The Effect Of Levosimendan Following Cardiac Surgery: Two Case Reports
A Colak, M Arar, T Ege, E Tarikci, Z Pamukcu

Citation

Abstract
Difficulty of weaning off the cardiopulmonary bypass (CPB) due to postcardiotomy heart failure is a serious problem in cardiac surgeries. Levosimendan, a calcium sensitizer, has been shown to expert a positive inotropic effect without disturbing the energy balance of the heart. Levosimendan combines with troponin C in the myocardium and stabilizes the troponin C-calcium complex, without increasing the intracellular calcium level. Its action produces improved myocardial contractility and cardiac output without increasing myocardial oxygen demand. This report describes the successful use of levosimendan infusion in two cases having difficulty in weaning from CPB pump during coronary artery bypass grafting (CABG) surgery. First case scheduled for CABG surgery.

A hemodynamically stable patient experienced cardiac arrest during skin closing after cardiopulmonary bypass. Resuscitation was started. The patient was taken to cardiopulmonary bypass again and cardiac pace marker was implanted. Hemodynamic stability was failed after dobutamin and dopamine infusions. The patient couldn't be weaned of cardiopulmonary bypass and intraaortic balloon pump was administered. Levosimendan treatment was the next step. The patient was weaned off cardiopulmonary bypass after starting levosimendan treatment. A second case CABG operation was performed by routine surgical procedure dobutamine and dopamine were both started during cardiopulmonary bypass. Cardiac pacemaker was implanted to the patient considering his cardiac rhythm as A-V block. Intraaortic balloon pomp was administered because of his hemodynamic failure. Despite this supportive treatment the patient failed to achieve adequate hemodynamic stability. The patient was weaned off cardiopulmonary bypass 40 minutes after starting levosimendan treatment.

BACKGROUND
Vasodilator and inotropic drugs and intra-aortic balloon pump are used to provide tissue perfusion and weaning from cardiopulmonary bypass (CPB) in the perioperative period (1). Levosimendan increases the sensitivity of myofilaments to calcium by binding to cardiac troponin C and also causes vasodilatation in systemic arterial and venous capacitance vessels by opening ATP-sensitive potassium-channels in vascular smooth muscles. Furthermore, levosimendan does not cause any increase in myocardial oxygen demand by reducing cardiac work load effectively (1). Here we evaluated two cases who failed to wean from CPB with their low cardiac outputs despite the support of the intraaortic balloon pump but successfully weaned off with the addition of levosimendan treatment.

CASE 1
The medical history of 41-years old male patient scheduled for coronary artery bypass grafting surgery includes Type I DM and femoropopliteal bypass surgery. Transthoracic echocardiography revealed; left ventricle end diastolic diameter: 68 mm; left ventricle end systolic diameter: 55 mm; left ventricle end diastolic volume: 203 mL; left ventricle end systolic volume: 120 mL, ejection fraction: 35% and a thrombus in the anteroapical region of the LV. Euroscore was scored as 4. No premedication was performed and the following drugs were given intravenously for induction: lidocaine 1 mg.kg⁻¹, diazepam 0.2 mg.kg⁻¹, fentanyl 10 µg.kg⁻¹, pancuronium 0.1 mg.kg⁻¹. Left radial artery cannulation was inserted. Arterial pressure monitorization was performed through this arterial catheter. Body temperature was measured using nasopharyngeal probe and urinary bladder catheter. Following adequate muscle relaxation, the patient was intubated and pulmonary artery catheter was inserted from right internal jugular vein. Membrane oxygenator with 9000 pump Sarns and Edwards Lifesciences (Resp Tecnico. Sergio L. Nogaroto CRF/SP N° 9.860 Brasileira) and 2.4 L dk⁻¹ m⁻² non pulsatile perfusion
were used for CPB. The patient was cooled to 33 °C. Thrombectomy was performed by means of 3 cm Left ventriculotomy with routine surgical procedure and LIMA-LAD anastomosis was conducted. (cross-clamp time 44 min, cardio-pulmonary bypass time 59 min). The hemodynamically stable patient (heart rate 95 beat.min⁻¹, systolic artery pressure 90 mmHg, systolic PAP 40 mmHg) experienced cardiac arrest during the closure of skin after cardiopulmonary bypass.

Following immediate administration of 1mg adrenaline and 1mg atropine incisions were opened and open heart massage and resuscitation was initiated. Following canulations after heparin the patient underwent cardiopulmonary bypass again. Due to the bradycardia pace maker was implanted. As hemodynamic stability could not be attained after dobutamine 10 µg.kg⁻¹.min⁻¹, dopamine 10 µg.kg⁻¹.min⁻¹ infusion, adrenaline 0.3 µg.kg⁻¹.min⁻¹ infusion (heart rate 120 beats.min⁻¹, systolic artery pressure 50 mmHg, systolic PAP 45 mmHg) and the patient could not be weaned off the cardiopulmonary bypass, an intra-aortic balloon pump was inserted. Despite this supportive treatment, the patient failed to achieve adequate hemodynamic stability to wean from cardiopulmonary bypass (heart rate 110 beats.min⁻¹, systolic artery pressure 55 mmHg, PAP 40 mmHg). Levosimendan treatment was planned as the next step. Levosimendan was first administered as a loading dose of 12 µg.kg⁻¹ and of 0.1 µg.kg⁻¹.min as a continuous infusion 10 minutes later. The patient became hemodynamically stable, was weaned off the cardiopulmonary bypass 35 minutes after starting levosimendan treatment (heart rate 90-100 beats.min⁻¹, systolic artery pressure 65-75 mmHg, systolic PAP 35 mmHg) and remained stable until the end of surgery. The patient's progress was stable in ICU and his cardiac pace was shut down 6 hours postoperatively. Levosimendan infusion was maintained for 20 hours postoperatively. Hemodynamic parameters were stable during postoperative period and the patient was extubated at 24 hours. Due to the nosocomial infection on the 3rd postoperative day the patient was reintubated and supported by mechanic ventilator. The patient was died of multiorgan failure following pulmonary infection on the 32nd postoperative day.

**CASE 2**

Coronary artery bypass grafting and mitral valve replacement surgery was planned for a 61-years old male patient; 3 weeks prior to the surgery he had anterolateral myocardial infarction. Transthoracic echocardiography revealed: 3° mitral regurgitation; left atrium: 53 mm; left ventricle end diastolic diameter: 71 mm; left ventricle end systolic diameter: 61 mm; left ventricle end diastolic volume: 296 mL, left ventricle end systolic volume: 223mL; ejection fraction 25%, and 1° tricuspid regurgitation.

Euroscore was scored as 6. In preoperative urea and creatinine values were 79 and 1.9 respectively. The patient’s preoperative physical effort capacity of the patients was rated as class IV according to NYHA classification. The patient received the following drugs intravenously for induction: 5 mg diezepam as premedication, and lidocaine 1 mg.kg⁻¹, diazepam 0.2 mg.kg⁻¹, fentanyl 10 µg.kg⁻¹, pancuronium 0.1 mg.kg⁻¹ were administered for induction. Following adequate muscle relaxation, the patient was intubated. Left radial artery cannulation was inserted. Arterial pressure monitorization was performed through this arteriel catheter. Body temperature was measured using nasopharyngal probe and urinary bladder catheter. Pulmonary artery catheter was inserted from right internal jugulare vane. Following sternotomy 2200 mL serous fluid was drained from both thoracal cavities. Membrane oxygenator with 9000 pump Sarns and Edwards Lifesciences (Resp Tecnico. Sergio L. Nogaroto CRF/SP N° 9.860 Brasileira) and 2.4 L dk⁻¹ m⁻² non pulsatile perfusion were used for CPB. The patient was cooled to 33 °C. Hemofiltration was performed starting with the cardiopulmonary bypass.

The mitral valve was replaced by 25 mechanic mitral valve (Sorin, Biomedica Cardio, Saluggia, Italia) and quadruple CABG operation was performed by routine surgical procedure (cross-clamp time 124 min, cardio-pulmonary bypass time 288 min). After removal cross clamps, inotropic support with 5-10 µg.kg⁻¹ dobutamine and dopamine was initiated as inotropic support to the patient undergoing cardiopulmonary bypass. Cardiac pacemaker was implanted to the patient with a cardiac rhythm as A-V block, heart rate 32 beats.min⁻¹. Anastomoses were performed under cardiopulmonary bypass. Intra-aortic balloon pump was administered to the patient failing hemodynamic improvement (heart rate 125 beats.min⁻¹, systolic artery pressure 40 mmHg, PAP 45 mmHg). The patient was weaned off the cardiopulmonary bypass about 30 minutes after this treatment support but hypotension and bradycardia developed within 10 minutes and the patient underwent the cardiopulmonary bypass again. Despite this supportive treatment we added adrenaline infusion at 0.3 µg.kg⁻¹.min⁻¹ as a next step. Despite this supportive treatment, the patient failed to be achieve adequate hemodynamic stability to wean...
from cardiopulmonary bypass (heart rate 115 beats.min⁻¹, systolic artery pressure 50 mmHg, PAP 25 mmHg). Levosimendan was administered as a loading dose of 12 µg.kg⁻¹ and as a continuous infusion of 0.1 µg.kg⁻¹.min 10 minutes later. The patient was weaned off the cardiopulmonary bypass 40 minutes after the start of levosimendan treatment and remained stable until the end of surgery. Levosimendan infusion was maintained for 24 hours postoperatively. Acute renal failure developed on the second day postoperatively in the ICU and hemofiltration procedure was performed. The patient was died of multiorgan failure after 13 days postoperatively.

DISCUSSION

Difficulty of weaning off the cardiopulmonary bypass due to postcardiotomy heart failure is a serious problem in cardiac surgeries (₁₋₄). In heart surgery, it was found that inotropic drugs were needed in 71 to 100% of cases with ejection fraction (EF) less than 46% in order to be weaned off the cardiopulmonary bypass (₅). In addition to pharmacotherapy, the use of intra-aortic balloon pump, and delayed sternum closure is suggested in some studies to support circulation (₆).

Both β-adrenergic agonists and phosphodiesterase inhibitors increase intracellular cyclic adenosine monophosphate, either via an increase in production (β-adrenergic agonists) or by inhibiting degradation (phosphodiesterase inhibitors). The available data on use of dopamine, dobutamine, and dopexamine in the postcardiac surgery period show that they produce an increase in cardiac output. However, there is an increase in myocardial oxygen requirement and an increased risk for postoperative myocardial infarction (₇₋₁₀). Despite the dopamine, dobutamine and adrenalin support, failure in weaning off CPB led to the usage of intraaortic balloon pump in both two cases with low ejection fraction. In these cases, we couldn't use noradrenaline and milrinon because we didn't have these drugs so we had to use levosimendan although it's expensive and restricted.

Levosimendan is a novel inotropic agent having a different pharmacological profile. It provides good cardiac performance without causing an increased myocardial oxygen demand or any change in myocardial metabolism (₁₁). Levosimendan is a promising new calcium sensitizer that improves hemodynamics in patients with acute heart failure. Its inotropic effect is mediated by calcium concentration-dependent stabilization of conformational changes in troponin C during systole, causingsensitization of the contractile apparatus to calcium ions; its vasodilator effect is linked to the activation of ATP-dependent potassium channels. Anti-ischemic properties can also be attributed to the latter mechanism. Hence, levosimendan enhances cardiac performance without advers effects on diastolic function. Levosimendan also reduces preload and afterload while improving both coronary blood flow and cardiac function in stunned myocardium (₁₂,₁₃).

It is known that levosimendan infusion after cardiac surgery provides improvement in hemodynamic parameters by increasing left ventricular functions and is effective in patients having difficulty to wean of from cardiopulmonary bypass (₁₄). In multicenter RUSSLAN study (₁₅), in patients with heart dysfunction due to myocardial infarction, three different levosimendan doses were compared with placebo; Levosimendan doses administered to the patients were as follows; 24 µg.kg⁻¹ bolus infusion followed by 0.4 µg.kg⁻¹ infusion; 24 µg.kg⁻¹ bolus infusion followed by 0.2 µg.kg⁻¹ infusion; 12 µg.kg⁻¹ bolus infusion followed by 0.2 µg.kg⁻¹ infusion; 6 µg.kg⁻¹ bolus infusion followed by 0.1 µg.kg⁻¹ infusion. In high dose levosimendan (24 µg.kg⁻¹ bolus infusion followed by 0.4 µg.kg.dk⁻¹ infusion) group the incidence of hypotension and ischemia was found to be increased compared to other groups. Nevertheless, it was determined that dose-response relationship was not significant and levosimendan was well tolerated in acute myocardial infarction. The results of these dose-dependent study showed the relatively wide therapeutic index of levosimendan (₁₆).

In randomized, double-blind LIDO study (₁₇), levosimendan 24 µg.kg⁻¹ bolus infusion followed by 0.1 µg.kg⁻¹ infusion and dobutamine 5 µg.kg.dk⁻¹ infusion for 24 hours were administered to 203 patients with EF less than 35%, CI 2.5/L/dk/m² and PCWP less than 15 mmHg. Infusion rates were doubled at the end 2 hours when drug response was found inadequate. An increase of cardiac output more than 30 % and pulmonary capillary wedge pressure decrease more than 25 % were considered as hemodynamic improvement criterion. As a result, it has shown that increase of cardiac output and decrease of pulmonary wedge pressure were statistically higher in levosimendan group compared to dobutamine group (₁₈).

In both of our cases, levosimendan 12 µg.kg⁻¹ bolus infusion followed by 0.1 µg.kg⁻¹ infusion was administered because of the inadequate hemodynamic improvement with
pharmacological inotropic support and use of intra-aortic balloon pump and levosimendan infusion was maintained for 20 hours. Our levosimendan dose is similar to the dose in LIDO study.

Underlying systemic disease, surgical intervention, invasive monitorization, surgical stress and systemic inflammatory response are important factors that contribute the development of nosocomial infection after cardiac surgery in intensive care follow up period. Our first case was intubated again in the third day in intensive care unit due to postoperative nosocomial infection and associated multiorgan failure requiring mechanical ventilation support. Despite all inotropic support the patient died from irreversible cardiac and multiorgan failure after 32 days postoperatively. We assume that levosimendan infusion improves the hemodynamic parameters and also effective during the weaning off stage in case with low ejection fraction and in cases where inotropic agents or intra-aortic balloon pump support are inadequate.

CORRESPONDENCE TO
Alkin Colak, MD, Staff Anesthesiologist
alkincol@yahoo.com Department of Anesthesiology Faculty of Medicine, Trakya University, 22030, Edirne, Turkey
Telephone: +90 284 2357641 Fax : +90 284 2358096

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Author Information

Alkin Colak, M.D.
Staff Anesthesiologist, Department of Anesthesiology, Faculty of Medicine, Trakya University

Makbule Cavidan Arar, M.D.
Assistant Professor, Department of Anesthesiology, Faculty of Medicine, Trakya University

Turan Ege, M.D.
Associate Professor, Department of Cardiovascular Surgery, Faculty of Medicine, Trakya University

Ebru Tariki, M.D.
Clinical Research Assistant, Department of Anesthesiology, Faculty of Medicine, Trakya University

Zafer Pamukcu, M.D.
Professor and Head of Anesthesiology Department, Department of Anesthesiology, Faculty of Medicine, Trakya University