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Original Article

Preoperative usages of levosimendan in patients undergoing coronary artery bypass grafting

Cuneyt Eris, Senol Yavuz, Faruk Toktas, Tamer Turk, Arif Gucu, Burak Erdolu, M Tugrul Goncu

Department of Cardiovascular Surgery, Bursa Yuksek Ihtisas Education and Research Hospital, Bursa, Turkey

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Abstract: Objectives: Levosimendan (LS) is a new inotropic drug which belongs to the group of drugs known as calcium sensitizers. It is different from other inotropic agents by its inotropic and vasodilatory actions without an increase in myocardial oxygen consumption and considered as a good choice in high-risk patients undergoing cardiac surgery. We aimed to investigate the proper time of the administration and the effect of prophylactic usage of LS in patients with low left ventricular ejection fraction (LVEF) undergoing coronary artery bypass grafting (CABG). Methods: Forty patients who underwent isolated CABG with LVEF) less than 30% were evaluated retrospectively. Patients were divided into 3 groups according to the induction time of LS during different phases of the operation and compared to a non-LS control group. LS infusion (0.2 μg/kg/min) was applied 12 hours before the operation in Group 1 (G1) (n=10), after the induction of anaesthesia in Group 2 (G2) (n=10) and during the pump removal period in Group 3 (G3) (n=10) and non-LS control group 4 (G4) (n=10). Demographic data, operative characteristics, hemodynamic parameters and serum lactate, troponin, creatinine levels were compared between groups before and after LS treatment during pre and postoperative period. Data were evaluated by Fisher exact, Kruskal-Wallis, Mann-Whitney U, Chi-square and Wilcoxon rank tests. Results: We found that the duration of tracheal intubation, the intensive care unit stay and the hospital stay were significantly decreased in G1 and G2 when compared to the patients in G3 and G4. During postoperative period, in G1 and G2 one (10%) patient from each required intraaortic balloon pump (IABP), while in G3 two (20%) patients and in G4 five (50%) patients required IABP. Cardiac index (CI) was significantly increased in all groups from baseline to intensive care unit (ICU)1h and ICU24h. When groups compared each other significant increase was found in G1-G4 (p=0.001) and G2-G4 (p=0.007) at ICU1h. There was a significant increase in % EF especially in G1-G4 (p=0.011) and G2-G4 (p=0.007) at ICU1h. Systemic vascular resistance index significantly decreased in G1 and G2 in comparison to G3 and G4. However there was no significant decrease in pulmonary capillary wedge pressure of all 4 groups before and after LS. There was a significant decrease in mean pulmonary arterial pressure in G1 and G2 according to G4. Compared with the other groups preoperatively LS-treated patients (G1 and G2) had lower postoperative troponin I, serum lactate and creatinine concentrations. Conclusions: Our study shows that the elective preoperative initiation of LS especially 12 hours before the operation onset is associated with better improvement on cardiac functions as well as with lower mortality and complication rates, lower use of additional inotropic and vasopressor drugs, less need for intra-aortic balloon pump support and shorter length of stay in the ICU in patients with high perioperative risk or compromised left ventricular function. As a result, patients who received an infusion of LS 12 hours before surgery showed an evidence of less myocardial damage which suggested the preconditioning effect of the drug.

Keywords: Levosimendan, cardiac surgery, low cardiac output, preoperative usage

Introduction

Besides our current treatment options, patients with high perioperative risk or compromised left ventricular function undergoing cardiac surgery is still a great problem. Preoperative evaluation and risk stratification of such patients in reducing postoperative morbidity and mortality is very important. Although cardioplegia were given for myocardial protection, during aortic cross-clamping and after the reperfusion of previously hypoperfused areas of myocardium lead to a variable degree of stunning which leads to postoperative low cardiac output syndrome (LCOS), even worsens the preoperatively normal ventricular function and causes depressed contractility. For reversing depressed cardiac contractility intraaortic balloon pump

(IABP) and inotropic agents were used. Conventional positive inotropic agents (phosphodiesterase inhibitors and adrenergic agonists such as dobutamine) enhance myocardial contractility by increasing concentrations of intracellular calcium, which leads to an increase in myocardial oxygen consumption [1].

Levosimendan (LS) is a new inotropic drug which belongs to the group of drugs known as calcium sensitizers. It increases the Ca+2 response to myofilament by binding to cardiac troponin C. As a result, myocardial contraction increases without increasing myocardial oxygen demand [2-4]. LS was also shown to open the mitochondrial ATP-dependent potassium (K) channels in myocytes and vascular smooth muscle cells, which causes vasodilatation [5, 6]. These properties decrease both preload and afterload, increase coronary and other organs blood flows [7, 8]. And also opens the cardiac mitochondrial ATP-sensitive K+ channels which are responsible for the potential preconditioning effect of the drug [9, 10].

LS is distinguished from other inotropic agents by these inotropic and vasodilatory actions and considered as a good choice in high-risk patients undergoing cardiac surgery [11-13]. Different investigators preferred to use LS at different doses and at different times, however a little is known on timing and doses of LS during cardiovascular surgery.

In this retrospective study, we aimed to determine the proper time of the administration of LS in high-risk patients who underwent cardiovascular surgery.

Materials and methods

Patients

In the present study, forty patients with isolated coronary artery disease whom left ventricular ejection fraction (LVEF) were less than 30%, was evaluated retrospectively for determining the most effective time of LS application in cardiac surgery. Patients were divided into 3 groups according to the application time of LS. Group 1 (G1) (n=10) consisted of patients who used LS 12 hours before the operation, Group 2 (G2) (n=10) consisted of patients who used LS after the induction of anaesthesia and Group 3 (G3) (n=10) consisted of patients who used LS during the pump removal period and non LS control Group 4 (G4) (n=10).

The study protocol was approved by the Ethical Committee of the hospital. The main criteria for inclusion were multi-vessel isolated coronary artery disease, impaired LVEF <0.30 evaluated with left ventricular echocardiography or signs of acute ischemic congestive heart failure (CHF) and EUROSCORE >6. The main exclusion criteria were previous coronary arterial bypass grafting (CABG) operation, indication for any cardiac valve operation, severe chronic obstructive pulmonary disease, severe renal insufficiency and emergent surgery.

Echocardiographic examination of the left ventricule (LV) was done in accordance with the 16 segment model of the American Society of Echocardiography [14]. Blood samples were obtained from peripheral vessels after the induction of anaesthesia (baseline), in the intensive care unit (ICU) 4th hour (ICU4h), and in the ICU 24th hour (ICU24h).

The age and gender of patients, type of operation, preoperative features, duration of aortic cross-clamp, the total duration of perfusion, duration of the operation, operative characteristics and hemodynamic parameters like mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI), cardiac index (CI), the echocardiographic estimation of left ventricular ejection fraction (EF), heart rate (HR); and also serum creatinine, lactate and troponin I levels were registered and compared between groups before and after LS infusion during pre and postoperative period.

Drug administration

LS (Simdax; Abbott, Luxemburg, Luxemburg) infusion was started intravenously 12 hours before the operation at a dose of 0.2 μg/kg/min in G1 at the intensive care unit through a central venous line; hemodynamics were closely monitored. In G2 infusion of LS started with the induction of anesthesia at a dose of 0.1 μg/kg/min till to the end of the solution. There was no initial loading dose in G1 and G2. In G3, LS was administered with an initial loading dose of

12 μg/kg for 10 minutes, followed by a continuous infusion of 0.1 μg/kg/min of LS. Conventional medication was used in G4.

Surgical approach

A conventional median sternotomy was performed in all patients. Anesthesia was induced with midazolam, propofol, and fentanyl. Anesthesia was maintained with sevoflurane before CPB and with propofol and remifentanil on CPB in accordance with the anesthetist's criteria. Anticoagulation was achieved with sufficient heparin (3-4 mg/kg) to maintain an activated clotting time >450 seconds. CPB was achieved with a roller pump and a membrane oxygenator. The pump flow rate was kept between 2.0 and 2.4 L/min per m^2 body surface area to maintain a mean arterial pressure of 60 to 70 mmHg. The systemic temperature was maintained between 30°C and 32°C. Myocardial protection was achieved by an initial antegrade infusion of St. Thomas' crystalloid cardioplegia and then continued with intermittent antegrade cold blood cardioplegia. Distal and proximal anastomoses were constructed during a single period of aortic cross-clamping. "Warm induction" was applied just before the removal of the cross-clamp. Reversal of heparin was achieved with protamine.

Hemodynamic measurements

Hemodynamic data were obtained before the start of the operation (baseline), in the intensive care unit (ICU) at the end of the first hour (ICU1h), and in the ICU at the end of the 24th hour (ICU24h). Cardiac output was measured in triplicate at end-expiration by thermodilution using 10 mL of iced saline. The patients recieved routine monitoring, hemodynamic measurements obtained before the administration of LS, after the operation at the 1st hr in the ICU and at the 24th hr in the ICU. Cardiac output (CO) was measured by thermo-dilution technique using a pulmonary-artery catheter (Edward Lifesciences, Irvine, CA, USA). PVRI and SVRI were calculated according to standard formulas: PVRI=(MPAP-PCWP)/CI and SVRI=(MAP-CVP)/CI, CI=CO/BSA, (BSA=body surface area).

Hemodynamic measurements, as well as other outcomes and complications of the operation, were recorded. Predicted mortality was calculated according to the European system for cardiac operative risk evaluation [15]. In all patients, CVP was kept between 12 and 14 mmHg and PCWP was kept between 14 and 18 mmHg by administration of intravenous fluids (crystalloids and colloids). If the cardiac index was below 2.2 L/m^2/min, dobutamine (Dobutamine; Eumedica, Manage, Belgium) was initiated to a maximum of 10 μg/kg/min. Hypotension, defined as a mean arterial blood pressure <60 mmHg, was treated with norepinephrine 0.1 μg/kg/min increased incrementally by 0.1 μg/kg/min until the mean arterial blood pressure >60 mmHg. An intra-aortic balloon pump (IABP) was applied when there was a pump insufficiency despite inotropic support with dopamine, dobutamine, adrenalin treatment.

Statistical analysis

Preoperative baseline values and values that can affect the study were evaluated for homogeneity first and these values were found homogeneous.

Kruskal-Wallis and Mann-Whitney U test was used for the comparisons between groups. To evaluate the differences in medians for each variable of interest between the two groups we used the Mann-Whitney non-parametric sum rank test. To evaluate the differences within one group we used the Friedman repeated-measures ANOVA on ranks followed by the Wilcoxon non-parametric sum rank test. Chi-square and Fisher exact test was used to compare categorical data. Because of the usage of non-parametric tests in the study descriptive values were given as median (minimum-maximum values). Statistical significance was accepted at *P*-values below 0.05. Statistical analysis was performed using SPSS software package version 10 (SPSS, Chicago, IL, USA).

Results

Thirty patients treated with LS and ten matched controls were enrolled in the study. The patients' characteristics and perioperative data are presented in **Table 1**. There were no significant inter-group differences with regard to age, gender, NYHA, Euroscore, preoperative ejection fraction, preoperative medication, number of grafted vessels, CPB and cross-clamping times. There were no adverse effects

Table 1. Patient characteristics

	Group 1 n=10	Group 2 n=10	Group 3 n=10	Group 4 n=10	*p* value
Gender (male/female)	8/2	7/3	7/3	8/2	
Age (years)	60.50 (43-73)	62.50 (44-74)	58.0 (48-68)	63.50 (49-74)	0.684
NYHA	3.50 (3-4)	3.50 (3-4)	4.0 (3-4)	3.50 (3-4)	0.961
Euroscore	6.0 (6-7)	6.0 (6-8)	6.0 (6-8)	6.0 (6-7)	0.924
Number of grafts	4.0 (3-5)	4.0 (3-5)	4.0 (3-5)	4.0 (3-5)	0.977
Diabetes %	60	50	50	60	
Hypertension %	50	40	50	50	
Aortic cross clamp time (min.)	89.0 (63-105)	88.5 (67-107)	80.5 (67-103)	79.5 (67-88)	0.207
CPB time (min.)	123.5 (87-154)	142.0 (102-157)	146.5 (103-163)	140.0 (115-156)	0.173
IABP	1	1	2	5	
Intubation time (hours)	15.5 (10-24)	18.0 (12-32)	22.5 (20-42)	37.0 (18-96)	0.001
ICU stay (hours)	45.0 (37-73)	45.0 (40-77)	55.5 (45-96)	73.5 (48-240)	0.005
Hospital stay (days)	8.0 (7-11)	9.0 (7-14)	10.0 (8-20)	12.0 (8-25)	0.007
postoperative data	*p* values between groups				
Intubation time	G1-G3 (0.001); G1-G4 (0.001); G2-G3 (0.019); G2-G4 (0.002)				
ICU stay	G1-G3 (0.043); G1-G4 (0.005); G2-G3 (0.035); G2-G4 (0.005)				
Hospital stay	G1-G3 (0.019); G1-G4 (0.002); G2-G4 (0.035)				

ICU = Intensive care unit. CPB = Cardiopulmonary bypass. NYHA = New york Heart Association Data are presented as median (min-max.).

related to LS and no withdrawals of LS were required. There were no major complications in either group and all survived to hospital discharge.

We found that the duration of tracheal intubation, the ICU stay and the hospital stay were significantly shorter in G1 (15.5 h; 45 h; 8 d) and G2 (18 h; 45 h; 9 d) when compared with the G3 (22.5 h; 55.5 h; 10 d) and G4 (37 h; 73.5 h; 12 d) respectively.

During postoperative period, one (10%) case in G1 and G2 from each required IABP pump while two (20%) patients in G3 and five (50%) patients in G4 required IABP.

Hemodynamic data are listed in **Table 2**. MAP was significantly increased only at baseline to ICU24h in G1 (69 to 71; p=0.012) and G4 (67.5 to 72; p=0.009); when we evaluate each group there was no significance between groups at the end of the first day of ICU. There was a significantly increase at CVP and PCWP levels from baseline to ICU1h period in all of the groups but there was no significant difference between the groups. The values of SVRI were significantly lower (p=0.005) in all of the groups when compared with baseline-ICU1h and baseline-ICU24h. When groups compared each other only in G1-G4 (1879.0 vs 1917.5; p=0.023), G2-G4 (1741.0 vs 1917.5; p=0.005), G3-G4 (1882.0 vs 1917.5; p=0.002) at ICU1h; and G1-G4 (1685.5 vs 1837.5; p=0.001), G3-G4 (1797.5 vs 1837.5; p=0.035) at ICU24h was found significantly lower. CI was significantly increased in all groups at ICU1h and ICU24h. When we compared the groups each other, there was significantly increase at ICU1h between G1-G3 (2.45 vs 2.40; p=0.001); G1-G4 (2.45 vs 2.35; p=0.001); G2-G4 (2.60 vs 2.35; p=0.007) and at ICU24h significantly increase was detected between groups G1-G2 (3.05 vs 2.90; p=0.023); G1-G3 (3.05 vs 2.75; p=0.001); G1-G4 (3.05 vs 2.65; p=0.001); G2-G4 (2.90 vs 2.65; p=0.023); G3-G4 (2.75 vs 2.65; p=0011).

HR was significantly increased in all groups from baseline to ICU1h and baseline to the end of the first ICU day. When groups compared each other statistically significant difference was found only in G1-G4 (p=0.001) at ICU1h and G1-G4 (p=0.001) at ICU24h.

In all groups EF was significantly inreased from baseline at the end of the first ICU day and postoperative 7th day. There was a significant difference between groups G1-G4 (36 vs 34; p=0.011) and G2-G4 (35 vs 34; p=0.029) at the first postoperative day in the ICU. Also there

Table 2. Perioperative hemodynamic data

		Base	ICU1.h.	ICU24.h.
Mean Arterial Pressure, mmHg	Group 1	69.0 (55-77)	68.5 (61-83)	71.0 (65-79)¥
	Group 2	70.0 (59-75)	65.0 (63-71)	71.0 (66-75)
	Group 3	70.0 (59-77)	67.5 (55-75)*	71.5 (63-77)
	Group 4	67.5 (62-75)	70.0 (60-77)	72.0 (63-78)¥
p values between groups: G1-G2 (p=0.035); G1-G3 (p=0.002); G2-G4 (p=0.019); G3-G4 (P=0.001) icu1h				
Heart Rate, bpm	Group 1	75.0 (64-84)	86.5 (77-95)*	86.0 (80-97)*
	Group 2	77.0 (57-84)	87.5 (80-101)*	92.0 (83-98)*
	Group 3	74.5 (65-89)	95.5 (79-103)*	98.5 (91-112)*
	Group 4	73.0 (59-88)	96.5 (86-113)*	98.5 (91-112)*
p values between groups: G1-G4 (P=0.001) icu1h; G1-G4 (P=0.001) icu24h				
Central Veneous Pressure, mmHg	Group 1	9.0 (7-12)	11.0 (8-13)¥	9.5 (7-12)
	Group 2	10.5 (6-13)	12.0 (8-14)¥	11.0 (6-12)
	Group 3	10.5 (7-15)	12.0 (8-16)¥	11.0 (7-13)
	Group 4	9.5 (7-13)	12.0 (9-15)*	10.5 (7-14)
Mean Pulmonary Aarterial Pressure, mmHg	Group 1	24.5 (21-29)	25.5 (23-32)¥	24.0 (18-28)¥
	Group 2	24.5 (19-29)	26.0 (20-30)§	22.0 (19-27)¥
	Group 3	24.0 (19-31)	25.0 (21-32)	23.0 (20-31)
	Group 4	23.5 (19-32)	25.5 (22-33)*	24.5 (21-32)§
p values between groups: G1-G4 (p=0.001); G2-G4 (p=0.002) icu24h				
Pulmonary Capillary Wedge Pressure, mmHg	Group 1	11.5 (9-16)	13.5 (10-17)¥	12.5 (8-14)
	Group 2	12.5 (7-16)	14.0 (10-17)§	12.5 (9-16)
	Group 3	11.0 (7-17)	13.5 (8-18)¥	12.0 (7-17)¥
	Group 4	11.0 (7-16)	13.5 (9-18)*	11.5 (7-17)
Systemic Vascular Resistance Index, dyn/s/cm-5/m²	Group 1	2220.0 (1472-2779)	1879.0 (1386-2272)*	1685.5 (1216-1765)*
	Group 2	2145.5 (1746-2526)	1741.0 (1538-2072)*	1698.0 (1445-1792)*
	Group 3	2247.0 (1700-2610)	1882.0 (1354-2067)*	1797.5 (1440-1956)*
	Group 4	2090.0 (1844-2527)	1917.5 (1600-2267)*	1837.5 (1571-2048)*
p values between groups: G1-G4 (p=0.023); G2-G4 (p=0.005); G3-G4 (P=0.002) icu1h; G1-G4 (p=0.001); G3-G4 (p=0.035) icu24h				
Pulmonary Vascular Resistance Index, dyn/s/cm-5/m²	Group 1	492.0 (256-691)	408.5 (213-553)¥	308.5 (110-442)*
	Group 2	516.0 (300-610)	400.0 (296-554)	295.0 (232-457)*
	Group 3	500.5 (400-674)	417.0 (266-556)¥	323.0 (286-456)*
	Group 4	475.0 (348-680)	469.5 (255-654)§	430.5 (237-640)§
p values between groups: G1-G3 (p=0.015); G1-G4 (p=0.001) icu24h				
Cardiac Index, L/min/m²	Group 1	2.05 (1.9-2.5)	2.45 (2.3-3.0)*	3.05 (2.6-3.6)*
	Group 2	2.20 (1.9-2.5)	2.60 (2.2-2.8)*	2.90 (2.5-3.2)*
	Group 3	2.15 (1.9-2.4)	2.40 (2.1-2.6)*	2.75 (2.6-3.0)*
	Group 4	2.20 (1.9-2.4)	2.35 (2.1-2.6)*	2.65 (2.4-2.8)*
p values between groups: G1-G3 (p=0.001); G1-G4 (p=0.001); G2-G4 (p=0.007) icu1h; G1-G2 (p=0.023); G1-G3 (p=0.001); G1-G4 (p=0.001); G2-G4 (p=0.023); G3-G4 (p=0.011) icu24h				

ICU = Intensive care unit. Data are presented as median (min-max.). Different compared with base-ICU1h and base-ICU24h *p≤0.005, ¥p<0.002, §p<0.05.

		Base	ICU24.h.	Postop. 7th day
Ejection Fraction %	Group 1	30.0 (24-30)	36.0 (31-40)*	42.0 (35-45)*
	Group 2	30.0 (25-30)	35.0 (30-42)*	40.0 (35-46)*
	Group 3	30.0 (25-30)	32.5 (29-40)¥	35.0 (33-42)*
	Group 4	30.0 (25-30)	34.0 (35-37)¥	35.0 (30-41)*
p values between groups: G1-G4 (p=0.011); G2-G4 (p=0.029) icu24h; G1-G3 (p=0.019); G1-G4 (p=0.011); G2-G3 (p=0.023); G2-G4 (p=0.005) postop.7th d				

ICU = Intensive care unit. Data are presented as median (min-max.). Different compared with base-ICU24h and Postop. 7th day *p≤0.005, ¥p<0.002, §p<0.05.

was a significant difference at EF between groups G1-G3 (42 vs 35; p=0.019); G1-G4 (42 vs 35; p=0.011); G2-G3 (40 vs 35; p=0.023); and G2-G4 (40 vs 35; p=0.005) at the end of the first week.

Perioperative troponin I, creatinin and lactate levels are listed in **Table 3**.

All 4 groups had higher troponin I levels when compared with the baseline at ICU4h and

Table 3. Biochemical data

		base	ICU4.h.	ICU24.h.
Troponin, ng/ml	Group 1	0.035 (0.01-0.13)	2.10 (1.80-3.10)*	3.45 (2.30-4.50)*
	Group 2	0.040 (0.02-0.12)	2.50 (1.80-3.50)*	4.15 (3.50-5.30)*
	Group 3	0.035 (0.02-0.12)	2.90 (2.50-3.50)*	4.80 (3.50-5.50)*
	Group 4	0.045 (0.02-0.12)	3.15 (2.10-4.10)*	4.90 (3.50-6.00)*
p values between groups: G1-G2 (p=0.04); G1-G3 (p=0.001); G1-G4 (p=0.001); G2-G3 (p=0.03); G2-G4 (p=0.01) icu4h; G1-G2 (p=0.01); G1-G3 (p=0.002); G1-G4 (p=0.004) icu24h				
Creatinine, mg/dl	Group 1	0.995 (0.68-1.30)	1.080 (0.74-1.45)¥	0.990 (0.61-1.25)
	Group 2	0.865 (0.67-1.22)	1.080 (0.71-1.42)¥	0.905 (0.70-1.31)
	Group 3	0.965 (0.65-1.34)	1.200 (0.85-1.58)¥	1.095 (0.70-1.51)§
	Group 4	0.965 (0.68-1.31)	1.305 (0.85-1.61)¥	1.140 (0.71-1.53)¥
p values between groups: G1-G3 (p=0.019); G1-G4 (p=0.001); G2-G4 (p=0.007) icu4h; G1-G4 (p=0.001); G2-G4 (p=0.001) icu24h				
Lactate, mmol/L	Group 1	1.25 (1.0-2.0)	2.25 (1.4-3.5)¥	1.35 (0.9-2.1)
	Group 2	1.25 (1.0-1.5)	2.60 (1.9-4.0)¥	1.45 (1.0-2.2)§
	Group 3	1.25 (1.0-1.7)	2.90 (1.9-4.0)¥	1.65 (1.0-2.1)¥
	Group 4	1.25 (1.0-1.5)	3.15 (2.3-4.3)¥	2.50 (2.0-5.0)¥
p values between groups: G1-G3 (p=0.002); G1-G4 (p=0.001); G2-G4 (p=0.011) icu4h; G1-G3 (p=0.009); G1-G4 (p=0.001); G2-G4 (p=0.001); G3-G4 (p=0.001) icu24h				

ICU = Intensive care unit. Data are presented as median (min-max.). Different compared with base-ICU1h and base-ICU24h
*p=0.002, ¥p=0.005, §p<0.05.

ICU24h, (p=0.002); When we compared the groups each other significantly lower troponin I levels was obtained at groups G1-G2 (p=0.04), G1-G3 (p=0.001), G1-G4 (p=0.001), G2-G3 (p=0.03), G2-G4 (p=0.01) at ICU4h and only in G1 had significantly lower troponin I levels at ICU24h than the other groups.

Compared with the baseline lactate levels significant increase was detected in all four groups at baseline-ICU4h and baseline-ICU24h. When groups compared each other at ICU4h there was no significant difference between groups G1-G2 and G3-G4, but significantly higher values was detected between groups G1-G3 (2.25 vs 2.90; p=0.002); G1-G4 (2.25 vs 3.15; p=0.001) and G2-G4 (2.60 vs 3.15; p=0.011). Significantly higher values obtained between groups G1-G3 (1.35 vs 1.65; p=0.009); G1-G4 (1.35 vs 2.50; p=0.001); G2-G4 (1.45 vs 2.50; p=0.001) and G3-G4 (1.65 vs 2.50; p=0.001) at the end of the first postoperative day.

In all groups postoperative creatinin levels were significantly higher than the baseline values (G1=1.08 vs 0.99, p=0.005; G2=1.08 vs 0,86, p=0.005; G3=1.20 vs 0.96, p=0.005; G4=1.30 vs 0.96, p=0.005) at ICU4h time period, but remained significantly high only in G3 (1.09; p=0.032) and G4 (1.14; p=0.005) at the end of the first postoperative day. When we compared the groups each other in G1-G3 (1.08 vs 1.20; p=0.019); G1-G4 (1.08 vs 1.30; p=0.001) and G2-G4 (1.08 vs 1.30; p=0.007) significant difference were detected at ICU4h and between groups G1-G4 (0.99 vs 1.14; p=0.001); and G2-G4 (0.90 vs 1.14; p=0.001) significant difference at ICU24h were determined.

Discussion

LS is a new inodilator mostly used in the treatment of decompensated heart failure and in patients with impaired left ventricular function who faced with difficulties at weaning off cardiopulmonary bypass [2]. Following the cardiac surgery, the ratio of patients who require positive inotropic support after CPB is 32.4% [16]. This ratio is inceased to 92% when the patient had preoperative EF <30% [3, 17]. Preoperatively, in patients with poor ventricular function, weaning failure without medical and/or mechanical support may be seen in up to 70% to 80% [18-20]. After ischemic cardioplegic arrest

and CPB, the systolic performance of the heart is invariably depressed by postischemic stunning [21].

Our patient group consisted of patients who were already preexisting impaired ventricular function and furthermore compromised by variable degrees of myocardial stunning and/or myocardial injury resulting from ischemia during aortic crossclamping. This may lead to a very high rate of LCOS and complicated weaning from CPB. LCOS and complicated weaning may lead to myocardial distension and damage, end-organ failure due to impaired perfusion, neurologic complications, increased operative room times, longer stay in the intensive care unit (ICU), prolonged mechanical ventilation, and increased risk of infection, sepsis and increased mortality. Therefore, for beneficial results and to avoid the development of LCOS, these patients should have treated preoperatively and intraoperatively. In such high risk CABG patients, cardioprotective strategies will improve short term and long-term outcomes. These strategies include intra-aortic balloon counterpulsation, assist devices, avoidance of catecholamine-induced cardiotoxicity and myocardial preconditioning [22].

Conventional positive inotropic agents improve contractility by increasing intracellular concentrations of calcium, either by increasing the intracellular concentrations of cyclic adenosine monophosphate (cAMP) (epinephrine, dobutamine, dopamine), or by blocking the degradation of cAMP (milrinone). But this time the risk of ischemia and arrhythmia was increased because of the increased myocardial oxygen comsumption and possibly due to the deleterious effects of raised intracellular calcium [23]. Therefore, LS use in cardiac surgery for patients requiring inotropic support in the perioperative period appears promising. Because one of the major theoretic advantages of levosimendan over conventional inotropic agents is its ability to augment systolic function without increasing myocardial oxygen demand.

Rajek and colleagues were the first whom report the use of LS in patients with congestive heart failure and a preoperative left ventricular ejection fraction of 19±5% undergoing elective cardiac surgery [24]. They reported a dramatic increase in CO after 60 minutes of levosimendan infusion and it stayed higher than 5 L/min during the first postoperative day, while pulmonary capillary wedge pressure (PCWP) decreased. Heart rate, mean arterial pressure (MAP), and pulmonary arterial pressure did not change during levosimendan infusion. Furthermore, there was a reduction in the need for intraaortic balloon pump support, catecholamine requirements and the duration of critical care stay. Although we have seen positive changes in most of the parameters using LS before the induction of the anesthesia, we determined that using LS 12 hours before the operation is more effective. We observed significant differences at weaning from mechanical ventilation between the four groups. On the other hand, shortening of the duration of intensive care unit and hospital stay, provides better evidence for early administration of this drug.

The general trend for reduced postoperative complications with levosimendan include a lower incidence of atrial fibrillation, less need for inotropic support, less time on the ventilator, and shorter ICU and hospital stays. Tritapepe and colleagues observed that LS allows the avoidance of high doses of conventional inotropes, which are implicated in negative consequences and complications in accordance to the exaggerated effect of vasoconstriction [25]. Lorusso and colleagues found that prophylactic use of intra-aortic balloon pump (IABP) improved outcomes in high-risk cardiac patients, but the main disadvantage of IABP is the development of complications associated with installation of the balloon, which include limb ischemia, damage of the vessel and bleeding [26, 27]. There was less need for IABP insertion. We succeed better tolerance and improvement of its dose dependent beneficial effects on the myocardium contractility without loading dose. Therefore, LS affords a therapeutic solution when other inotropes become inefficient or even dangerous, if they are used in high dosages.

The main observation of the present study was that, in cardiac surgery patients with low preoperative ejection fraction, the cardiac functions and the other organ functions were better maintained with the early use of LS. LS, through the activation of the KATP, produces arterial, coronary, and venous vasodilatation therefore decreased pre-load and after-load and coronary, pulmonary and mammary vasodilation [9]. The same mechanism of action suggests

both anti-ischemic and cardio-protective effects for LS. The agent itself would generate pharmacological preconditioning which favors the recovery of stunned myocardium. Bergh et al. demonstrated that LS establishes a decrease in both preload and afterload. And besides this, continuous infusions of levosimendan decreased the pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance, and pulmonary arterial pressure, which have not been demonstrated by conventional inotrope infusions [28]. In our study PCWP, MPAP, PVRI and SVRI values showed significant decrease according to base to T1 and T2 in all of the groups but when the groups compared dually only in G1 and G2 according to G4 had significant decrease in PVRI, SVRI and MPAP. When we compared the CI, MAP and % EF G1 had the superiority according to the other groups.

LS has a short half-life about 1.5 hours but its active metabolite (OR-1896) has approximately 80 hours. Because of the long half-life of the active metabolite, its effects last till up to 7 to 9 days after discontinuation of a 24-hour infusion of LS [29, 30]. We believed that the statistically significant improvement in cardiac functions in G1 when compared with other groups and even compared to G2, may be the cause of the superiority of the active metabolite (OR-1896) even more effective than the original molecule. Further studies are necessary to clarify the effects of the active metabolite of LS on postoperative patients.

When we compared the biochemical values, G1 and G2 had better results than the other groups. Cardiac troponin I release is a recognized marker of myocardial damage [31]. There are several reasons for troponin elevation in cardiac patients operated on under CPB. The most important include inadequate myocardial protection, surgical manipulations, and reperfusion injury [32]. Tritapepe et al., in their pilot study investigated whether a short infusion of levosimendan (24 μg/kg/min for 10 minutes) before patients were being placed on CPB would provide myocardial protection and improve hemodynamics associated with lower postoperative troponin I concentrations [25]. These data suggest that levosimendan may have a preconditioning effect on the myocardium. Baggish et al showed a positive correlation between postoperative troponin I levels and intensive care length of stay [33]. In our study, patients in G1 and G2 had lower troponin I levels and better cardiac performance than the other groups postoperatively, a finding consistent with a beneficial cardioprotective effect.

Our study demonstrates that pharmacological preconditioning with a 12 hours duration infusion of LS in cardiac surgical patients before commencing CPB appears to confer additional myocardial protection beyond that provided by cardioplegia alone, as manifested by a beter hemodynamic recovery and lower postoperative troponin I levels at the postoperative 24 hours period. The beneficial trends seen in outcome variables and lower troponin I concentrations recorded in our levosimendan-treated patients are in agreement with the aforementioned studies.

In the literature, there are studies regarding timing of LS use; however no such a comprehensive comparison was performed as we did [34].

We believe that the earlier infusion of LS protects not only myocardium but also the other organ targets and preserves the tissue oxygenation. Because lactate levels were lower in the levosimendan treated patients especially in G1 in our study, which may reflect improved tissue oxygenation. Lactate may be a relevant prognostic marker for outcome, because using lactate levels of less than 2 mmol/L as a goal to direct hemodynamic optimization in postoperative cardiac patients resulted in a shorter ICU stay and less organ damage [35]. We observed that lactate levels were increased according parallel to the increase in doses of epinephrine, dobutamine and dopamine.

Although some of the data were not statistically significant, the observed hemodynamic effects are consistent with the known pharmacological actions of LS as a calcium sensitizer and a direct vasodilator. With the use of LS, most patients could be weaned off conventional inotropic support and IABP successfully. De Hert et al. demonstrated that LS produces beneficial hemodynamic effects in patients with preoperative LV dysfunction (ejection fraction <30%) undergoing cardiac surgery who required inotropic support after cardiopulmonary bypass [3].

The time of onset of LS infusion might be essential for preventing low cardiac output

state after CPB. There is also no information in the literature to suggest an optimum duration of LS therapy. Furthermore, data for determination of an optimum dosage also are limited. Beneficial hemodynamic effects are dose dependent; as well as most of the adverse effects. Two important dose-ranging studies have shown that infusion dose of 0.6 mcg/kg/minute and bolus doses of 2-4 mg result in an increase in ventricular extrasystoles compared with placebo [36, 37]. On the other hand, in patients undergoing CABG, lower dosages (0.4 mcg/kg/min) have not been associated with an increase in ventricular ectopy compared with placebo [38]. In a pooled analysis of 10 studies, no increase in the development of ventricular ectopy was detected when levosimendan was used at recommended dosages (0.05-0.2 mcg/kg/min) [39].

The typical dosage of intravenous LS as used in most clinical trials is 12 μg/kg loading dose over 10 minutes followed by 0.05 μg/kg/min continuous infusion. The most common side effects related with the use of levosimendan are nausea, dizziness, headache and hypotension [40]. All these side effects are most likely because of the vasodilatory effects of this drug and we thought that the loading dose is responsible for this action. We did not see any adverse effect at the patients whom we applied the drug at the intensive care unit during the preoperative period. In this study three patients from G3 had hypotensive episodes during infusion. These patients in the first 4 h required temporary noradrenaline to maintain blood pressure. Other side effects include arrhythmias, particularly atrial fibrillation, extrasystoles, atrial or ventricular tachycardia, myocardial strain or ischemia, hypokalemia, or preexisting severe nausea.

According to our clinical practice, no bolus dose of LS was administered because of concern for severe hypotension associated with the bolus dose of the drug. Most of the reported adverse effects of LS were related to the bolus loading dose. For this reason, our approach is to refrain from the loading dose and start with the continuous infusion allowing sufficient time to reach effective plasma concentrations.

Despite being an expensive drug, this pilot study demonstrates that pretreatment with LS in high risk patients undergoing CABG may result in less myocardial injury, a reduction in tracheal intubation time, less requirement for inotropic and IABP support. Therefore LS may constitute a cost effective option as it decreases significantly ICU and hospital stay and consequent risk of complications after CABG surgery in high risk patients with compromised cardiac function.

Limitations

Our study was a retrospective randomized clinical trial with a limited numbers of patients. Data are generalized to a large patient population. LS is expensive and there is not yet a specific time to start the therapy during an episode of decompensation. It is not clear whether levosimendan should be used solely or as an adjunct to traditional treatments.

Regardless, it is clear that more prospective, controlled randomized clinical trials with larger number of patients are warranted in the investigation of LS and its role in patients with compromised LV function after CPB.

Conclusions

In conclusion, our study shows that the elective preoperative initiation of LS especially 12 hours before the operation onset is associated with better improvement on cardiac functions as well as with lower mortality and complication rates, lower use of additional inotropic and vasopressor drugs, less need for intra-aortic balloon pump support and shorter length of stay in the ICU in patients with high perioperative risk or compromised left ventricular function. As a result, patients who received an infusion of LS 12 hours before surgery showed an evidence of less myocardial damage which suggested the preconditioning effect of the drug. However studies with larger numbers of patients will help to determine the value of the present findings.

Disclosure of conflict of interest

All authors have no conflict of interests.

Address correspondence to: Dr. Cuneyt Eris or Senol Yavuz, Department of Cardiovascular Surgery, Bursa Yuksek Ihtisas Education and Research Hospital, 16330 Bursa, Turkey. Tel: +9-0-2243605050; Fax: +9-0-2243605055; E-mail: dr_ceris@hotmail.com (CE); syavuz@ttmail.com (SY)

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