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The effects of levosimendan on renal functions in open-heart surgery patients with a low ejection fraction

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ABSTRACT

Purpose. This study investigated the effects of levosimendan on renal functions in patients with a preoperative low ejection fraction undergoing open-heart surgery and cardiopulmonary bypass (CPB). *Materials and Methods*. The study retrospectively evaluated 64 patients with a diagnosis of mitral valve insufficiency and left ventricular dysfunction undergoing open-heart surgery with CPB. Patients were divided depending on the preoperative blood creatinine level less (Group 1) or more than 1.2 mg/dL (Group 2). A bolus dose of levosimendan was administered through the aortic arch at the end of the CPB, preceding an infusion of levosimendan intravenously in all patients. Demographic data, preoperative and 48-hour postoperative echocardiographic studies were done. The blood urea and creatinine levels were collected preoperatively and on postoperative days 1, 3, and 10. The use of inotropic support, intra-aortic balloon pump, and complications were recorded. *Results*. The demographic data were similar between groups ($p>0.05$). Preoperative serum creatinine levels were higher in Group 1 in comparison to Group 2 ($p=0.01$, $p<0.001$, respectively). The aortic cross-clamp and cardiopulmonary bypass times were similar between groups ($p>0.05$). Preoperative serum creatinine levels were higher in Group 1 in comparison to Group 2 ($p<0.001$). On postoperative day 1, serum creatinine levels of Group 1 were significantly lower than Group 2 ($p<0.001$). On postoperative days 3 and 10, no differences were observed regarding serum creatinine levels between groups ($p>0.05$). Complications were similar between groups ($p>0.05$). *Conclusions*. In patients with low ejection fraction undergoing open-heart surgery, the use of levosimendan intraoperatively and 24 hours postoperatively prevents deterioration of renal functions in patients with or without preoperative disturbance in serum creatinine level.

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Introduction

Heart failure is a progressive systemic perfusion disorder which consists of hemodynamic deterioration, diminished exercise capacity, activation in the neurohormonal mechanisms. The most commonly encountered reasons for heart failure include; decrease in the myocardial contractility and activation in the sympathetic and renin-angiotensin systems [1]. Positive inotropic agents are frequently used in patients with decompensating heart failure and left ventricular systolic dysfunction. For this reason, beta-adrenergic drugs, dobutamine and dopamine, or phosphodiesterase inhibitors, milrinone and enoximone, are often administered however, these agents have been reported to increase morbidity and mortality in heart failure [2,3]. Levosimendan is a calcium sensitizer that has a positive inotropic action as well as peripheral and coronary vasodilation by opening of the ATP-sensitive potassium channels [4]. This dual mechanism of action results in an improved myocardial contractility without increase in myocardiac oxygen consumption that has been reported to decrease the myocardial ischemic events after cardiopulmonary bypass [4,5]. The positive inotropic action of levosimendan is due to its binding to troponin C which facilitates the interaction between actin and myosine filaments without changes in intracellular Ca++ ion concentrations.

There is neither an increase in the amount of consumption of ATP nor a reduction in the relaxation time in diastole. In the vascular smooth muscle, vasodilatation occurs by the opening of the ATP related K+ channels. In summary, the clinical effects of the levosimendan are related to its inotropic action, decrease in preload and afterload along with no increase in myocardial oxygen demand [3-5].

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In congestive heart failure, it has been reported that there is moderate amount of increase in the levels of blood urea and creatinine secondary to a reduction in the renal blood flow and glomerular filtration rate [6]. In addition to renal hypoperfusion, intrarenal vasoconstriction has been reported to occur due to activation of the renin angiotensin system and increase in the blood levels of vasopressin, endothelin and catecholamines [7]. Various patho-physiological mechanisms cause decrease in renal perfusion and development of ischemic tubular necrosis in patients with heart failure [8].

The postoperative incidence of acute kidney injury (AKI) ranges between 0.33 % and 9.5% following cardiac surgery with cardiopulmonary bypass (CPB) [9]. The postoperative development of renal insufficiency after cardiac surgery is usually associated with poor outcome and high in-hospital mortality [10]. Recently, there are studies on development of the best efficient scoring system to detect patients at risk of postoperative renal failure following cardiac surgery. The Cleveland score system evaluates preoperative risk factors including; age, gender, history of congestive heart failure, diabetes that required medical treatment or insulin therapy, chronic obstructive pulmonary disease that was treated with bronchodilators, previous cardiac surgery, preoperative serum creatinine (sCr in mg/dl), preoperative ventricular function (assessed either by angiography or by echocardiography), presence of an intra-aortic balloon pump before surgery, type of cardiac surgery (isolated coronary artery bypass graft (CABG), valve procedures, combined CABG and valve surgery, and other major surgical procedures),and operative status (elective, urgent, or emergent) to determine the risk of development of AKI after cardiac surgery [9-11].

The protective effects of levosimendan on renal functions have been demonstrated by the studies that provided data on improvement in renal blood flow after establishment of hemodynamic stability [12] and potent vasodilatory action by the agonistic effects on K-ATP channels [13]. Levosimendan has been reported to have anti-inflammatory actions as well as various actions at cellular level of renal system such as reversal of AT-2 mediated mesangial cell contraction with consequent increase in glomerular capillary surface area and glomerular filtration rate that inhibits the injury of the renal tubular functions. In general, levosimendan acts mainly by an increase in renal blood flow and enhancement of glomerular filtration rate [14,15].

An important effect of levosimendan is its potential to improve renal function that is shown by a reduction in serum creatinine levels in patients with decompensated acute heart failure [5,6,9,16]. The recent guidelines of the European Society of Cardiology suggest the use of levosimendan in cases of symptomatic low cardiac output heart failure secondary to cardiac systolic dysfunction [1,2,16].

Although recent guidelines suggests that levosimendan is an effective in low cardiac output heart failure, there is an ongoing debate on whether levosimendan is effective for improving renal functions in open-heart surgery or not. Therefore, we aimed to discuss our findings with recent data in the literature and to evaluate the effects of calcium sensitizer levosimendan on renal functions in patients with a preoperative low ejection fraction undergoing open-heart surgery with CPB.

Materials and Methods

Between July 1 2009 and June 30 2011, a retrospective study design was conducted on 64 patients diagnosed with mitral valve insufficiency and left ventricular dysfunction. Surgery A Local Ethical Committee approval was obtained from Istanbul Provincial Health Directorate Kartal Kosuyolu High Speciality Educational and Research Hospital, Istanbul, Turkey, Ethical Committee Approval Number: 2013.2/1.

During surgical operation of all patients mitral reconstruction and ring annuloplasty were performed depending on pathological findings on mitral valve. If co-existing coronary artery disease was detected, coronary artery bypass graft (CABG) operation was performed. Patients with aortic valvular disorders were excluded from the study.

Table 1. Risk factors and points in Cleveland Score

Risk factors		Cleveland points
Female gender		1
History of CHF*		1
LVEF*	<35%	1
	<40%	1
Preoperative IABP*		2
COPD* treated with bronchodilators		1
Diabetes that required treatment with insulin		1
Previous cardiac surgery		1
Type of surgery		
Valvular		1
Combined CABG*+valvular		2
Other surgeries		2
Preoperative renal function; sCr*(mg/dL)		
1.2 to 2.09		2
≥2.10		5
Operative status		
Emergent		1
Score range		0 to 17

Abbreviations: CHF; congestive heart failure, IABP; intra-aortic balloon pump, COPD; chronic obstructive pulmonary disease, CABG; coronary artery disease, sCR; serum creatinine

Patients were divided into two groups depending on the preoperative serum creatinine level less (Group 1) or more than 1.2 mg/dL (Group 2). The Cleveland score system evaluates preoperative risk factors to detect patients at risk of postoperative renal failure following cardiac surgery and uses serum creatinine level of 1.2 mg/dL in its scoring system to calculate the risk to develop renal insufficiency postoperatively (Table 1) [10,11].

The inclusion criteria to study include: patients undergoing valve surgery and/or CABG with a preoperative ejection fraction of 40 % or less were included into the study. Exclusion criteria include: emergent operation, normal echocardiographic study, aortic valve disease, chronic renal and liver disease, insulin dependent diabetes mellitus, severe obstructive and/or restrictive lung disease, infective endocarditis.

Parameters

The collected demographic data include; age, weight, height, body mass index and gender. The cardiovascular risk factors including; diabetes mellitus, hypertension, hypercholesterolemia, obesity, history of smoking as well as history of chronic obstructive pulmonary disease and peripheral vascular disease were sought. Lung functions were evaluated by radiographic studies of chest and lung function tests. Electrocardiogram was obtained routinely in preoperative and postoperative periods to detect rhythm disturbances. Preoperative and 48-hour postoperative echocardiographic studies were performed to evaluate the ejection fraction and valvular functions by the same cardiologist using Vivid 3 echocardiography (Vivid 3, Berlin, Germany).

The blood urea and creatinine levels were collected preoperatively and on postoperative day 1, 3 and 10. Prognostic risk parameters that have influence on morbidity and mortality were collected and these include; aortic cross-clamp, and cardiopulmonary bypass time, the use of inotropic support and intra-aortic balloon pump and prognostic risk factors influencing morbidity and mortality such as prolonged mechanical ventilation, development of pneumonia, myocardial infarct, cerebrovascular event, development of low cardiac output syndrome, atrial fibrillation and other rhythm disturbances, need for renal replacement therapies and dialysis, need for permanent pacemaker, reoperation secondary to bleeding, intensive care unit and hospital stay [17].

The induction and maintenance of anesthesia.

Routine monitoring for cardiac anesthesia was established prior to induction of anesthesia and these include; 5-lead electrocardiogram, radial artery catheterization, pulse oximetry, central venous catheter (7.5 or 8 French), urine catheterization and esophageal temperature probe. After premedication with oral benzodiazepine at an appropriate dose, standard anesthesia induction was administered with intravenous doses of midazolam (Roche, Basel, Switzerland) at a dose of 0.2 mg kg-1, fentanyl (Janssen-Cilag, Beerse, Belgium) at a dose of 5 to 10 mcg kg-1 and pancuronium (Organon, Turkey) at a dose of 0.1 mg kg-1 were administered. For maintenance, all patients received sevoflurane at an end-tidal concentration of 0.5 % to 2 % and intravenous maintenance doses of midazolam and fentanyl every hourly. Administration of levosimendan during the operative procedure was performed by an anesthesiologist. At the end of CPB, a bolus dose of levosimendan (SimdaxTM, Orion Pharma, Finland), was administered at a dose of 100 mg in 50 ml of 5 % dextrose solution through aortic arch before cross clamp opening. After removal of CPB, a continuous infusion of levosimendan was administered from a central venous catheter intravenously for 24 hours in all patients at a dose of 0.1 mcg kg-1 min-1.

The operation procedure.

Median sternotomy was performed on all patients. Before the beginning of the CPB, heparin at a dose of 300 IU kg-1 was administered intravenously to keep the ACT (Active Clotting Time) greater than 450 seconds. In all patients, arterial cannulation was performed from the ascending aorta and the venous cannulation was provided by cannulation of both superior and inferior vena cava. The left superior pulmonary vein was used for vent cannulation. Mild hypothermia (28 to 32°C) was established during all cases. Antegrade and retrograde blood cardioplegia were supplied to each patient through appropriate cannulation. A retrograde coronary sinus cannula was inserted transatrially for cardioplegia infusions. The first isothermic blood cardioplegia infusion was given antegrade via an aortic root for 3 min then repeated every 20 minutes which was followed by a continuous infusion of retrograde cardioplegia. Cardioplegia include 0.3 mEq kg-1 KCL within 10 ml kg-1 of pump blood as well as appropriate doses of MgSO4 and NaHCO3. Retrograde cardioplegia was provided at a rate of 50 ml min-1 with addition of appropriate doses of the same electrolytes in every 500 ml of pump blood. Cardiopulmonary bypass circulation was provided by a roller Biomedicus pump (Biomedicus, Germany) in all patients. Systemic blood flow during CPB was kept between 2-2.5 L min-1 m2-1 and systemic blood pressure was kept between 50 to 80 mmHg. Arterial blood gas values are followed every 60 minutes to keep the levels as; PO2 greater than 250 mmHg, PCO2 between 35 to 45 mmHg, pH between 7.35 to 7.40, hematocrit between 22 to 28 %, blood sugar between 100 to 180 mg dL-1. The operating time, type of oxygenator, quantity of blood prime used, and the types and numbers of valves replaced were recorded.

After rewarming with a 37°C maximal heat-exchanger temperature, CPB was discontinued at 36–37°C nasopharyngeal temperature. Intraoperative ventricular tachyarrhythmias were treated with internal cardioversion or lidocaine (1–1.5 mg kg−1). Reversal of heparin was

achieved with protamine 1 mg per milligram of heparin. Inotropic support, initially with dopamine (5–10 μg kg−1 min−1) and secondly with dobutamine (5–10 μg kg−1 min−1) and/or epinephrine (0.02–0.15 μg kg−1 min−1), was commenced if the mean arterial pressure (MAP) was < 65 mm Hg in the presence of a pulmonary artery wedge pressure (PAWP) of 15 mm Hg and a heart rate of 70–110 beats min−1.

In patients with coronary artery disease, distal anastomosis was completed by the use of saphenous veins and then the replacement or repair of the mitral valve was performed. After this procedure, mitral valve reconstruction was controlled by transmitral injection of the intraventricular isotonic sodium chloride solution and additional sutures were done if needed. Under partial cross clamp, proximal saphenous anastomosis was performed.

Statistical analysis.

All analyses were performed using SPSS Statistical Package 15.0 (SPSS Inc., California, USA). Patients' baseline characteristics in Group 1 and 2 are reported as mean (sd), frequencies and percentages. Differences were assessed using $\chi 2$ or the Fisher exact test for categorical variables and Mann–Whitney U-test for continuous or non-parametric data. For repeated measure analysis of the data, Friedman nonparametric one-way repeated measure analysis of variance by ranks is used to compare three or more matched groups. Interaction analysis revealed whether effects of time (repetitive measurements) were different between groups. P values <0.05 was considered statistically significant.

Results

The mean age of the whole group of 64 patients were 67.40±9.33. Fifteen patients were female (23 %) whereas, 49 were male (77 %). Group 1 consisted of 36 patients whereas, Group 2 had 28 patients. The demographic data were similar in both group of patients (p>0.05) except, male gender was greater in Group 1 in comparison to Group 2 (p<0.01) (Table 2).

Table 2. The comparison of demographic data in Group 1 and 2.

	Group 1 (n=36)	**Group 2 (n=28)**	**p***
Age	56.31±13.14	56.92±10.77	0.86
Gender (Male/Female) (%)	23/13(64/36)	26/2(93/7)	**0.007***
Height (cm)	159.44±8.11	157.64±6.76	0.56
Weight (kg)	66.94±12.64	68.93±11.87	0.73
BMI (kg m2-1)	26.77±7.64	27.77±8.64	0,66
Preoperative serum urea (mg dL-1)	45.39±25.22	60.11±28.45	**0.01***
Preoperative serum creatinine (mg dL-1)	0.88±0.12	1.37±0.28	**<0.001***
Preoperative EF* (%)	33.25±8.68	34.50±9.92	0.90
Mitral insufficiency (n, %)	36(100)	28(100)	1.00
Tricuspid insufficiency (n, %)	13(36)	10 (36)	0.97
CAD*(n, %)	9(25)	8(28.6)	0.75
PHT*(n, %)	9(25)	8(28.6)	0.75
Cardiovascular risk factors			
Diabetes mellitus (non-insulin dependent) (n, %)	5(18)	6(17)	0.90
Hypertension (n, %)	13(36)	10(35.7)	0.97
Hypercholesterolemia (n, %)	2(5,6)	4(14.3)	0.24
Obesity (n, %)	2(5,6)	3(10.7)	0.45
History of smoking	7(25)	8(22)	0.80
Co-existing diseases			
COPD* (n, %)	5(18)	6(17)	0.90
PAH* (n, %)	2(5.6)	4(14.3)	0.24
Other (n, %)	2(5.6)	3(10.7)	0.45
Drug use effecting preoperative renal functions			
Diuretics	36(100)	28(100)	1.00
Beta blockers	13(36)	10(35,7)	0.97
Calcium channel blockers	5(18)	6(17)	0.90
ACE inhibitors	13(36)	10(35,7)	0.97
Angiotensin receptor blockers	7(25)	8(22)	0.80

*p<0.05 statistically significant, CAD; coronary artery disease, PHT; pulmonary hypertension, COPD; chronic obstructive pulmonary disease, PAH; peripheral arterial disease, ACE; angiotensin converting enzyme

Patients with insulin dependent diabetes mellitus were not included in the study. The distribution of mitral and/or tricuspid insufficiency, coronary artery disease and pulmonary hypertension showed no difference (p>0.05) (Table 2). The comparison of the operative data showed that there were no significant differences between groups

in parameters including; aortic cross-clamp time, cardiopulmonary bypass time, distribution of different operative procedures depending on preoperative diagnosis, postoperative 48-hour echocardiographic evaluation that provided data on ejection fraction, mitral insufficiency and PHT (p>0.05) (Table 3).

Table 3. The comparison of operative parameters in Group 1 and 2.

	Group 1 (n=36)	Group 2 (n=28)	p*
Mitral reconstruction (n, %)	36(100)	28(100)	1.00
Mitral reconstruction and single vessel CABG * (n, %)	5(14)	3(11)	0.70
Mitral reconstruction and two vessel CABG (n, %)	4(11)	4(14)	0.70
Mitral reconstruction and TDVA* (n, %)	8(22)	5(18)	0.68
ACC* (minute)	67.47±20.83	67.21±17.29	0.68
CPB* (minute)	90.58±29.03	85.61±18.68	0.64
Postoperative EF* (%)	31.24±4.68	32.68±3.96	0.90
Postoperative mitral Insufficiency (n, %)	2(6)	3(11)	0.45
Postoperative PHT*(n, %)	2(5.6)	3(10.7)	0.45

*p<0.05 statistically significant, CABG; coronary artery bypass graft, TDVA; tricuspid De Vega, ACC; aortic cross-clamp time, CPB; cardiopulmonary bypass time, EF; ejection fraction, PHT; pulmonary hypertension.

Table 4. The comparison of preoperative and postoperative serum urea and creatinine levels between Group 1 and 2.

Parameters	Group 1 (n=36)	Group 2 (n=28)	p*
Preop. urea (mg dL-1)	65.4±25.2	60.1±28.5	**0.01***
Postop.urea Day 1	46.2±18.5	59.6±28.7	**0.03***
Postop. urea Day 3	60.4±36.3	61.6±33.9	0.95
Postop.urea Day 10	56.5±50.7	57.9±25.2	0.09
p	**0.001***	0.28	
Preop. creatinine (mg dL-1)	0.88±0.1	1.37±0.3	**<0.001***
Postop. creatinine Day 1	1.05±0.4	1.35±0.4	**<0.001***
Postop. creatinine Day 3	1.01±0.5	1.14±0.4	0.06
Postop. creatinine Day 10	1.04±0.7	1.11±0.3	**0.02***
p	0.10	**<0.001***	

*p<0.05 statistically significant; preop: preoperative; postop: postoperative

Preoperative serum urea and creatinine levels were higher in Group 1 in comparison to Group 2 (p=0.01, p<0.001, respectively). On postoperative day 1, serum urea and creatinine levels of Group 1 was significantly lower than Group 2 (0.03 and p<0.001, respectively). On postoperative day 3 and 10, no differences were observed between groups (p>0.05) (Table 4).

In Group 1, serum urea levels showed a significant decrease in comparison of preoperative levels and postoperative day 1, 3 and 10 (p=0.001) however, no difference was observed in Group 2 (p>0.05) (Table 4). In Group 1, the comparison of serum creatinine levels showed no significant difference in repetitive measurement points whereas, in Group 2, the serum creatinine levels showed a significant decrease in comparison of preoperative levels and postoperative day 1,3 and 10 (p<0.001) (Figure 1 and 2).

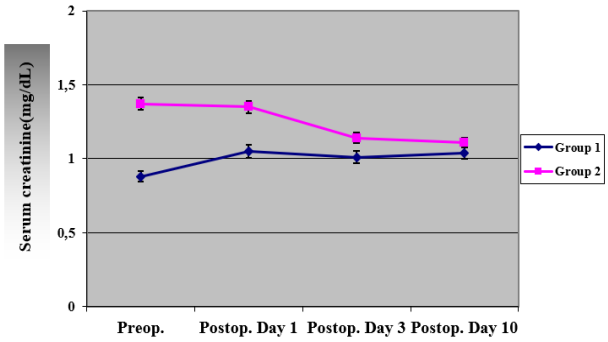

Figure 1. The comparison of the preoperative and postoperative serum creatinine levels on postoperative day 1,3 and 10 in Group 1 and 2.

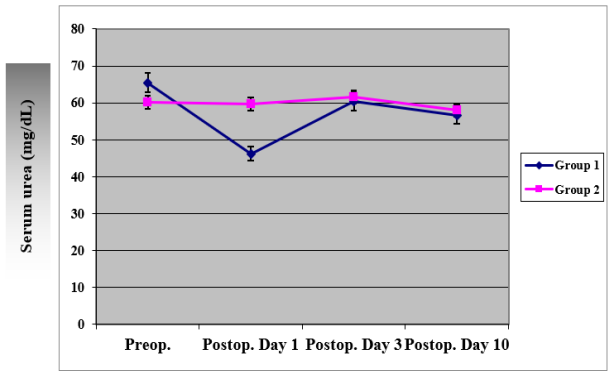

Figure 2. The comparison of the preoperative and postoperative serum urea levels on postoperative day 1, 3 and 10 in Group 1 and 2.

The prognostic risk factors affecting morbidity in the first 10 day postoperatively showed no difference between groups (p>0.05) (Table 5). Low cardiac output state was reported in 2 (6 %) patients in Group 1, and 1 (3 %) patient in Group 2. In Group 1, 32 (89 %) patients and in Group 2, 26 (93 %) patients required dobutamine and the need of epinephrine was 17 (47 %) and 10 (36 %) respectively. In Group 1, 8 patients (22 %) and in Group 2 10 patients (36 %) received renal dose of dopamine at a dose of 3 mcg

kg-1 min-1. The use of IABP was 8 patients in Group 1 (22%) and 8 patients in (29 %). The use of IABP were not different between groups. The requirement of dialysis was in 2 patients (6 %) in Group 1 and in 1 patient (3 %) in Group 2 and there was no significant difference between groups (p>0.05) (Table 5).

Three patients (8 %) in Group 1 and 1 patient (4 %) in Group 2 died within 30 days of surgery in the hospital.

Table 5. The comparison of postoperative parameters between Group 1 and 2.

Parameters	**Grup 1 (n=36)**	**Grup 2 (n=28)**	**p***
Epinephrine (n, %)	17(47)	10(36)	0.36
Norepinephrine (n, %)	9(25)	11(39)	0.22
Dobutamine (n, %)	32(89)	26(93)	0.59
Dopamine (n, %)	8(22)	10(36)	0.17
Dialysis	2(6)	1(3)	0.71
IABP*	8(22)	8(29)	0.56
Mortality (%)	3(8)	1(4)	0.44
The prognostic factors effecting morbidity in the first 10 day postoperatively			
Pneumonia (n, %)	2(6)	3(11)	0.45
Prolonged mechanical ventilation (n, %)	3(8)	3(11)	0.59
Myocardial infarction	2(6)	3(11)	0.45
Atrial Fibrillation	2(6)	3(11)	0.45
Other rhythm disturbances	5(14)	3(11)	0.70
Permanent pacemaker	1(2)	1(3)	0.33
Reoperation secondary to bleeding	2(6)	2(7)	0.41
Cerebrovascular event	5(14)	4(14)	0.63
Low cardiac output syndrome	2(6)	1(3)	0.71
Intensive care unit stay (day)	4.30±2.9	4.68±2.8	0.50
Hospital stay (day)	9.89±3.9	10.39±5.0	0.31
*p<0.05 statistically significant; IABP: intra-aortic balloon pump			

Discussion

In this retrospective study where the renal effects of levosimendan in patients undergoing open heart surgery with low ejection fraction is sought, our most significant finding is that patients having preoperative serum creatinine level of greater than 1.2 mg dL-1 had a decrease in the level of serum creatinine in the first 10 days postoperatively in comparison to the preoperative level whereas, patients having a preoperative serum creatinine level of less than 1.2 mg dL-1 had maintained their level of serum creatinine. This study provides data on the clinical effects of levosimendan on serum creatinine levels in patients with low ejection fraction undergoing open-heart surgery with CPB.

The effects of levosimendan on kidney functions after open-heart surgeries with CPB has been studied in randomized clinical studies especially in patients with a diagnosis of low cardiac output [18-22]. A study by Yilmaz and his colleagues demonstrated that in a group of 88 patients with heart failure (HF), intravenous levosimendan infusion showed beneficial effects on glomerular filtration rate (GFR) 24 and 72 hours after surgery when compared to a group of patients receiving a traditional inotrope which is dobutamine [18]. The preoperative and postoperative 24- and 72-hours glomerular filtration rate (GFR) median values were compared providing data that in group of patients that received levosimendan had higher GFR values in comparison to patients with dobutamine at 24 hours after surgery and GFR increased by 15.3% under levosimendan versus −1.33% under dobutamine and a similar finding was observed at 72 hours after surgery as well [18]. In the study by Zemljic et al, 40 patients with severe congestive heart failure and increased serum creatinine values were enrolled and while half of the patients received levosimendan infusion the other half received no inotrope and these patients were followed for three months. The study evaluated the serum creatinine and creatinine clearance values of the patients which revealed that in comparison to the basal values before start of the study (1.92 ± 0.13 mg dL-1), the patients in the levosimendan group showed reduced levels of serum creatinine (1.60 +/- 0.26 mg dL-1 vs. 1.90 +/- 0.14 mg dL-1, respectively p = 0.005) and increased creatinine clearance in comparison to the control group (53.6 +/- 8.6 mL min-1 ve 44.0 +/- 3.3 mL min-1, respectively, p = 0.005) [20]. There are other recent studies that supports the beneficial clinical effects of levosimendan on serum creatinine levels in patients with low ejection fraction undergoing open heart surgeries with CPB. [19-22]. In a meta-analysis study that reviewed 10 randomized controlled studies and included 440 patients, it has been reported that there were no differences in the parameters including myocardial infarction, acute renal failure, duration of mechanical ventilation, intensive care unit and hospital stay in comparison of levosimendan and control groups (p>0.05) [23].

Recent studies point out that the use of levosimendan may be beneficial in low cardiac output states after open heart surgery with CPB [18-26]. In our study, the prognostic risk factors effecting morbidity in the first 10 day postoperatively showed no difference between groups where serum creatinine 1.2 mg dL-1 was a cut-off value for division of the patients into two groups. (Table 5). Recent studies point out that the use of levosimendan may be beneficial in low cardiac output states after open heart surgery with CPB [23-25,27]. The most common factors

correlating with the need for inotropic or vasoactive support at the time of CPB separation are female sex, older age, low ejection fraction, cardiac enlargement, diastolic dysfunction, longer duration of CPB, and longer duration of aortic cross-clamp time [28]. In our study, low cardiac output state was reported in 2 (6%) patients in Group 1, and 1 (3%) patient in Group 2. This finding is important in transient myocardial dysfunction, which is more pronounced in patients with impaired left ventricular function before surgery, resulting in the need for postoperative inotropic support [23,24,29]. The reduction of ejection fraction below 46 % is associated with the need of inotropes in a range between 71 % to 100% in the first 24 hours postoperatively after heart surgery [30]. These findings are similar to our study that around 90 % of our patients required at least one inotrope and 30 to 40 % of our patients required a second inotropic agent postoperatively in addition to levosimendan infusion in the first 24 hours. It has been discussed in the literature that cardiac surgical patients with postoperative myocardial dysfunction resistant to dobutamine, the addition of levosimendan to dobutamine was effective in reversing LCOS, a complication with an estimated prevalence of about 10 % and a mortality of 17 % [26,27,31]. The vasodilator and inotropic therapies, as well as intra-aortic balloon counterpulsation is frequently used to restore adequate tissue perfusion in the immediate postoperative period especially in critically ill intensive care unit patients and in patients with cardiogenic shock after cardiac surgery. [27,31-34]. The use of IABP in our study was between 22 and 29 % ($p>0.05$).

Acute kidney injury (AKI) in the postoperative cardiac surgery population remains a significant cause of perioperative morbidity and mortality. The postoperative incidence of AKI ranges between 5 % to 20 % and has been reported to be associated with increased mortality up to 60 % among patients requiring dialysis. Postoperative renal insufficiency is defined as a 2-fold or greater elevation of creatinine that must exceed 2.0 mg/dL whereas, renal failure is defined as AKI requiring dialysis by The Society of Thoracic Surgeons [32]. Specific risk factors were identified and these include; advanced age, diabetes, congestive heart failure, low cardiac index, preexisting renal dysfunction, and more complex cardiac surgery. [23-27,30-34].

There are several clinical studies that investigated the renal effects of levosimendan in patients undergoing open-heart surgeries and a recent meta-analysis reveals that, in a total of six randomized clinical trials including 1200 patients with preoperative reduced low EF of less than 35%, mortality was reduced with levosimendan as compared to placebo and levosimendan significantly decreased the need for postoperative renal replacement therapy after open-heart surgeries with CPB [32].

Cardiopulmonary bypass time was not found as a risk factor for the development of AKI. The role of age is stil under debate as well. [23,27]. In the study by Barkhordari and his colleagues, the risk factors for AKI include; preoperative serum creatinine, advanced age, combined valvular and CABG operation procedure [31]. In a meta-analysis study that reviewed 10 randomized controlled studies and included 440 patients, there were no differences in the parameters including myocardial infarction, acute renal failure, duration of mechanical ventilation, intensive care unit and hospital stay in comparison of levosimendan and control groups [23,32]. We also considered preoperative creatinine value and combined valvular and CABG operation procedures under risk of AKI and for this reason we retrospectively analyzed the data of patients undergoing open-heart surgeries with CPB with preoperative low EF of less than 40%.

The risk of AKI that requires dialysis is reported to be low and has been reported to range between 1.1 % and 3% [31-34]. In our study 2 patients (6 %) in Group 1 and 1 (3 %) patient in Group 2 required dialysis and the incidence of dialysis was over all 4.7 %. A dose reduction of the levosimendan in patients who have higher serum creatinine levels have been put forward however, recent data showed that there is no need for dose reduction. In our study, we did not observe a need for a dose reduction and no significant side effects were reported [27,32]. A meta-analysis by Harrison and colleagues also highlighted the beneficial effects of perioperative levosimendan on renal function, as it showed significant reductions in the need for dialysis in levosimendan-treated patients ($P = 0.003$) [24]. There were several consensus papers on the overall renal effects of levosimendan in the literature [19,23,24,26,27,30-34].

The present study has the limitations inherent to the small number of patients and the lack of a control group however, our result on serum urea and creatinine values provides valuable data for further research on larger group of patients with levosimendan that includes randomized clinical trials with addition of a placebo group.

Conclusions

Recently, levosimendan has been studied for patients with low left ventricular ejection fraction undergoing open-heart surgery with CPB and there is a consensus on its use for patients with low ejection fraction as it decreases mortality and also reduces the need for renal replacement therap. Levosimendan has systemic effects on hemodynamical parameters as it increases the cardiac output, causes preglomerular vasodilation, anti-inflammatory, and antiapoptotic effects leading to an improved immediate postoperative renal function and reduced need for renal replacement therapy. This is in line with our findings, showing a significantly decreased

incidence of postoperative acute kidney injury and a need for renal replacement therapy in patients receiving levosimendan for open-heart surgeries with CPB.

In patients with low ejection fraction undergoing openhearted surgeries, the use of levosimendan intraoperatively and for a duration of twenty-four hours postoperatively has a potential role of prevention of deterioration of renal functions in all patients regardless of the preoperative serum creatinine level.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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