Research Article

The Clinical Short-Term Outcome of Intravenous Levosimendan In Patients With Acute ST Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention -

Jiang Y. Wang*, Xi Su, Xiang-ming Wu, Chen W. Liu, Chen YiXu, Zhi P. Zhang, Dan Song, Jian Peng, Hua Yan

Department of cardiology, Wuhan Asia heart hospital, Wuhan, China

*Address for Correspondence: Xi Su, Department of Cardiology, Wuhan Asia heart hospital, Wuhan 430022, China; Tel: +8615172496706; E-mail: yaxin_suxi@163.com

Submitted: 04 June 2017; Approved: 06 June 2017; Published: 09 June 2017


Copyright: © 2017 Wang JY, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
ABSTRACT

Background and Objectives: The goal of this study was to evaluate the effects of intravenous levosimendan (Levo) in patients with acute ST Segment Elevation Myocardial Infarction (STEMI) undergoing Primary Percutaneous Coronary Intervention (PPCI).

Subjects and Methods: This was a randomized, single-center, single-blind study that included 92 patients. Patients were randomly divided into 2 groups: 1 received levosimendan (n = 48) and the other received placebo (n = 44). Echocardiography was executed and plasma N-terminal pro brain natriuretic peptide (NT-pro-BNP) levels were measured just prior to intravenous levosimendan treatment and 30 days after intravenous levosimendan treatment. The main end point was a 30-day incidence of major adverse cardiac events (MACE; death, myocardial infarction, or target vessel revascularization).

Result: Major adverse cardiac events occurred in 12.8% of patients in the Levo group and 20.62% of those in the control group. NT-pro-BNP of the two groups were decreased 30 days after intravenous levosimendan treatment, however, NT-pro-BNP in the Levo group were significantly lower than those in the control group (P < 0.05). Cardiac function in STEMI patients, as reflected by the increased LVEF, FS as well as decreased LVEDd (P < 0.05) in all groups at 30 days after intravenous levosimendan treatment, but cardiac function parameters were more obviously improved in the group administered with levosimendan (P < 0.05).

Conclusion: Levosimendan can significantly improve the myocardium function of patients with STEMI undergoing PPCI.

Keywords: Levosimendan; Percutaneous Coronary Intervention; NT-pro-BNP; Cardiac Function.

INTRODUCTION

In recent years, there has been a good long-term prognosis for ST-Segment Elevation Myocardial Infarction (STEMI) patients treated with Primary Percutaneous Coronary Intervention (PPCI). As the numbers of coronary care units, reperfusion techniques, and medical therapies increases, have significantly improved the clinical outcome in patients with STEMI. However, despite intensive therapies with hemodynamically effective agents, many patients with ischemic disease do not recover fully and remain at high risk for undesired further events. Hence, it is imperative to attempts to develop novel therapies.

Levosimendan has been developed for the treatment of acute heart failure and other cardiac conditions where the use of an inodilator is considered appropriate. At least three major pharmacological actions have been identified [1], i.e. (i) the selective binding to Ca2+-saturated cardiac troponin C, (ii) the opening of ATP-sensitive potassium (KATP) channels in the vasculature, and (iii) the opening of KATP channels in the mitochondria. The pharmacology of levosimendan includes positive inotropy with energy-sparing effects, positive effects on ventriculo-arterial coupling, peripheral vasodilation and increasing tissue perfusion, anti-stunning effects and anti-inflammatory and anti-apoptotic effects [2]. And, recent studies revealed that the protective effects of levosimendan on ischemia/reperfusion injury and primarily related to the regulation of apoptosis [3,4]. The goal of this study was to evaluate the effects of intravenous levosimendan in patients with STEMI undergoing PPCI.

Subjects and Methods

Study population and protocol

This was a random, prospective, double-blind, placebo-controlled clinical trial. A total of 70 patients fulfilling the inclusion criteria from August 2015 to February 2016 were initially evaluated. Four patients were excluded because of 2nd- or 3rd-degree atrioventricular block, two because of a supine systolic blood pressure < 90 mm Hg, two for liver, and two for renal failure. A total of 60 patients fulfilling the inclusion criteria were included in the study. Patients were randomly divided into 2 groups: 1 received levosimendan (n = 30) and the other received placebo (n = 30). Levosimendan (12.5 mg in 45 ml of 5% dextrose) was administered for 24 h as a continuous infusion of 0.1 μg/kg/min. The patients in the placebo group received the same volume of 5% pure dextrose in water at a rate of 20 μg/kg/min for 24 h. All patients received baseline therapy for STEMI and heart failure, including the use of Bay aspirin, Ticagrelor, heparin, β-blockers, angiotensin-converting enzyme inhibitors, diuretics and nitrates; however, they did not receive any intravenous fluids other than levosimendan and placebo.

Inclusion criteria were chest pain lasting for > 30 min that was not relieved by treatment with sublingual nitroglycerin, ST-segment elevation ≥ 2 mm in at least two electrocardiographic leads and increases in serum troponin I to levels at least twice their upper limits of normal. Receipt of emergency PCI within 12 h of STEMI, without antecedent thrombolysis. Re-establishment of thrombolysis in myocardial infarction (TIMI) 3 flow in the infarct-related artery. NYHA class III–IV symptoms despite optimized interventional and medical therapy. LVEF of ≤ 0.40.

Exclusion criteria were as follows: a supine systolic blood pressure < 90 mm Hg, 2nd- or 3rd-degree atrioventricular block, severe arrhythmias, acute or chronic inflammatory or infectious diseases, cardiac shock or post cardiac pulmonary resuscitation, uncorrected primary stenotic valve disease, pericardial disease, obstructive cardiomyopathy, primary renal or hepatic impairment (creatinine > 2.5 mg/dl), contrast-media allergy, hypokalaemia or hyperkalaemia (potassium < 3.5 or > 5.5 mmol/l), pregnancy, breast-feeding or any other reason or condition determined by the investigator to interfere with the subject’s participation in the study.

Interventional Procedure

PCI was performed using a standard technique, through the radial artery route. Routine care was taken before and after the procedure for all patients, including pretreatment with a loading dose of Ticagrelor (180 mg) or clopidogrel (300 mg initial oral bolus) the day before the procedure, followed by Ticagrelor (90 mg bid) or clopidogrel (75 mg/day) for 12 month, in addition to lifelong aspirin medication (100 mg/day). Intravenous bolus of unfractionated heparin (100 IU/kg), with activated coagulation time adjusted (200-300 s with Hemochron devices), was administered at the beginning of the procedure. The radial artery sheath was removed immediately after the end of the procedure.
Angiographic analysis

Classification of coronary artery morphology based on the report of the American Heart Association/American College of Cardiology Task Force was used [5]. Coronary angiograms were reviewed by independent observers blinded to the results of biochemical assays. Intimal major or minor dissection, thrombus, abrupt closures in a previously patent vessel, no-reflow, spasm and side-branch occlusion were assessed. The degree of perfusion was evaluated according to TIMI criteria [6]. No-reflow phenomenon was defined as TIMI flow grade 0, 1, or 2 without a mechanical obstruction on angiograms after PCI. Left ventricular function was assessed by angiography in all patients.

Echocardiography

One experienced investigator who was blinded to the study protocol captured the transthoracic echocardiogram using a GE VIVID 7 system and a 3.5 MHz transducer. Briefly, the 3.5 MHz transducer was placed on the left anterior chest wall to obtain the Left Ventricular End-Diastolic Dimension (LVEDd), Left Ventricular Fractional Shortening (FS), and Left Ventricular Ejection Fraction (LVEF) were calculated using a cubic formula. All parameters were averaged from more than three consecutive cardiac cycles.

Blood Sampling and Analyzing

All samples were collected by venipuncture into ethylene diamine tetra acetic acid tubes. The samples were analyzed within ten minutes using the Fluorescence Immunoassay technique and Biosite (CA, USA) using a NT-pro-BNP Triage Kit in the Biochemistry Lab, Emergency Unit.

Statistical Analysis

Statistical analyses were performed with SPSS version 17.0 software. Data are expressed as mean ± SD or percentages for categorical variables. To compare parametric continuous variables, the independent Student t-test was used. For categorical variables, the χ² test was used. P<0.05 was considered to be statistically significant.

RESULTS

The studied population was composed of 48 patients in the Levo group, 44 patients in the control group. Pretreatment with intravenous levosimendan was well tolerated and there were no instances of serious adverse events during the in hospital follow-up. Clinical and procedural variables in the Levo and control groups are shown in (Tables 1, 2 and 3), respectively. The two groups were similar with regard to age, sex, cardiovascular risk factors, mean time to angiography, and medical therapy at the time of intervention. Coronary anatomy, lesion type, procedural characteristics, use of drug-eluting stents, diameter and length of implanted stents were similar. Primary composite end point: 30 days incidence of major adverse cardiac events (MACE; death, myocardial infarction, or target vessel revascularization). The result shows MACE in 9.1% of patients (four of 44) in the control group and in 4.2% (two of 48) of those in the Levo-group (P=0.189).

LVEF (Levo group-51.24 ± 5.63 % and 55.62 ± 4.89 %; control group-52.46 ± 4.82 % and 54.29 ± 3.29 % at the baseline and at 30 days, respectively; p > 0.05) did not significantly change after 30days of treatment as well as LVFS (Levo group-27.53 ± 3.59% and 35.53 ± 3.72mm; control group-28.31 ± 3.48% and 31.42 ± 3.26% at the baseline and at 30 days, respectively; p < 0.05), and LVEDd was lower in the group administered Levo treatment and LVFS was higher in the group administered Levo treatment. NT-Pro-BNP was used.
pro-BNP (Levo group=456.82 ± 89.53 pg/ml and 219.64 ±72.82 pg/ml; control group=438.52 ± 82.94 pg/ml and 279.35 ± 68.26 pg/ml at baseline and at 30 days, respectively; p<0.05) significantly changed after 30 days of treatment. NT-pro-BNP levels significantly decreased in both groups during the 30-day follow-up period (229.34 ± 59.25 and 150.67 ± 63.48, respectively). However, the decrease of NT-pro-BNP levels was higher in the group administered Levo than the control group (p<0.05). (Table 4)

DISCUSSION

The present study demonstrated that short-term (30-day) intravenous levosimendan treatment in patients with STEMI undergoing PCI reduces plasma levels of NT-pro-BNP, reduces LVEDd, and increase LVFS. Major adverse cardiac events occurred did not significantly change after 30 days of treatment. However, the decrease of major adverse cardiac events was higher in the group administered levosimendan than the control group.

The benefits of levosimendan maybe attributed to its actions as an ATP-sensitive potassium (KATP) channel opener in coronary vascular smooth muscle [7] and the enhancement of coronary blood flow. In addition, levosimendan can inhibit phosphodiesteraseII in the myocardium [8], but this may not be the major mechanism by which it causes coronary vasodilation, as with milrinone [9]. This effect is only pronounced at higher concentrations. Levosimendan increases the responsiveness to calcium, leaving the cytosolic Ca2+ concentration unchanged, and activates the KATP channels to protect the ischaemic-reperfused myocardium; this appears to be accomplished by the conservation of energy metabolism and other mechanisms, as of yet unknown. The cardio protective effect of the KATP channels has attracted much attention recently [10,11]. The reason for this effect and the mechanism of levosimendan are relatively unclear at the present stage and will need to be elucidated in more detail. The improvement of cardiac function after the infusion

Oflevosimendan was accompanied by beneficial neurohumoral regulation. The neurohumoral effects were represented by the concomitant reduction in plasma BNP levels, and the improvement of LV function may be the main contributing factor.

NT-pro-BNP is released in response to ventricular myocardial contraction, indicating myocardial wall stress [12]. It has been established in several clinical studies that increased NT-pro-BNP is related to ischemia, rather than myocardial necrosis in acute coronary syndrome. NT-pro-BNP is considered an important prognostic indicator for acute coronary syndrome [13].The present study demonstrated that short-term (30-day) intravenous levosimendan treatment in patients with STEMI undergoing PCI reduces plasma levels of NT-pro-BNP.

To ensure patient safety, the study was designed to use a continuous intravenous infusion of low-dose levosimendan without a loading dose. The levosimendan infusion was well tolerated in this study. There were no significant differences in the incidences and types of adverse events in the 2 groups. In conclusion, the results of our study indicate that levosimendan improves the function of myocardium after PCI in STEMI patients. As a novel inotropic agent, levosimendan could play an important role in the treatment of heart failure due to ventricular dysfunction by myocardial injury after cardiac surger

Study limitations

This study was based on a limited number of observations made in a small population of patients and a brief follow-up period, potentially diminishing the validity of the drawn statistical inference. The present study results should be applied only with caution to clinical situations in which STEMI is potentially involved, and further investigation is required. Future studies are required for these findings to be applied to clinical practice.

FUNDING STATUS

Wuhan Health and Family Planning Commission Research Foundation funded (WX17Q36).

REFERENCES


