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Preoperative levosimendan in heart failure patients undergoing noncardiac surgery

S. Katsaragakis[1], A. Kapralou[1], H. Markogiannakis[1*], G. Kofinas[2], E-M. Theodoraki[3], A. Larentzakis[1], E. Menenakos[1], D. Theodorou[1]

Departments of [1]Surgical Intensive Care Unit, First Propaedeutic Surgery and [3]Biostatistics, [2]Intensive Care Unit, Hippokrateion Hospital, Athens Medical School, University of Athens, Athens, Greece,
[*]corresponding author: tel.: +30 697678 88 06, fax: +30 210779 05 18,
e-mail: markogiannakis@easy.com

ABSTRACT

Background: Heart failure (HF) is a major cause of perioperative morbidity and mortality in noncardiac surgery. Preoperative optimisation of these patients is, thus, of utmost importance. Levosimendan seems promising for patients undergoing cardiac surgery; however, its safety and efficacy in HF patients undergoing noncardiac surgery have not been evaluated.

Objective: To evaluate the effects of prophylactic preoperative levosimendan administration on left ventricular function in HF patients undergoing noncardiac surgery.

Methods: HF patients with ejection fraction <30% undergoing elective noncardiac surgery in 2005 were included in this prospective study. Patients were admitted to our surgical intensive care unit one day preoperatively. Under continuous haemodynamic monitoring, the treatment protocol consisted of an initial loading dose (24 μg/kg) for ten minutes followed by a continuous 24-hour infusion (0.1 μg/kg/min) at the end of which patients underwent surgery. Echocardiography was performed before infusion (day 0) and on the 7th postinfusion day (day 7). Measurements included left ventricular ejection fraction (LVEF), velocity time integral (VTI), pre-ejection period (PEP), ejection time (ET), maximum (P_{max}) and minimum (P_{min}) transvalvular aortic pressure gradient, and maximum (V_{max}) and minimum (V_{min}) aortic velocity.

Results: Twelve consecutive patients were enrolled. Levosimendan resulted in a significant increase in LVEF, VTI, P_{max}, P_{min}, V_{max}, and V_{min} ($p<0.01$) and, moreover, a significant reduction in PEP, ET, and PEP/ET ($p=0.04$) on day 7 compared with day 0 values. No adverse reactions, complications or mortality occurred during 30-day follow-up.

Conclusion: Prophylactic preoperative levosimendan treatment may be safe and efficient for perioperative optimisation of heart failure patients undergoing noncardiac surgery.

KEYWORDS

Elective noncardiac surgery, heart failure, inotropes, left ventricular function, perioperative optimisation, prophylactic preoperative levosimendan infusion

INTRODUCTION

Heart failure (HF) is an important public health problem, with a 6 to 10% incidence in the population over 65, and a common reason for hospitalisation among elderly adults.[1] It is also a frequent and significant risk factor for perioperative morbidity and mortality[1,2] that results in a twofold higher mortality after major noncardiac surgery compared with patients with coronary artery disease or the general population.[2] The importance of HF as an independent risk factor is underlined by the fact that patients with coronary artery disease but without HF have a similar 30-day mortality rate to the general population.[1] HF patients are undergoing noncardiac surgery with an increased frequency due to their advanced age.[1] Despite advances in perioperative care, however, they still suffer substantial morbidity and mortality. Although their preoperative optimisation is of utmost importance, guidelines for their perioperative management have not been clarified. Prophylactic inotropic therapy remains controversial;[3,4] its efficacy is debatable and it has been

associated with increased myocardial oxygen consumption, arrhythmias, and even mortality.[4]

In contrast, levosimendan, a novel positive inotrope, improves cardiac performance and haemodynamics in HF patients without increasing myocardial oxygen demand or causing arrhythmias.[5-8] Its pharmacological effects last for at least seven days after discontinuation, the postoperative period in which most cardiac complications occur.[8] It has been used for perioperative optimisation in patients undergoing cardiac surgery in a few studies with promising results;[9-11] however, it has not been evaluated in noncardiac surgery before. Taking advantage of its pharmacological profile, this prospective study aimed to evaluate the safety and efficacy of prophylactic preoperative levosimendan treatment on left ventricular function in the perioperative period in HF patients undergoing elective noncardiac surgery.

MATERIALS AND METHODS

This prospective study was conducted in the surgical intensive care unit (SICU), 1st Department of Propaedeutic Surgery of the University of Athens, Hippokrateion Hospital, Athens, Greece from January to December 2005. Patients with chronic cardiac failure with a left ventricular ejection fraction <30% undergoing elective noncardiac surgery were included in the study. Exclusion criteria were heart failure due to restrictive or obstructive cardiomyopathy or to nontreated severe valvular disease, history of ventricular tachycardia or fibrillation, second- or third-degree atrioventricular block, systolic arterial blood pressure <85 mmHg, heart rate >120 beats/min at rest, severe renal failure (defined as creatinine clearance <30 ml/min), and severe hepatic cirrhosis (defined as class C according to the Child-Pugh scoring system).[12] Institutional Review Board approval was obtained prior to study initiation and written, informed consent was signed in all cases.

Preoperative risk stratification for each patient was performed according to the Goldman Cardiac Risk Index,[13] New York Heart Association (NYHA),[14] and American Society of Anaesthesiologists (ASA) classification.[15] All patients were admitted to the SICU the day before surgery for levosimendan treatment and close haemodynamic monitoring, including continuous arterial blood pressure monitoring via a radial artery catheter (systolic: SAP, mean: MAP, and diastolic arterial pressure: DAP), heart rate (HR) via electrocardiogram, urine output through a bladder catheter, pulmonary artery catheter data, and pulse oximetry. In addition, blood gas analysis was performed every three hours and blood tests every 12 hours. Blood tests included white blood cells, platelets, haematocrit, haemoglobulin, coagulation, glucose, urea, creatinine, electrolytes, amylase, lactic dehydrogenase, creatinine phosphokinase and creatinine phosphokinase-MB, troponin, and liver function tests.

Transthoracic echocardiographic evaluation was performed on admission to the SICU, prior to levosimendan administration (day 0), and on the 7th postinfusion day (day 7). Measurements included left ventricular ejection fraction (LVEF), velocity time integral (VTI), pre-ejection period (PEP), ejection time (ET), maximum (P_{max}) and minimum transvalvular aortic pressure gradient (P_{min}), maximum (V_{max}) and minimum aortic velocity (V_{min}). The VTI x HR product and PEP/ET fraction were also estimated.

After right cardiac catheterisation, echocardiography, and initiation of haemodynamic monitoring, levosimendan was administered. The levosimendan treatment protocol consisted of an initial loading dose (24 μg/kg) for ten minutes which was followed by a continuous 24-hour infusion (0.1 μg/kg/min). Criteria for dose reduction were hypotension (systolic arterial pressure <80 mmHg), heart rate >140 beats/min or increased by >25 beats/min for at least ten minutes and arrhythmias. If these continued after dose reduction or anaphylactic or other adverse reactions occurred, levosimendan treatment protocol was immediately terminated.

All patients remained under continuous haemodynamic monitoring in the SICU during the whole administration period and underwent surgery immediately after the end of infusion under the same intraoperative haemodynamic monitoring. Monitoring was continued postoperatively in the SICU until 24 hours postinfusion. Patients were then discharged from the SICU to the ward. Noninvasive monitoring in the ward included arterial pressure, heart rate, electrocardiogram, pulse oximetry, and urine output every three hours, clinical evaluation by the same surgical team every three hours, blood gas analysis every 12 hours, and blood tests once daily. After discharge from the hospital, patients were seen on the 7th, 14th, and 30th postoperative day.

Statistical analysis was performed with the SPSS 12.0 software statistical package. Data are expressed as median ± SD (standard deviation) and ranges. Comparisons between recorded data on day 0 and day 7 were performed using the nonparametric Wilcoxon signed-rank test. Haemodynamic variables at 0 min, 10 min, and 24 hours were compared using paired-samples t-test. A p value <0.05 was regarded as statistically significant.

RESULTS

During the one-year study period, 12 consecutive patients were included in our study. Patients' demographics, surgical procedures, and preoperative Goldman Cardiac

Risk Index, NYHA functional class, and ASA physical status are shown in *table 1*. Median age was 75 ± 3 years (range: 64-83 years); 8 (66.7%) of them were men. Median hospital stay was 5 ± 2.2 days.

The cause of HF was coronary artery disease in ten (83.3%) and hypertension in two (16.7%) patients. Four patients (33.3%) had previously had a myocardial infarction, all of whom more than six months prior to surgery, four (33.3%) had diabetes mellitus, seven (58.3%) hypertension, four (33.3%) peripheral arterial occlusive disease, three (25%) hypercholesterolaemia, and one patient (8.3%) had undergone coronary artery bypass surgery. Regarding concomitant medication of the study patients, eight (66.7%) were receiving angiotensin-converting enzyme inhibitors, five (41.6%) digoxin, five (41.6%) loop diuretics (furosemide), four (33.3%) nitrates, three (25%) β-blockers, three (25%) statins, two (16.7%) spironolactone and one patient (8.3%) diltiazem.

Levosimendan was well tolerated in all patients. No hypotension, heart rate >140 beats/min or increase in heart rate by >25 beats/min, or arrhythmias were identified during the observation period. Discontinuation or dose reduction was not necessary in any of the patients. No adverse reactions, complications or mortality occurred during 30-day follow-up.

Haemodynamic data of the patients during levosimendan infusion are presented in *table 2*. Levosimendan showed no significant effect on SAP, MAP, DAP, PAP or PWP, whereas a significant increase in CO (p=0.01) and a reduction of SVR (p=0.01) were observed. Heart rate increased from 75 ± 9.2 beats/min to 89 ± 7.6 beats/min and 90 ± 5.4 beats/min at 24 hours and on day 7 (p=0.05), respectively.

Echocardiographic measurements before levosimendan administration (day 0) and on the 7th postinfusion day (day 7) are presented in *table 3*. Levosimendan resulted in a significant increase of 11% in LVEF (from 21 ± 4.2 to 32 ± 7.8, p<0.01). Effects of levosimendan on ejection fraction in each patient are depicted in *figure 1*; all patients experienced a significant improvement in LVEF on day 7. In addition, compared with day 0 values, VTI and VTI x HR product were significantly increased (from 21.2 ± 3.6 cm to 23.5 ± 3.2 cm, p<0.01 and from 1396.7 ± 418.3 cm/min to 2168.9 ± 235.1 cm/min, p<0.01, respectively). Moreover, PEP, ET and PEP/ET were significantly decreased on the 7th postinfusion day when compared with preinfusion values (70 ± 22.2 msec *vs* 90 ± 24.5 msec, p=0.04, 260 ± 34.4 msec *vs* 270 ± 30.4

Table 1. *Demographics, surgical procedures and preoperative risk stratification of the patients*

Patient	Sex	Age	Operation	Goldman Cardiac Risk Index	NYHA	ASA
1	Female	64	Open cholecystectomy	I	2	3
2	Male	72	Abdominal hernia repair	I	2	4
3	Male	78	Abdominal hernia repair	I	2	3
4	Female	77	Abdominal hernia repair	I	2	3
5	Male	83	Abdominal hernia repair	I	3	4
6	Male	77	Hartmann's procedure	III	3	4
7	Male	78	Adhesiolysis	III	3	4
8	Male	75	Choledochojejunostomy	II	2	4
9	Male	83	Open cholecystectomy	III	3	4
10	Female	67	Abdominal hernia repair	II	2	4
11	Female	77	Abdominal hernia repair	II	3	4
12	Male	70	Abdominal hernia repair	II	2	4

NYHA = New York Heart Association functional class; ASA = American Society of Anaesthesiologists physical status.[15]

Table 2. *Haemodynamic data during levosimendan infusion*

Variable	Value 0 min	Value 10 min	Value 24 hrs	p value (0 *vs* 10 min)	p value (0 min *vs* 24 hrs)
Heart rate (beats/min)	75 ± 9.2	85 ± 8.4	89 ± 7.6	NS	0.05
Systolic arterial pressure (mmHg)	154 ± 17.5	150.5 ± 22.9	149 ± 15.6	NS	NS
Diastolic arterial pressure (mmHg)	73 ± 6.2	72 ± 9.4	71 ± 10.9	NS	NS
Mean arterial pressure (mmHg)	99 ± 9.3	97.5 ± 13.4	96 ± 11	NS	NS
Pulmonary artery pressure (mmHg)	19.5 ± 7.8	19 ± 7.2	20 ± 5.2	NS	NS
Pulmonary wedge pressure (mmHg)	10 ± 5.9	10 ± 6.3	11 ± 4.1	NS	NS
Cardiac output (l/min)	4.2 ± 0.5	5.1 ± 0.7	6.7 ± 0.8	0.01	0.01
Systemic vascular resistance (dyn. sec/cm^5)	1710.5 ± 223.2	1342 ± 264.6	970.5 ± 212.3	0.01	0.01

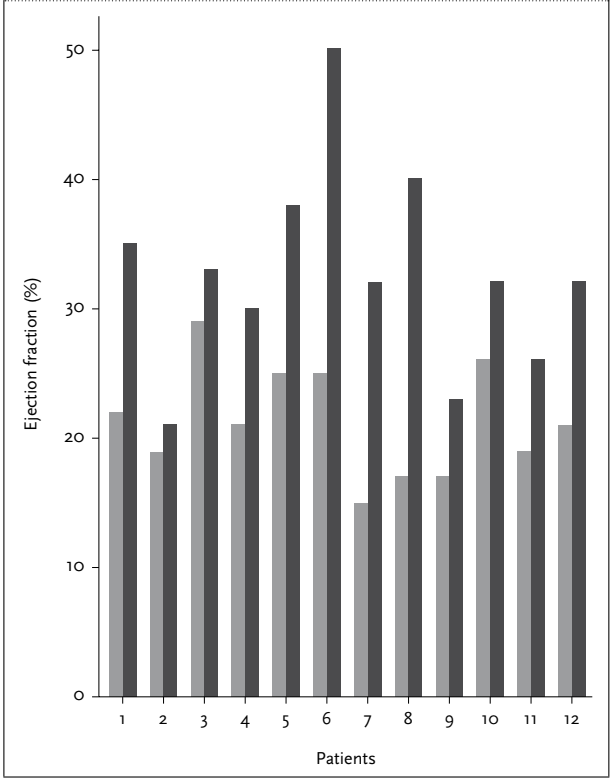
NS = not statistically significant.

Table 3. *Comparison between echocardiographic measurements before levosimendan administration (day 0) and on the 7th postinfusion day (day 7)*[1]

Variable	Day 0	Day 7	p value
Left ventricular ejection fraction (%)	21 ± 4.2	32 ± 7.8	<0.01
Velocity time integral (cm)	21.2 ± 3.6	23.5 ± 3.2	<0.01
Velocity time integral x heart rate (cm/min)	1396.7 ± 418.3	2168.9 ± 235.1	<0.01
Pre-ejection period (msec)	90 ± 24.5	70 ± 22.2	0.04
Ejection time (msec)	270 ± 30.4	260 ± 34.4	0.04
Pre-ejection period/ejection time	0.3 ± 0.1	0.2 ± 0.1	0.04
V_{max} (m/sec)	1.2 ± 0.1	1.4 ± 0.1	<0.01
V_{min} (m/sec)	0.8 ± 0.1	0.9 ± 0.1	<0.01
P_{max} (mmHg)	6.1 ± 1.6	8 ± 1.1	<0.01
P_{min} (mmHg)	3 ± 0.5	4.3 ± 0.8	<0.01

[1]**Values are expressed as median ± SD (standard deviation). V_{max} = maximum aortic velocity; V_{min} = minimum aortic velocity; P_{max} = maximum transvalvular aortic pressure gradient; P_{min} = minimum transvalvular aortic pressure gradient.**

Figure 1. *Ejection fraction before levosimendan infusion (■) and on the 7th postinfusion day (■)*



msec, p=0.04, and 0.2 ± 0.1 *vs* 0.3 ± 0.1, p=0.04, respectively). Levosimendan treatment also exerted a significant effect on P_{max} (from 6.1 ± 1.6 mmHg on day 0 to 8 ± 1.1 mmHg on day 7, p<0.01), P_{min} (from 3 ± 0.5 mmHg to 4.3 ± 0.8 mmHg, p<0.01), V_{max} (1.2 ± 0.1 m/sec *vs* 1.4 ± 0.1 m/sec, p<0.01), and V_{min} (0.8 ± 0.1 m/sec *vs* 0.9 ± 0.1 m/sec, p<0.01).

DISCUSSION

Heart failure is a major cause of perioperative morbidity and mortality in patients undergoing noncardiac surgery, making strategies to reduce cardiac events in such high-risk patients of utmost importance.[1,2,16] Perioperative cardiac evaluation and therapeutic interventions for prevention of cardiac complications, however, are mostly focused on the management of myocardial ischaemia. In contrast, there is still very little known about the perioperative cardiac optimisation of HF patients scheduled for elective noncardiac surgery. The lack of strict guidelines for the management of these patients underlines the complexity of the problem.

Prophylactic use of inotropic support remains controversial. Flancbaum *et al.* suggested that preoperative correction of abnormal haemodynamic parameters with inotropes, crystalloids, packed red blood cells, and/or afterload reduction may reduce postoperative cardiovascular complications in a retrospective study of patients undergoing major elective noncardiac, nonthoracic surgery[3] while, in a prospective randomised trial, Hayes *et al.* reported that dobutamine failed to improve outcome and was associated with increased mortality.[4]

Levosimendan is a calcium sensitiser with inotropic and vasodilatory properties, the safety and effectiveness of which have been shown in several studies of HF patients.[5-8,17-21] Levosimendan in patients with left ventricular systolic dysfunction results in beneficial haemodynamic effects with decreases in left and right filling pressures and systemic vascular resistance and increases in stroke volume and cardiac index. Moreover, the current literature, although limited, suggests that prophylactic levosimendan in cardiac surgery is safe and efficient in terms of cardiac performance, haemodynamics, duration of intubation, and survival.[9-11] However, it has not been evaluated in HF patients undergoing noncardiac surgery. Given its long-lasting effects on cardiac performance, the objective of this study was to evaluate the safety and efficacy of prophylactic preoperative levosimendan administration in these patients and, particularly, its effects on left ventricular function.

A significant increase in LVEF, VTI, VTI x HR, P_{max}, P_{min}, V_{max}, V_{min}, and CO along with a reduction in PEP, ET, PEP/ET, and SVR were identified seven days after levosimendan treatment. These effects were observed in each study patient. Levosimendan had no significant effect on arterial blood pressure while heart rate was marginally increased. Levosimendan infusion was well tolerated in all patients and no additional inotropic support, dose reduction or withdrawal were necessary and no arrhythmias, adverse reactions, complications or mortality occurred during 30-day follow-up.

Levosimendan has been shown to improve left ventricular function without having an effect on arterial pressure or proarrhythmic properties.[5,8-10,18,20] Such effects may be significant since perioperative left ventricular dysfunction is a predictor of postoperative cardiovascular complications and mortality, while left ventricular ejection fraction is one of the most important predictors of prognosis in HF patients.[22,23] It has also been reported to increase survival compared with dobutamine or placebo, a result that was maintained for 180 days.[5,6,20] Regarding heart rate, some studies suggest that it may be increased particularly with high doses of levosimendan[11,21] while others found no significant effect.[9,20] Since a higher heart rate may be detrimental in such patients, the effect of levosimendan on heart rate and its relation to the administered dose merit further study.

Calcium sensitisers are a new class of inotropic agents that enhance myocardial contractility through augmenting the sensitivity of the myofilaments to calcium by binding to troponin C. Levosimendan has unique characteristics as it stabilises the interaction between calcium and troponin C by binding to troponin C in a calcium-dependent manner.[7,24] Increased sensitivity to calcium is probably its main mechanism of action while phosphodiesterase enzyme inhibition is a less important mechanism.[7,25] In contrast to other agents, levosimendan has the advantage that the increased contractility is achieved without energy expenditure, thus improving cardiac performance and haemodynamics without increasing myocardial oxygen consumption.[5-7,25] Furthermore, it exerts vasodilatory properties through activation of ATP-dependent potassium channels in smooth muscle of peripheral, pulmonary, and coronary vessels. It thus results in coronary vasodilatation improving heart oxygenation and showing protective effects to the myocardium.[7,25] Interestingly, it also has beneficial anti-inflammatory, antioxidant, and antiapoptotic effects.[17-19] These immunomodulatory properties may contribute to improvement of cardiac performance.

The active metabolite of levosimendan, OR-1896, has a long half-life of approximately 80 hours and can be detected in the circulation up to two weeks after discontinuation of a 24-hour infusion.[25] Beneficial effects on cardiac performance are, therefore, sustained for at least seven days after termination of a single 24-hour infusion.[8] In agreement with this observation, improvement in left ventricular function was identified on the 7th postinfusion day in our patients. This characteristic of levosimendan seems very important since optimisation of cardiac performance is maintained throughout the immediate postoperative period when perioperative stress is higher and cardiovascular complications are, therefore, more likely to occur.

Our results indicate that levosimendan may have promising effects for perioperative cardiac optimisation of HF patients undergoing elective noncardiac surgery in terms of safety and efficacy. The present study, however, is limited due to the small number of patients and the lack of a control group in order to exclude any potential effects of other factors than the infusion of levosimendan. Our study shows, however, that levosimendan can be safely administered in chronic heart failure patients undergoing noncardiac surgery. These data would support a prospective, randomised, controlled trial. Further studies are, therefore, needed to evaluate the cardioprotective benefit and safety of levosimendan in these patients. Sound clinical judgment, close perioperative monitoring, and individualised therapeutic approach are essential for reduction of postoperative cardiac morbidity and mortality in this fragile group of patients.

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