronary invasive procedures have increased, and more recently, patients who undergo surgery appear to be composed of those with advanced perioperative risks.[6] In this case, it is important to establish good surgical strategies. Low EF and pulmonary hypertension are known to be among the main factors influencing postoperative prognosis.[7] The presence of these factors causes difficulties in weaning from CPB, which may appear as advanced impairments in both left and right ventricular functions after CPB.[6] Standard treatment methods used in cardiac surgery for patients experiencing difficulty in weaning from CPB include inotropic drugs, vasodilators, IABP, and ECMO. Levosimendan may be one of these treatment options. Levosimendan has a positive inotropic effect by increasing calcium retention of myofilaments, and a vasodilator effect by opening adenosine triphosphate-sensitive potassium channels.[8] Unlike other positive inotropic drugs, it does not increase myocardial oxygen consumption, but increases coronary perfusion and decreases preload while making this effect.[9,10]

In the literature, there exist many studies on the use of levosimendan in cardiac surgery. However,

TABLE 3: Patients' postoperative parameters.

	Group 1	Group 2	p value
Duration of intubation (hours)	14.7±16.6	12.2±12.9	
Duration of ICU stay (days)	3.9±5.4	3.7±6.4	p<0.047
Revision	9 (10.0%)	2 (4.8%)	
Postoperative MI	5	0	
Postoperative CVE	3 (3.3%)	2 (4.8%)	
Inotrope use	40 (44.4%)	40 (52.4%)	
IABP	15 (16.7%)	2 (4.8%)	p<0.057
ECMO	2 (2.2%)	0 (0%)	
Echocardiography			
EF (%)	38.4±9.2	37.5±8.4	
LVEDD (cm)	5.3±0.5	5.5±0.68	
LVESD (cm)	3.9±0.7	4.05±0.8	
PAPs (mmHg)	33.6±2.06	33.04±1.01	
TAPSE (cm)	1.11±0.07	1.10±0.01	
Mean follow-up duration (days)	24,70 (±29.62)	24.70 (±29.62)	
Mortality	5 (5.6%)	0 (0%)	

ICU: Intensive care unit; MI: Myocardial infarction; CVE: Cerebrovascular event; IABP: Intra-aortic balloon pump; ECMO: Extracorporeal membrane oxygenation; EF: Ejection fraction; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; PAPs: Pulmonary artery pressure systolic; TAPSE: Tricuspid annular plane systolic excursion.

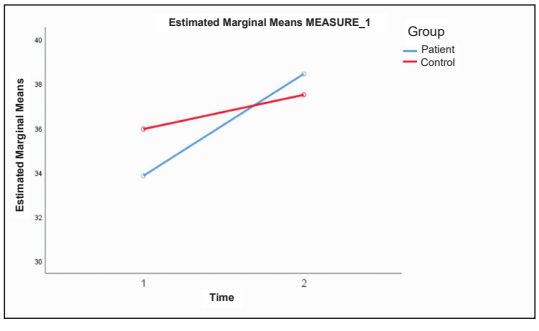

FIGURE 1: Improvements in ejection fraction values by time.

there exist a limited number of studies in the literature on its preoperative use.[11] Tritapepe et al. stated that the use of levosimendan before coronary bypass surgery preserved the myocardium and contributed to postoperative hemodynamics with improvement in the cardiac index.[12] In our study, cardiac index could not be measured due to the lack of some retrospective parameters. However, in order to evaluate the postoperative hemodynamic improvement, postoperative venous oxygen saturations were examined, and a positive change over time was found statistically significant in the group using levosimendan.

No statistical contribution of levosimendan use was observed in a randomized LICORN study, in which the effect of levosimendan use on 30-day mortality was evaluated.[13] Similarly, there was no statistical difference in our study in terms of early postoperative mortality. In addition, there was no significant difference in terms of surgical parameters.

The higher number of patients with recent MI in the group who received levosimendan compared to controls was noteworthy, which, we think, may have been caused by more frequent use of postoperative IABP in this group. Postoperative inotrope use was statistically similar between groups.

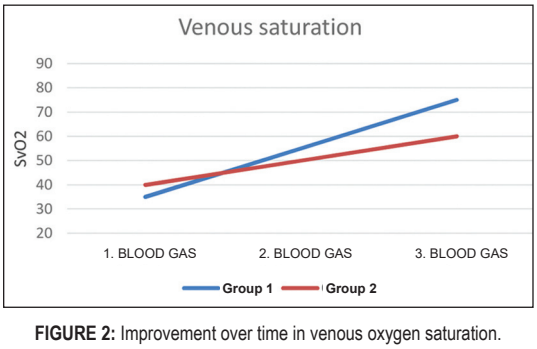

FIGURE 2: Improvement over time in venous oxygen saturation.

In our study, the ICU stay durations were found to be statistically higher than those reported in the literature. This may be due to the presence of patients with recent MI and patients with higher risk in our study.

It is noteworthy that the improvement in time in the postoperative EF of patients using levosimendan was statistically significant. García-González et al. also reported that acute heart failure symptoms and hemodynamic parameters improved with levosimendan use in patients with low EF.[14] In our study, no statistical difference was found in the evaluation in terms of ventricular diameters. The contribution of coronary revascularization in the improvement of EF is undeniable. However, in our study, the time-dependent improvement in EF was more positive in the group who received levosimendan.

There is no consensus in the literature about the time of levosimendan administration.[15] In our study, patients were taken to the ICU the day before the surgery and the treatment dose was completed in 24 hours.

It is known that one of the most important stages of cardiac surgery is the stage of weaning from CPB. There are publications in the literature showing that levosimendan protects the right ventricle by decreasing pulmonary pressures with the vasodilator effect.[16] However, there is no consideration that it has a significant contribution by perioperative use in high-risk coronary artery disease. There are studies suggesting that levosimendan contributes to the improvement of postoperative renal functions.[13] However, no statistical difference was observed in our study.

LIMITATIONS

This is a retrospective study and the low number of controls should be noted. The reason for this is that patients who underwent off-pump bypass were excluded to ensure homogeneity between groups. Another limitation is that the cardiac index could not be measured due to the lack of some data. EF and venous oxygen saturations were based on postoperative hemodynamic evaluations. Another limitation may be that not the same surgical team performed all the surgeries.

CONCLUSION

Preoperative use of levosimendan in coronary artery patients with low EF provided improvement in some hemodynamic parameters, while no apparent hemodynamic and clinical contribution was found in the success of surgery in high-risk patients. It is clear that more studies involving a larger series are needed in terms of routine use.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Veysel Başar, Ferit Çiçekçioğlu, Ali Fedakar;* ***Design:*** *Veysel Başar, Mehmed Yanartaş;* ***Control/Supervision:*** *Veysel Başar, Fatih Yiğit, Ahmet Zengin;* ***Data Collection and/or Processing:*** *Fatih Öztürk, Fatih Yiğit, Hakan Hançer;* ***Analysis and/or Interpretation:*** *Veysel Başar, Ferit Çiçekçioğlu, Ali Fedakar;* ***Literature Review:*** *Ahmet Zengin, Fatih Öztürk, Fatih Yiğit;* ***Writing the Article:*** *Veysel Başar, Ali Fedakar, Hakan Hançer;* ***Critical Review:*** *Ferit Çiçekçioğlu, Ali Fedakar, Mehmed Yanartaş;* ***References and Fundings:*** *Veysel Başar, Fatih Yiğit, Ahmet Zengin;* ***Materials:*** *Veysel Başar, Fatih Öztürk.*

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