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Research Article

An Evaluation on the Effect of Preoperative Levosimendan Administration as an Inotropic Agent in Patients Undergoing Open Heart Surgery with Poor Ventricular Function

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Abstract

Aim: Nowadays, we frequently encounter with articles related with preoperative use of Levosimendan in literature. Aim of this paper was to present our clinical experience which was in accordance with the literature rather than comparing or suggesting new clinical data.

Background and Objectives: Most important preoperative risk factor in cardiac surgery is poor ventricular function which directly affects morbidity and mortality. An effective agent named Levosimendan has inotropic and myocardial anti-ischemic effects without increasing myocardial oxygen demand. In this paper, we aimed to present our experience with levosimendan infusion started at 24 hours before operation in patients undergoing open heart surgery with poor ventricular function.

Subjects and Methods: Patients underwent cardiac surgery in our clinic between August 2009-August 2015 were retrospectively evaluated. Among them, 26 patients whose preoperative left ventricular ejection fraction (LVEF) value below 30% were enrolled. These patients had been receiving Levosimendan after admitted to intensive care unit at 24 hours before operation according to our clinical protocol. Pre-operative and post-operative characteristics of patients were collected.

Results: All patients weaned from cardiopulmonary bypass (CPB) without complications. There was no intraoperative or early postoperative mortality. Post-operative EF values were 32% and 37% at first postoperative week and first postoperative month; respectively.

Conclusion: Both of our results and our clinical experience suggested that Levosimendan use during early preoperative period in these patients with high risk is more advantageous than administration during other periods.

Keywords: Inotropic Agent; Levosimendan; Open Heart Surgery; Preoperative Use; Poor Ventricular Function

Introduction

Patients who will undergo open heart surgery are usually presented to the surgeon with various risk factors. Most important risk factor of these patients is Low Ventricular Ejection Fraction (LoVEF). This condition is directly related with perioperative mortality and morbidity [1,2]. These patients with high risk may experience serious problems during weaning from cardiopulmonary bypass (CPB) and through postoperative intensive care period [3].

It is aimed that obtaining highest benefit from surgery by providing some inotropic or mechanical supports to the patients undergoing cardiac operation with poor ventricular function. For this purpose, various agents like dopamine, dobutamine, noradrenaline etc. have been used. However; administration of these agents has risks such as increased myocardial ischemia. Recently, a new drug named Levosimendan is commonly used as an inotropic support. Levosimendan increases contractility by increasing sensitivity of cardiac myofibrilles to the calcium ion. In addition, it also shows vasodilatator effect by opening ATP-sensitive potassium channels (KATP channels) with only insignificant decrease on mean arterial systolic pressure. During performing these effects; it does not increase oxygen demand of myocardium [4].

We operated elective cases with LoVEF (EF≤30%) who will undergo open heart surgery by starting levosimendan infusion for 24 hours before surgery. Also, we retrospectively evaluated these patients and literature related with levosimendan administration. In literature, we observed growing evidence from many recent studies suggesting superior beneficial effects of levosimendan infusion starting at preoperative period in patients undergoing cardiac surgery with LoVEF. In addition; levosimendan infusion starting at preoperative period was seem to have additional beneficial effects on parameters such as glomerular filtration rate, troponin levels

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Table 1: Preoperative data.

GENDER(M/F)(n)	21/5
MEAN AGE (YR)	63,4 (41-90)
BODY MASS INDEX (BMI)	26,2
PAD†(n)	3
DIABETES(n)	6
HYPERTENSION(n)	11
COPD‡(n)	6
CRF§(n)	2
MEAN EUROSCORE POINT(%)	6.15
PRE-OP MEAN EF (%)	26.7

†: Peripheral Arterial Disease; **‡:** Chronic Obstructive Pulmonary Disease; **§:** Chronic Renal Failure.

etc. which all of them have utmost importance in cardiovascular patients with multiple comorbidities. Therefore; we aimed to present our experience with preoperative levosimendan administration in patients with multiple comorbidities as well as comparing our results with related literature in this study.

Subjects and Methods

Patient population

A total of 642 patients underwent cardiac surgery in our clinic between August 2009-August 2015 was retrospectively evaluated. Among them, patients whose preoperative left ventricular ejection fraction (LVEF) value below 30% were enrolled. These patients had been receiving Levosimendan (Simdax©, 2.5mg/ml, Daiichi-Sankyo) infusion (10μg/kg/10min. loading dose followed by 0.1μg/kg/min continuous infusion) after admitted to intensive care unit at 24 hours before operation according to our clinical protocol. Pre-operative and post-operative characteristics of patients were collected (Table 1-2).

Surgical technique

Patients received peroral alprazolam at preoperative night and 2mg im midazolam before being transferred to operation room as premedication following standard anesthesic regime. Hemodynamic monitorization and radial artery catheterization of patients were performed in operation room. Whole Bispectral Index Monitorization (BIS) and cerebral oximetry (Near infrared spectroscopy (NIRS)) values of all patients were recorded. Thoracic epidural catheter was preoperatively inserted to patients. Levobupivacaine or Bupivacaine was administered through epidural catheter for analgesia. Anesthesia induction was performed with iv Thiopental as sedative-hypnotic intravenous anesthetic, Fentanyl as analgesic and Rocuronium as musculorelaxant in accordance with patient age and weight. Central venous catheters were placed through right internal jugulary vein with ultrasound assistance. Anesthetic maintenance was sustained by sevoflurane inhalation in controlled mechanical ventilation. Midazolam, fentanyl and rocuronium were administered to pump as intermittent additional boluses during CPB for keeping BIS monitorization between 40-50. Intermittent arterial blood gas analyses were performed and recorded at initiation, pre-pump, peri-pump and post-pump periods. CPB was performed with standard-membrane oxygenator and alphastat-blood gas control as keeping pump flow at 2.4lm-2, venous temperature at 34-36 ^{0}C and mean arterial pressure at 50-70 mmHg.

Table 2: Intra-postoperative data.

MEAN CPB TIME (min)	147,3 (44-420)
MEAN CROSS-CLAMP TIME (min)	79,5 (22-147)
OPERATIVE PROCEDURE (CABG/VALVE/CABG+VALVE) (n)	15/4/7
NUMBER OF DISTAL ANASTOMOSES (n)	3.1 (1-4)
NUMBER OF ENDARTERECTOMY(n)	1
MEAN DURATION OF STAY IN ICU¶(day)	5.3(3-15)
NUMBER OF REOPERATION	1
NUMBER OF POST-OP UF¥/HD#	2
POST-OP MEAN EF (%) (first week/month)	32/37

¶: Intensive Care Unit; **¥:** Ultrafiltration; **#:** Hemodialysis.

Conventional median sternotomy was performed in all patients by same surgical team. After systemic heparinization (300IU/kg IV bolus Liquemine 25000IU/5 ml), CPB was initiated. Myocardial protection was achieved by intermittent antegrade cold blood cardioplegia. LIMA and saphena grafts were used in patients undergone CABG and proximal anastomoses were performed after cross-clamp. Heparine notralization was performed with protamine sulphate. Then, patients were transferred to cardiovasculary intensive care unit after operation as intubated.

Our study was conducted in accordance with ethical protocols included by Declaration of Helsinki. Ethical approval or informed consent was not required due to our post-hoc analysis performed for study.

Results

A total of 26 patients were enrolled in our study. 21 of them were male whereas 5 of them were female. Mean age of our patients was 63, 38 (41-90). In our study; there were 3, 6, 11, 6 and 2 patients with peripheral arterial disease (PAD), diabetes, hypertension, chronic obstructive pulmonary disease (COPD) and chronic renal failure (CRF), respectively. Preoperative mean Euroscore point of our patients was 6.15%. Preoperative mean body mass index (BMI) point of our patient was 26.2 whereas preoperative mean Ejection Fraction (EF) of our patients was 26,7% (15-30).

In terms of operative data; mean cross-clamp time and mean cardiopulmonary bypass (CPB) time of our patients were 79,5 min. (22-147) and 147,3 min. (44-420); respectively. In terms of operation procedure; there were 4, 15 and 7 patients who underwent valve operation alone, CABG alone and combined CABG+Valve operation; respectively. Among CABG cases, mean number of distal anastomoses was 3.1 (1-4) whereas only 1 patient underwent endarterectomy.

Only 1 patient required reoperation due to excessive bleeding whereas 5 patients needed ultrafiltration (UF) and/or hemodialysis (HD). Mean duration of stay in intensive care unit (ICU) was 5.3 days (3-15). There was no intraoperative and early postoperative mortality.

Post-operative EF values were 32% and 37% at first postoperative week and first postoperative month; respectively.

Discussion

Levosimendan is generally used at acute or chronic decompansated heart failure or in situations when additional inotropic support

is needed after open heart surgery if conventional treatment is insufficient. It binds to Troponin C and makes cardiac myofibrilles more sensitive to calcium as well as activating KATP channels. It induces stronger contractions even with lower intracellular calcium concentrations. During performing these effects, it does not increase oxygen demand of myocardium. Its active metabolite, OR-1896 which its pharmacologic effects may persist for approximately 1 week; also has similar effects [1-5].

With these pharmacodynamic effects, levosimendan increases cardiac performance and cardiac output without impairing diastolic function. It reduces preload and after load; and increases coronary blood flow [6]. It reduces endothelin-1 levels in circulation and does not significantly increase catecholamine levels. As Raja et al. suggested; most important superiority of Levosimendan against conventional inotropic agents is improving systolic functions without increasing oxygen demand of myocardium [7].

Most common use of levosimendan in patients undergoing open heart surgery is as starting levosimendan during weaning from CPB. Recently, there are many articles related with infusions which were started preoperatively and maintained perioperatively [8-12]. In the light of these articles, we also preoperatively started levosimendan infusion and maintained it during operation. Our results are favourable as most of our patients did not experience serious problems during weaning from CPB.

Most prominent difficulty in patients with preoperative LoVEF occurs during weaning from CPB. In literature, there are studies suggesting problems for weaning from CPB with an occurrence rate of 70-80% if there is neither medical nor mechanical support [13]. Therefore, it provides a basis to both cardiac and extracardiac problems. In these cases, inotropic agents are commonly used for improving myocardial contractility. However, myocardial oxygen consumption may be increased due to increased cAMP concentration by the effects of these agents and they may also impair supply/demand balance [5]. Levosimendan has reached an advantageous place due to its capability of increasing myocardial performance without affecting myocardial oxygen demand with a different mechanism compared to other inotropic agents [13,14]. In addition, required dosage of other inotropic agents also decreases with Levosimendan administration [15-17]. Similarly, need for inotropic agents were lower than expected in our serie.

As both a medical and a mechanical support; intraaortic baloon pump (IABP) is conventionally used during weaning from CPB in patients with preoperative ventricular dysfunction [18,19]. These patients may require postoperative extracorporeal membrane oxygenator (ECMO) support [20,21]. Inserting these mechanical support systems requires additional surgical intervention. Therefore, these systems have their own potential risks as well as risk and complications related with additional surgical procedures for insertion. In literature, there are studies suggesting decreased rate of mechanical support usage in cases preoperatively received Levosimendan [3,8,22]. Among our cases, only one geriatric patient with multiple comorbidities needed ECMO insertion. Other cases in our serie did not need any mechanical support.

There are many studies related with various administration timing of Levosimendan in literature such as starting at preoperative period; during weaning from CPB; in operation theatre; during anesthesia induction or at second postoperative day. However, number of articles comparing administration times is rare. In the study performed by Eris et al., it was suggested that starting infusion at 12 hours before operation has better results. They related these results with preconditioning effect of Levosimendan [8]. Its effect is thought to be related with its long-lasting metabolite and its pharmacological effect which continues for 1 week [4,23]. In addition, there are very few studies starting levosimendan infusion at 24 hours before operation like our study.

In our case serie, there was no side-effect related with Levosimendan. Also, there was no rebound effect related with drug after drug discontinuation. All of our cases weaned from CPB without complication. Our patients were followed with routine dosage of inotropic support in post-operative period. Only one patient needed ECMO support in post-operative period. Durations of mechanical ventilation and stay in intensive care unit were not significant compared with patients without preoperative LoVEF. There was significant improvement in LVEF values at first post-operative month.

Conclusion

In conclusion, it was observed that Levosimendan use during early preoperative period in patients undergoing cardiac surgery with LoVEF decreases mortality, morbidity and need for mechanical support as well as decreasing need for mechanical inotropic agents to acceptable levels; and shortens duration of stay in ICU. Both of our results and our clinical experience suggested that Levosimendan use during early preoperative period in these patients with high risk is more advantageous than administration during other periods. However, we couldn't make any definitive conclusion due to small number of our patients and retrospective nature of our study. Therefore, comparative studies related with administration timing of Levosimendan in larger serie are needed.

Ethics Committee Approval

Our study was conducted in accordance with ethical protocols included by Declaration of Helsinki. Ethical approval or informed consent was not required due to our post-hoc analysis performed for study.

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