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Research Article

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

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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 2groups: 1 received levosimend an (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 30th 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 30th 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 70patients 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 antecedentthrombolysis. 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 cardio pulmonary resuscitation, uncorrected primary stenoticvalve 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 > 5.5mmol/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 (180mg) or clopidogrel (300 mg initial oral bolus) the day before the procedure, followed by Ticagrelor (90mg/bid)or clopidogrel (75mg/day) for 12 month, in addition to lifelong aspirin medication (100mg/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 χ^2test was used. *P<0.05* was considered to be statistically significant.

RESULTS

The studied population was composed of 48 patients in the Levogroup, 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. However, LVEDd (Levo group-52.62 ± 4.53mm and 42.53 ± 5.84mm; control group-53.27 ± 3.86% and 47.46 ± 4. 28% at the baseline and at 30 days, respectively; *p< 0.05*) 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-

Table 1: Clinical characteristics of the study population.
ACEI: Angiotensin-Converting Enzyme Inhibitors; CABG: Coronary Artery Bypass grafting; PCI: Percentaneous Coronary intervention; NSTEMI: Non-ST Segment Elevation Myocardial Infarction; BMI: Body Mass Index. Levo: Levo-simendan

Variables	Control group(n=44)	Levo group(n=48)	P Value
Mean (SD) age (years)	63.21±12.35	62.34 ±15.58	0.849
Sex, male, n (%)	28(64)	32(67)	0.760
History, n (%)			
Earlier myocardial infarction	4(9)	6(13)	0.742
Earlier PCI	6(14)	9(19)	0.507
Earlier CABG	2(5)	3(6)	1.000
Unstable angina	25(57)	23(48)	0.393
NSTEMI	19(43)	25(52)	0.393
Risk factors, n (%)			
Smoking (past or current)	26(59)	28(58)	0.941
Hypercholesterolaemia	23(52)	25(52)	0.986
Hypertension	28(64)	33(69)	0.604
Diabetes mellitus	16(36)	19(43)	0.751
Family history	8(18)	7(15)	0.641
Mean (SD) BMI (kg/m^2)	26.23 ± 3.28	25.75 ± 3.16	0.783
Medication, n (%)			
ACE inhibitors or ARB	35(80)	40(83)	0.640
β Blockers	36(82)	41(85)	0.641
Calcium antagonist	12(27)	11(23)	0.630
Aspirin	44(100)	48(100)	1.000
Clopidogrel	18(41)	22(46)	0.509
Ticagrelor	26(59)	26(54)	0.634
Insulin	6(14)	8(17)	0.686
Nitrates	36(82)	38(80)	0.749

Table 2: Angiographic characteristics of the study population
Levo: Levosimendan; *According to the American Heart Association/American College of Cardiology classification.

Variable, n (%)	control group(n= 44)	Levo group(n=48)	P Value
Lesion class*			
A+B1	32(73)	36(75)	0.804
B2+C	12(27)	12(25)	0.804
Artery involved			
Left main artery	0	0	1.000
Left anterior descending artery	33(75)	35(73)	0.820
Left circumflex artery	24(55)	28(58)	0.714
Right coronary artery	30(68)	30(63)	0.568
Single-vessel disease	12(27)	15(31)	0.676
Double-vessel disease	21(48)	21(44)	0.702
Three-vessel disease	11(25)	12(25)	1.000

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 the baseline and at 30 days, respectively; *p< 0.05*) significantly change after 30days 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 PPCI reduces plasma levels of NT-pro-BNP, reduces LVEDd, and increase LVFS. Major adverse cardiac events occurred did not significantly change after 30days 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 (K_{ATP}) channel opener in coronary vascular smooth muscle [7] and the enhancement of coronary blood flow. In addition, levosimendan can inhibit phosphodiesteraseIII 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 Ca^{2+} concentration unchanged, and activates the K_{ATP} 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 K_{ATP} 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 PPCI reduces plasmalevels 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.

Table 3: Procedural characteristics and complications of the study population TIMI: Thrombolysis in Myocardial Infarction Trial; Levo: Levosimendan.

parameters	Control group(n=44)	Levo group(n=48)	P Value
Stent length (mm)	23.26 ± 3.82	21.89 ± 2.87	0.553
Stent diameter (mm)	2.82 ± 0.64	2.93 ± 0.58	0.686
Total inflation time (s)	38.42 ± 8.96	42.32 ± 5.75	0.162
Inflation maximal pressure (atm)	14.36 ± 3.67	15.42 ± 4.26	0.737
TIMI flow grade ≤ 1, n (%)	2(5)	1(2)	0.328
TIMI flow grade = 2, n (%)	5(7)	2(4)	0.328
TIMI flow grade = 3, n (%)	37(88)	45(94)	0.328
ST change during inflation, n (%)	8(18)	11(23)	0.575
Procedural complication, n (%)			
Side-branch occlusion	4(9)	4(10)	1.000
Coronary dissection	2(5)	2(4)	1.000
Coronary spasm	5(11)	6(13)	0.867
Coronary embolisation	1(2)	1(2)	1.000

Table 4: LVEF, LVEDd, LVFS and NT-pro-BNP differences between the baseline and the 30th day NT-pro-BNP,N-terminal pro brain natriuretic peptide; LVEDd, left ventricular end-diastolic dimension; FS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; Levo: Levosimendan. Comparison baseline, [a]*p<0.05*; Comparison ATV group, [b]*p<0.05*.

Levo	Variables	Baseline	30 days
(n=30)	NT-pro-BNP(pg/ml)	456.82 ± 89.53	219.64 ± 72.82[ab]
	LVEF (%)	51.24 ± 5.63	55.62 ± 4.89
	LVEDd (mm)	52.62 ± 4.53	42.53 ± 5.84[ab]
	LVFS (%)	27.53 ± 3.59	35.53 ± 3.72[ab]
Control			
(n=30)	NT-pro-BNP (pg/ml)	438.52 ± 82.94	279.35 ± 68.26[a]
	LVEF (%)	52.46 ± 4.82	54.29 ± 3.29
	LVEDd (mm)	53.27± 3.86	47.46 ± 4.28[a]
	LVFS (%)	28.31± 3.48	31.42 ± 3.26[a]

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REFERENCES

1. Papp Z, Édes I, Fruhwald S, De Hert SG, Salmenperä M, Leppikangas H, et al. Levosimendan: molecular mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol 2012; 159: 82-7. DOI: 10.1016/j.ijcard.2011.07.022. https://goo.gl/2mLGaZ

2. Maytin M, Colucci WS. Cardio protection: a new paradigm in the management of acute heart failure syndromes. Am J Cardiol 2005; 96: 26G-31G. DOI: 10.1016/j.amjcard.2005.07.018. https://goo.gl/dAwQuu

3. Grossini E, Pollesello P, Bellofatto K, Sigaudo L, Farruggio S, Origlia V, et al. Protective effects elicited by levosimendan against liver ischemia/reperfusion injury in anesthetized rats. Liver Transpl 2014; 20: 361-75. DOI: 10.1002/lt.23799. https://goo.gl/oQAQKq

4. Grossini E, Molinari C, Pollesello P, Bellomo G, Valente G, Mary D, et al. Levosimendan protection against kidney ischemia/reperfusion injuries in anesthetized pigs. J PharmacolExpTher 2012; 342: 376-88. DOI: 10.1124/jpet.112.193961. https://goo.gl/nsjMPL

5. Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, et al. ACC/AHA guidelines for percutaneous coronary intervention. Circulation 2001;103: 3019-41. https://goo.gl/g7zYnH

6. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 1994; 89: 1545-56. https://goo.gl/hs22Xk

7. Caimmi PP, Molinari C, Uberti F, Micalizzi E, Valente G, Mary DA, et al. Intracoronary levosimendan prevents myocardial ischemic damages and activates survival signaling through ATP-sensitive potassium channel and nitric oxide. Eur J CardiothoracSurg 2011; 39: 59-67. DOI: 10.1016/j.ejcts.2010.11.044. https://goo.gl/8PM37o

8. Edes I, Kiss E, Kitada Y, Powers FM, Papp JG, Kranias EG, et al. Effects of Levosimendan, a cardiotonic agent targeted to troponin C, on cardiac function and on phosphorylation and Ca2+ sensitivity of cardiac myofibrils and sarcoplasmic reticulum in guinea pig heart. Circ Res 1995; 77: 107-13. https://goo.gl/X6Y50K

9. Gruhn N, Nielsen-Kudsk JE, Theilgaard S, Bang L, Olesen SP, Aldershvile J. Coronary vasorelaxant effect of levosimendan, a new inodilator with calcium-sensitizing properties. J CardiovascPharmacol 1998;31:741-9.

10. Garlid KD, Dos Santos P, Xie ZJ, Costa AD, Paucek P. Mitochondrial potassium transport: the role of the mitochondrial ATP-sensitive K(+) channel in cardiac function and cardioprotection. BiochimBiophysActa 2003;1606:1-21. DOI: S0005272803001099. https://goo.gl/ukzdSS

11. Okorie MI, Bhavsar DD, Ridout D, Charakida M, Deanfield JE, Loukogeorgakis SP, et al. Post conditioning protects against human endothelial ischaemia-reperfusion injury via subtype-specific KATP channel activation and is mimicked by inhibition of the mitochondrial permeability transition pore. Eur Heart J 2011; 32:1266-74.DOI: 10.1093/eurheartj/ehr041. https://goo.gl/L5yQx8

12. Yoshimura M, Yasue H, Okumura K, Ogawa H, Jougasaki M, Mukoyama M, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. Circulation 1993; 87: 464-9. https://goo.gl/SKjBtO

13. Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. J Am CollCardiol 2002; 40: 437-45. DOI: S0735109702019861. https://goo.gl/PTbYz2