Timing of levosimendan in cardiac surgery

Kardiyak cerrahide levosimendan kullanımında zamanlama

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Abstract

Objective: Levosimendan (LS) is a new inodilator agent that improves cardiac contractility by increasing the sensitivity of troponin C to calcium, which usage in cardiac surgery has been growing in the recent years. We aimed to determine the best timing of the administration of LS in high-risk patients who underwent cardiovascular surgery.

Methods: Fifteen patients were evaluated retrospectively who have left ventricular dysfunction, underwent open-heart surgery and were applied LS in different phases of operation. Patients were divided into 3 groups according to timing of LS. Levosimendan infusion (0. 1 $\mu g^{-1}kg^{-1}min$) was applied after the induction of anaesthesia (n=5) (Group 1), during the pump removal period (n=5) (Group 2) and in postoperative period (n=5) (Group 3). Demographic data, operative characteristics, mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary wedge capillary pressure (PWCP), cardiac index (CI), inotropic agent consumption, postoperative urine output, lactate levels of groups were compared between before and after LS treatment. Data were evaluated by Fisher exact, Kruskal-Wallis, Mann-Whitney U and Wilcoxon rank tests.

Results: In all patients, urine output was satisfactory 24 hours after LS application. There was a significant increase in CI of all 3 groups (p=0.04). Also, there was a significant decrease in PCWP of all 3 groups before and after LS (p=0.04). There was a significant decrease in MPAP in Group 2 and 3 (p=0.04). Twenty- four hours after LS application, whereas all inotropic agents could be stopped in Group 1 and 2, in Group 3 inotropic infusion (dopamine [10 $\mu g^{-1}kg^{-1}min$ (5-17.5)], dobutamine [15 $\mu g^{-1}kg^{-1}min$ (5-20)] and adrenaline [0.4 $\mu g^{-1}kg^{-1}min$ (0.15–0.65)]) couldn't be stopped (p= 0.007). During postoperative period, in Groups 1 and 2 one case from each required intraaortic balloon pump, while in Group 3 four patients were applied intraaortic balloon pump (p=0.08).

Conclusion: According to our experience, LS is effective in high-risk cases during cardiac surgery, especially during the intra-operative and pump removal periods; however, no successful outcomes were observed during the post-operative period. As a result, case selection and timing should be performed well when using LS. *(Anadolu Kardiyol Derg 2009; 9: 223-30)*

Key words: Levosimendan, cardiac surgery, low cardiac output

Özet

Amaç: Levosimendan (LS), troponin C'nin kalsiyuma duyarlılığını artırarak kardiyak kontraktiliteyi güçlendiren yeni bir inodilatatör ajandır ve son zamanlarda kardiyak cerrahide kullanımı artmaktadır. Bu çalışmada kardiyovasküler cerrahiye giden yüksek riskli hastalarda LS kullanımında en uygun zamanlamanın tespit edilmesi hedeflenmiştir.

Yöntemler: Kısıtlı sol ventrikül fonksiyonuna sahip, açık kalp cerrahisi geçiren ve operasyonun çeşitli evrelerinde LS uygulanan toplam 15 hasta retrospektif olarak incelendi. Hastalar LS kullanım zamanlarına göre 3 gruba ayrıldılar. Anestezi indüksiyonundan sonra (n=5) (Grup1), pompa çıkışında (n=5) (Grup 2) ve postoperatif periyodda (n=5) (Grup 3) LS infüzyonu (0.1 $\mu g^{-1}kg^{-1}dak$) uygulanmıştır. Grupların demografik verileri, operatif karakteristikleri, ortalama arter basıncı (OAB), ortalama pulmoner arter basıncı (OPAB), pulmoner kapiller uç basıncı (PKUB), kardiyak indeksi (Kİ), inotropik ajan tüketimi, postoperatif idrar çıkışı, laktat düzeyleri LS öncesi ve LS sonrası dönemde karşılaştırıldı. Veriler Fisher exact, Kruskal-Wallis, Mann-Whitney U and Wilcoxon rank tests ile değerlendirildi.

Bulgular: Tüm hastalarda LS uygulanmasından 24 saat sonra idrar çıkışı yeterliydi. Levosimendan öncesi ve LS sonrası kardiyak indekslerde her üç grupta da anlamlı artış oldu (p=0.04). Levosimendan öncesi ve LS sonrası PKUB'da her üç grupta da anlamlı azalma saptandı (p=0.04). Pulmoner arter basıncında Grup 2 ve 3'de anlamlı düşme saptandı (p=0.04). Levosimendan uygulamasından 24 saat sonra Grup 1 ve 2'de tüm

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This work was presented at 18th World Congress of World Society of Cardio-Thoracic Surgeons, Kos Island, Greece, April 30-May 3, 2008.

inotropik ajanlar kesilebilmişken, Grup 3'de inotrop infüzyonu (dopamin [10 $\mu g^{-1}kg^{-1}dak$ (5-17.5)], dobutamin [15 $\mu g^{-1}kg^{-1}dak$ (5-20)] ve adrenalin [0.4 $\mu g^{-1}1kg^{-1}dak$ (0.15–0.65)]) kesilememiştir (p= 0.007). Postoperatif dönemde Grup 1 ve 2'de 1'er hastaya intraaortik balon uygulanmışken Grup 3'de 4 hastada intraaortik balon uygulanmıştır (p=0.08).

Sonuç: Deneyimlerimiz LS'nın kardiyak cerrahide, yüksek riskli olgularda özellikle intraoperatif ve pompa çıkışı kullanımlarının etkin olduğu, postoperatif kullanımlarında ise çok başarılı sonuçlar alınamadığı yönündedir. Bu yüzden LS kullanımında olgu seçimi ve zamanlama iyi yapılmalıdır. *(Anadolu Kardiyol Derg 2009; 9: 223-30)*

Anahtar kelimeler: Levosimendan, kalp cerrahisi, düşük kalp debisi

Introduction

Surgical manipulations, underlying cardiac disease, ischemia and reperfusion are predominant causes of cardiac dysfunction encountered after cardiopulmonary bypass (CPB). Endothelin-1 secreted during CPB, has coronary vasoconstrictive and C3a has negative inotropic and strong chemotactic effects.

During reperfusion, activated neutrophils adhere to cardiac myocytes and endothelial cells by MAC-1 adhesion receptors (1, 2). Activated neutrophils lead to the release of cytokines and free oxygen (O_2) radicals. Extracorporeal circulation increases the myocardial edema. The most important reasons for this increase are reduction in the osmotic pressure of plasma colloids, high coronary perfusion pressure, distension of the ventricles and ventricular fibrillation. Loss of contractility during ventricular fibrillation may result in a decreased lymphatic flow through the heart. Moreover, antibodies that develop against MAC-1 receptors also could lead to neutrophil adhesion, diastolic dysfunction and myocardial edema. Myocardial stunning inevitably occurs during cross clamping. These factors lead to temporal abnormalities in cardiac function during the early stage of the surgery (1). Thus, there is a general requirement for the use of inotropic agents in order to facilitate weaning off from CPB and maintain sufficient cardiac output (CO).

Most inotropes used in the clinics function by increasing the levels of cytosolic calcium (Ca^{+2}), whereas LS stimulates myocardial contractility without raising the intracellular Ca^{+2} concentration (2, 3). Levosimendan increases the Ca^{+2} response to myofilament by binding to cardiac troponin C. As a result, myocardial contraction increases without a higher myocardial O_2 consumption (3, 4, 5). Levosimendan also exhibits vasodilatory effect through the activation of adenosine triphosphate-dependent potassium (K^+) channels (6, 7). Levosimendan is distinguished from other inotropic agents by this dual mechanism and considered as a good choice in high-risk patients undergoing cardiac surgery (8-10). However, few is known on timing of LS during cardiovascular surgery.

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

Methods

A total of 15 consecutive patients, who underwent open heart surgery in Cardiovascular Surgery Clinic between March 2005 and March 2007 were administered LS during various stages of the procedure, were investigated retrospectively. Our first experience with LS was about usage of LS in cardiac failure at the postoperative period. In the next 5 cases we used LS in the patients with early usage claim of LS and those had difficulties with ending the pump, afterwards we thought we can get better results with using LS before pump, so we used LS after induction in 5 patients.

The patients were divided into three groups according to their timing of LS use; five patients who received LS infusion following the induction of anesthesia formed Group 1, five patients who received LS infusion during the pump removal formed Group 2 and five patients who received LS infusion during the post-operative period formed Group 3.

The method of anesthesia was equally applied to all cases. Induction of anesthesia was provided through titration of 2 mg of midazolam i.v., 2-5 $\mu g\ kg^{-1}$ of fentanyl i.v. and 3-5 mg kg^{-1} of thiopental sodium i.v. Muscle relaxation was achieved by 0.1 mg kg^{-1} pancuronium bromide and anesthesia was maintained by high dose fentanyl. Hemodynamic measurements were performed by using the thermodilution method, by the placement of pulmonary artery catheter after induction of anesthesia.

Levosimendan infusion was administered to all patients at a rate of 0.1 $\mu g^{-1}\ kg^{-1}$min without a loading dose. At the end of the CPB, dopamine infusion was initiated in cases with a mean arterial pressure (MAP) ≤60 mmHg within the adequate perfusion period; other inotropic agents were added in cases with MAP ≤60 mmHg and pulmonary capillary wedge pressure (PCWP) ≥15 mmHg. During the post-operative period, when hemodynamic stability was maintained the inotropic agents were ceased, by reducing the dosage. An intra-aortic balloon pump (IABP) was applied when there was a pump insufficiency despite inotropic support with dopamine, dobutamine, adrenalin treatment and LS infusion. The measurements were performed prior to LS infusion and after 24 hours.

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, preoperative ejection fraction (EF) and hemodynamic data [MAP, mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI)], doses of inotropic agents, post-operative (24 hours) urine output, and lactate levels before and after LS were registered and compared.

Statistical analysis

Statistical analyses were performed using SPSS software version 13.0 (SPSS Inc. Chicago, IL, USA). Normal distribution of data was checked with Shapiro-Wilk test. Continuous variables were expressed as mean ± SD and categorical variables were presented as number of patients. Due to the fact, that measured data of inotrope consumption were markedly skewed, values

are expressed as median, first and third quartiles. Categorical variables were compared with Fisher exact tests. Continuous variables and inotrope consumptions were compared with Kruskal- Wallis analysis. Mann Whitney U test was used to find differences while comparison of 2 groups. Comparison analyses between before and after LS values were made by using Wilcoxon rank test. A p value of <0.05 (2-tailed) was considered as significant.

Results

When the patients separated into three groups according to the starting time for LS were compared no significant differences were determined between the groups with regards to age, gender, preoperative EF, duration of the operation, duration of cross clamp and the total duration of perfusion (p>0.05) (Table 1).

Comparison of hemodynamic effects of LS showed statistically significant differences between the 1st and 2nd measurements of the MAP in Group 1 and Group 2. Although a difference was found between the measurements in Group 3, this difference was not statistically significant. (p>0.05) (Table 2). There were statistically significant differences between the 1st and 2nd measurements of the MPAP in Group 2 and Group 3. The difference between these measurements in Group 1 was not statistically significant. (p>0.05) (Table 2). The PCWP decreased in all groups (p<0.05), while CI significantly increased after LS infusion (p<0.05) (Table 2). No statistically significant differences between groups were found in MAP, MPAP, PCWP and CI values between before and after LS treatment. There was a statistically significant difference in lactate levels before LS between Groups 1 and 3 (p<0.05) (Table 2). The differences in lactate levels before and after LS in all groups were not statistically significant (p>0.05) (Table 2). No statistically significant difference was verified between the three groups according to post-operative urine output (p>0.05) (Table 2).

The usage of inotropic agents in all of our patients was inevitable. While in groups 1 and 2 all inotropic agents could be stopped after 24 hours, in Group 3 no regression could be established in the inotropic posology, with exception of one patient (Table 3). There was no statistically significant difference between the 1st and 2nd measurements of each of the three inotropic agents in Group 3 (p>0.05) (Table 3).

During the post-operative period, IABP was applied to one patient of groups 1 and 2, whereas it was applied to four patients in Group 3 (p=0.08) (Table 1).

Discussion

In our retrospective study, adequate urine output, increased CI and decreased PCWP were observed in all of our patients who underwent cardiac surgery and having poor left ventricular function. The MPAP was decreased in LS administered patients during pump removal period and post-operative period. Twenty-four hours after LS application, whereas all inotropic agents could be stopped in Group 1 and 2, in Group 3 inotropic infusion could not be stopped. As a result, we observed that use of LS during intraoperative and pump removal periods was effective.

The frequency of low-output syndrome following cardiac surgery is 3-10% (7). Following the cardiac surgery, the ratio of patients who require positive inotropic support after CPB is 32.4% (13). The ratio of patients who require positive inotropic support during and after CPB and CABG with preoperative EF<30 was 92% (4, 12). When our patient-groups were examined, it was verified that all of them were composed of high-risk patients.

Levosimendan has superior pharmacologic features when compared to conventional inotropic agents. It enhances the sensitivity of myofilaments to calcium during cardiac systole by calcium dependent binding to troponin C. This interaction strengthens the actin-myosin cross-bridges through the stabilization of calcium-induced conformational changes in tropomyosin. Levosimendan accomplishes this effect by enhancing the intracellular Ca^{+2} sensitivity of troponin C without increasing the intracellular Ca^{+2} concentrations (3, 15-18). Since LS does not increase intracellular Ca^{+2} levels, its arrhythmogenic potential is reported to be low (3, 19). The hemodynamic effects of LS were found to be higher in patients who used β-blockers. Its superiority over other inotropic agents can also be evidenced with this feature (20).

In the latest guideline of the European Society of Cardiology, LS is recommended for the diagnosis and treatment of heart failure with low cardiac output secondary to cardiac systolic dysfunction. On the other hand, there is still limited evidence regarding the use of LS in post-operative myocardial dysfunction (21). However, publications concerning the use of LS in cardiac surgery are raising in parallel to our experience.

Levosimendan, a new inodilator used in the treatment of decompensated heart failure, has been reported to be effective in patients with high perioperative risks, with abnormal left ventricular function, and who face difficulties in weaning off cardiopulmonary bypass (3). It can be used during various stages of cardiac surgery. Rajek et al. (22) reported the first case of LS application in eight patients with congestive heart failure and preoperative left ventricular EF of 19±5%, who were planned to undergo elective cardiac surgery. Of these patients, 5 underwent coronary artery bypass surgery, 2 - mitral valve replacement and 1 - undergo aortic valve replacement. Levomisendan was administered before sternotomy, after a loading dose of 0.6 μg^{-1}kg for 10 minutes, a full maintenance infusion dose of 0.2 μg^{-1} kg^{-1}min. There was a dramatic increase in cardiac output after 60 minutes following LS infusion, and while there was a decrease in PCWP, cardiac output remained above 5 L/min. There was no change in heart rate, MAP and MPAP during LS infusion. On the other hand, it was possible to successfully wean off cardiopulmonary bypass on every patient without the requirement of an IABP, and also confirm a decrease in both catecholamine need and permanence in the intensive care unit. There are other publications which confirmed the results of Rajek et al. (3, 7).

In our study, LS infusion was administered in a different from previous studies (22) way to all patients at a rate of 0.1 μg^{-1} kg^{-1} min

Table 1. Demographic and procedural characteristics of patients

Variables	Group 1	Group 2	Group 3	Chi-square	p*
Age, years	58.00±15.34 62.00 (45.00- 69.00)	61.4±6.6 59.0 (56.0-68.0)	61.8±10.3 60.0 (52.5-72.0)	0.02	0.99
Male/Female	5/0	3 / 2	3 / 2		0.26
Ejection fraction, %	28.00±4.47 25.00 (25.00-32.50)	31.00±7.47 30.00 (25.00 -37.50)	31.00±5.48 30.00 (27.50-35.00)	1.19	0.55
Euroscore, points	5.6±2.5 5.0 (3.5-8.0)	6.6±2.5 8.0 (4.0-8.5)	5.4±1.9 6.0 (3.5-7.0)	0.89	0.64
Cross- clamp duration, min	90.2±41.4 95.0 (50.5-127.5)	64.2±33.16 72.0 (32.0-92.5)	81.0±28.8 90.0 (52.5-105.0)	1.34	0.51
Pomp duration, min	160.4±61.2 153.0 (108.0-216.5)	102.6±44.3 108.0 (62.5-140.0)	143.2±42.2 150.0 (103.0-180.0)	3.02	0.22
Operation duration, min	280.0±61.2 280.0 (225.0-335.0)	213.0±52.6 210.0 (165.0- 262.5)	266.0±45.7 270.0 (220.0- 310.0)	3.64	0.16
Type of operation					p
CABG, n	3	2	2		0.765
CABG+AVR, n	0	0	1		0.343
AVR, n	1	1	0		0.562
AVR+MVR, n	0	0	1		0.343
Redo AVR, n	1	0	0		0.343
Redo MVR, n	0	2	1		0.282
Diabetes Mellitus, n	0	1	0		0.34
COPD, n	1	2	1		0.71
IABP use, n	1	1	4		0.08
Hypertension, n	2	1	2		0.74
MI suffered, n	2	2	1		0.74
Mortality, n	2	2	5		0.08

Data are presented as the mean ± SD, median (25%-75%) values and proportions

*Kruskal-Wallis test for comparison of continuous variables and Fisher exact test for comparison of categorical variables

AVR – aortic valve replacement, CABG – coronary artery bypass surgery, COPD - chronic obstructive pulmonary disease, IABP - intraaortic balloon pump, MI - myocardial infarction, MVR – mitral valve replacement

without loading dose. The findings in groups 1 and 2 were similar to results of Rajek et al. (22).

The positive inotropic and cardioprotective effects of LS have been demonstrated in high-risk patients with acute myocardial ischemia who would undergo emergency surgery revascularization (3, 23).

Labriola et al. (7) investigated whether LS was effective or not for patients with a low output after cardiac surgery, by administering a loading dose of 12 μg^{-1} kg in 10 min followed by a continuous infusion dose of 0.1 $\mu g^{-1} kg^{-1}$ min for a period of 12 hours. A combined hemodynamic improvement (increase of more than 30% in CI, improvement in PCWP) was established within three hours after initiating LS infusion in 8 (73%) of the 11 patients with a severe decrease in output and hemodynamic disorder following the surgery. After admission to the intensive

Table 2. Hemodynamic parameters of patients

Variables	Group 1	Group 2	Group 3	Chi-square	p
MAP, mm Hg					
Before LS	65.0±9.3 66.0 (55.5-74.0)	62.8±16.0 65.0 (48.00-76.5)	66.0±13.9 65.0 (52.5-80.0)	0.02	0.99
After LS	76.4±13.5 Ψ(p=0.043) 76.0 (65.0-88.0)	74.8±12.6 Ψ(p=0.042) 80.0 (61.5-85.5)	81.0±7.4 80.0 (75.0-87.5)	0.46	0.79
PAP, mm Hg					
Before LS	26.4±9.7 25.0 (18.5-35.0)	30.8±17.2 24.0 (16.0-49.0)	24.6±7.4 22.0 (18.0-32.5)	0.01	0.99
After LS	22.4±11.3 22.0 (12.5-32.5)	19.0±7.0 Ψ(p=0.043) 18.0 (13.0-25.5)	20.2±7.7 Ψ(p=0.041) 17.0 (14.0-28.0)	0.08	0.96
PCWP, mm Hg					
Before LS	18.4±7.1 15.0 (13.5-25.0)	15.4±2.1 15.0 (13.50-17.5)	16.2±2.3 16.0 (14.50-18.0)	0.38	0.82
After LS	11.2±2.8 Ψ(p=0.043) 12.0 (8.5-13.5)	8.8±1.9 Ψ(p=0.042) 8.0 (7.5-10.5)	11.0±2.3 Ψ(p=0.034) 10.00 (9.5-13.0)	3.46	0.18
CI, l/min/m^2					
Before LS	2.22±0.22 2.30 (2.00-2.85)	2.08±0.46 1.80 (1.75-2.55)	2.22±0.22 2.20 (2.05-2.40)	1.42	0.49
After LS	3.56±0.74 Ψ(p=0.043) 3.40 (2.90-4.30)	3.14±0.89 Ψ(p=0.043) 3.20 (2.30-3.95)	2.72±0.23 Ψ(p=0.043) 2.80 (2.50-2.90)	3.03	0.22
Lactate, mmol/L					
Before LS	1.68±0.84 1.70 (1.00-2.35)	3.16±1.29 3.00 (2.10-4.30)	3.46±0.92* 3.30 (2.75-4.25)	6.96	0.03
After LS	2.64±1.16 2.50 (1.60-3.75)	2.18±0.63 2.50 (1.50-2.70)	3.08±0.55 3.20 (2.60-3.50)	2.65	0.26
Urine output, ml	3924±1125 3920 (2900-4950)	2620±1245 3000 (1380-3670)	2380±1435 2200 (1000-3850)	3.62	0.16

Data are presented as the mean value ± SD and median (25%-75%) values Kruskal Wallis test for comparison of variables between 3 groups

* Mann Whitney U test - p=0.009 as compared with group 1

Ψ Wilcoxon rank test for intragroup comparison before and after levosimendan treatment

CI – cardiac index, LS – levosimendan, MAP – mean arterial pressure, PAP – pulmonary arterial pressure, PCWP – pulmonary capillary wedge pressure

care unit, no inotropic drug was initiated in 4 of these patients except LS; however, other inotropic agents were administered to 7 patients. Those who did not receive other inotropic agents were administered LS within four hours following admission to the intensive care unit. Although LS was administered to only 1 patient within two hours after intensive care unit admission, adrenalin was initiated; however, the left ventricular EF of this patient was very low compared to the other patients. Specifically,

Table 3. Inotrope consumption

Variables	Group 1	Group 2	Group 3	Chi-square	p
Dopamine, $\mu g^{-1}kg^{-1}min$					
Before LS	15.00 (12.5-20.0)	15.00 (8.75-17.5)	15.00 (12.5-20.0)	1.07	0.58
After LS	0^{Ψ}	0^{Ψ}	10 (5-17.5)*	9.91	0.007
Dobutamine, $\mu g^{-1}kg^{-1}min$					
Before LS	15.0 (5.0-17.5)	15.0 (5.0-17.5)	20.0 (20.0-17.5)	4.82	0.09
After LS	0	0	15 (5-20)*	9.91	0.007
Adrenaline, $\mu g^{-1}kg^{-1}min$					
Before LS	0 (0-0.25)	0.1 (0-0.45)	0.50 (0.25-0.70)	5.824	0.054
After LS	0	0	0.40 (0.15-0.65)*	9.882	0.007

Data are presented as the mean value ± SD and median (25%-75%) values Kruskal Wallis test for comparison of variables between 3 groups

* Mann Whitney U test - p=0.04 as compared with groups 1 and 2

Ψ Wilcoxon rank test for intragroup comparison before and after levosimendan treatment – p=0.03

it was reported that there was a significant increase in CI and stroke volume, and a significant decrease in MAP, systemic vascular resistance index, MPAP, right atrial pressure and PCWP. These changes were associated with the conditions related to improvement in cardiac function - significant decrease in preload and afterload concomitant with a decrease in cardiac output; and as a result it was reported that LS provide better outcomes during the short term treatment of patients with low cardiac output following cardiac surgery. We also oberved good effects of LS on PAP, CI, PCWB, MAP and urine output values in the patients received LS in postoperative period. But we determined that inotropic agents could be stopped in Groups I and 2 patients in whom LS infusion was started earlier.

Waris et al. (8) applied a continuous preoperative LS infusion to 8 of the 16 patients underwent cardiac surgery, and continuous postoperative LS infusion to the remaining 8 patients. When the preoperative baseline level of LS infusion was compared to the continuous LS infusion, there was a significant increase in the CI of both groups and no significant change in PCWP and systolic blood pressure. Successful results with LS were obtained in all patients including those who experienced ineffective weaning off CPB with catecholamine, and three deaths were recorded: one high-risk patient in the preoperative group and two patients in the postoperative group. They concluded that LS could be used as a postoperative recovery treatment for patients with difficulties in weaning off CPB, and also that elective initiation of preoperative LS was applicable for high preoperative risk patients or patients with left ventricular dysfunction. They have found that LS usage was also successful in the postoperative period, a different finding from ours. Although we have seen positive changes in most of the parameters in the postoperative use of LS, we determined that using LS following the induction of the anesthesia and pump removal is more effective because of absence of requirements for inotropic agents and the decrease in the need of IABP.

In the prospective, randomized, placebo controlled and double-blinded study of Eriksson et al. (24), which included 3 patients with coronary artery disease and 60 patients with left ventricular EF<50%, LS was administered in 12 μg^{-1} kg bolus for 10 minutes and, immediately after induction of anesthesia, and was maintained at a dose of 0.2 μg^{-1} kg^{-1} min for 23 hours and 50 minutes. They standardized anesthesia, hemodynamic treatment and weaning off CPB, and did not allow additional use of inotropes after induction of anesthesia. If after 10 minutes of weaning off CPB the CI was >2.2 L/min/m^2, mixed venous O_2 ≥70%, central venous pressure ≤12 mmHg and PCWB ≤16 mmHg success was obtained; however, if such was not achieved, CPB was repeated by initiating epinephrine infusion (0.01 mg^{-1} kg^{-1}min). An IABP was attached after failure of the second weaning-off trial. The mean time after commencing the weaning off CPB was similar in each of the two groups; primary weaning off was successful in 73% of the patients in the LS group and in 33% of the placebo group. The IABP was required in 4 patients of the placebo group who had two unsuccessful weaning-off attempts, but no patient in the LS groups required IABP. As a result, the comparison of LS and placebo revealed that there was a significant increase in primary weaning off CPB and a decrease in the need for additional inotropic or mechanic therapy in LS administration.

As mentioned above, different investigators preferred LS at different times, such as immediately after induction of anesthesia, during pump removal or during the postoperative period; and very favorable results were obtained from all of these.

Tasouli et al. (25) have performed 0.1 μg^{-1} kg^{-1} min LS infusion without initially doses as ours in 45 patients in the operating room and intensive care unit in a prospective study. The aim of their study was to compare the LS effect on duration of intensive care unit and hospital stays in association with the timing of its infusion. In their study patients were prospectively selected to receive LS in addition to conventional inotropic support (epinephrine and dobutamine) and IABP. The patients were

randomized to receive LS in the operating theatre during the operation or in the intensive care unit the second postoperative day. They added simultaneous norepinephrine infusion, when required, to maintain MAP >70 mmHg. They investigated the hemodynamic profile, EF, the B-type natriiuretic peptide plasma levels 48 hours after the beginning of LS infusion, the duration of IABP and classical inotropic support, the weaning success from mechanical ventilation and the patients' outcome. The efficacy of LS was identical in both groups with improvement in the hemodynamic and functional status of patients. They found that the intensive care unit stay and hospital stay were significantly decreased in patients who receive LS in operating room compared to patients of intensive care unit group. Consequently they found that, early infusion of LS in patients with compromised cardiac function, immediately after the confirmation of low-output syndrome from the operating theatre, was associated with improved in-hospital outcomes.

In the present study, the most effective time of LS application in cardiac surgery was intended to be determined by dividing the patients into 3 groups retrospectively according to their LS use. Group 1 consisted of patients who used LS from the beginning, Group 2 consisted of patients who used LS during pump removal, and Group 3 consisted of patients who used LS after post-operative 24 hours. Despite inotropic support in all groups, IABP was placed in the case of a pump insufficiency.

During the process, an infusion dose of 0.1 μg^{-1} kg^{-1} min was administered without loading dose by taking into consideration the fact that hypotension may occur with bolus doses. In the literature, there are studies regarding timing of LS use; however no such comparison was performed. According to our results, when LS was administered, there was an increase in urine output and CI, and a decrease in MPAP in all groups at the end of LS infusion.

While in groups 1 and 2 all inotropic agents were stopped after 24 hours, in Group 3 no regression could be established in the inotropic posology, except for one patient. During the post-operative period, IABP was applied to one patient of each groups 1 and 2, whereas it was applied to four patients of the Group 3.

Significant increases of CI and urine output, and significant reductions in MPAP and PCWP are the signs of improvement in cardiac function. Early elective initiation of LS in patients with poor left ventricular function at preoperative examination may reduce the inotropic support and the need for IABP by ensuring comfortable weaning-off balloon pump, decreasing the permanence time in the intensive care unit, and ultimately providing a significant reduction in mortality.

In our clinic, we administer LS infusion at a rate of 0.1 μg^{-1} kg^{-1} min without a loading dose. Because vasodilator effect of the drug commences first during the application of loading dose, probable hypotension forced us to an application like this as preferred by many researchers. Activity starting in 12 minutes with loading dose appears in much longer times in solely infusion applied cases. By keeping this in mind, beginning of LS after the induction and during removal from the pump may be more effective according to postoperative use.

Limitations of the study

The major limitation of the study was the small number of cases. Additionally, no application of loading dose and absence of different doses were also the limitations of this study. For this reason, prospective, controlled randomized studies of LS are needed to be urgently performed in more extended series with different loading and maintenance doses and at more different timing periods (e.g. prior to operation).

Conclusion

We suggest that administration of LS to high- risk patients with poor left ventricular function during the cardiac surgery leads to favorable results; however, timing of LS infusion is very important due to its effectiveness at early stages. If one decides to use LS as an inotropic support for patient with severe left ventricular dysfunction, the infusion should be started very early, before CPB and aortic cross-clamp.

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