



Efficacy and safety of levosimendan in Chinese elderly patients with Takotsubo syndrome

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Background: Takotsubo syndrome has a low global incidence, but it is observed more and more in clinical practice. Only case reports and series have been published, while prospective studies are still necessary. This study aimed to explore the efficacy and safety of levosimendan in elderly with Takotsubo syndrome.

Methods: This study followed a prospective, randomized and double-blinded design. All 200 consecutive patients (>65 years) with Takotsubo syndrome were randomly assigned into a levosimendan group (n=100) and a control group (n=100). The control group underwent regular treatment, and the levosimendan group was additionally administered with levosimendan.

Results: Age of all patients was 71 [66–85] years, and there were 138 females (69%). Baseline characteristics between the two groups had no significant difference before treatment ($P>0.05$ for all). In the levosimendan group on the 30 and 180 days after treatment, left ventricular ejection fraction was significantly higher, and New York Heart Association class and N-terminal pro-brain natriuretic peptide levels were significantly lower, than those in the control group ($P<0.05$ for all). Systolic blood pressure, diastolic blood pressure, heart rate and serum creatinine levels had no significant difference between the two groups ($P>0.05$ for all).

Conclusions: Levosimendan showed reliable efficacy and safety in Chinese elderly patients with Takotsubo syndrome, supporting the idea that levosimendan has the potential to be an essential drug applied for patients with Takotsubo syndrome.

Keywords: Chinese elderly; levosimendan; Takotsubo syndrome

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Introduction

Although Takotsubo syndrome has a low global incidence, it is observed more and more in current clinical practice (1,2). Levosimendan is a new type of Ca^{2+} sensitizer that can improve cardiac function without severely affecting stable hemodynamics and renal function (3,4). However, to date there has hardly been any prospective study to observe the application of levosimendan in patients with Takotsubo

syndrome, and there are only controversial results based on the clinical experience (1). As advised by the current position statement from the Heart Failure Association of European Society of Cardiology, the published literature on the Takotsubo syndrome only consists of case reports and series, while prospective studies to probe the efficacy and safety of levosimendan in patients with Takotsubo syndrome are still necessary (1).

China, the largest developing country in the world, has

become an aging society, and there are increased morbidity and mortality rates in the elderly (5,6). Clinical data on the levosimendan application in Chinese elderly patients with Takotsubo syndrome remain very rare, and it is essential to analyze the efficacy and safety of levosimendan in these patients. The current study aimed to explore the efficacy and safety of levosimendan in patients with Takotsubo syndrome.

Methods

Study participants

The current study followed a prospective, randomized and double-blinded design. A total of 200 consecutive patients over the age of 65 who had Takotsubo syndrome were admitted to the Department of Cardiology in our hospital from January 2013 to December 2016. Takotsubo syndrome was diagnosed according to the consensus from chief physicians of the Cardiology Department and in line with the diagnostic criteria of the Mayo Clinic and the position statement from the Heart Failure Association of the European Society of Cardiology. Inclusion criteria were in the following: (I) transient regional ventricular wall motion abnormalities; (II) absence of culprit atherosclerotic coronary artery disease or other pathological conditions, such as hypertrophic cardiomyopathy and viral myocarditis, to explain the pattern of ventricular dysfunction; (III) new electrocardiography abnormalities; (IV) significantly elevated serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels; (V) positive but relatively small elevation in cardiac troponin T; (VI) recovery of ventricular function at follow-up (6 months) (1,7,8). Patients were excluded based on the following criteria: (I) sensitivity or intolerance to levosimendan and other formulation ingredients; (II) severe ventricular filling and outflow obstruction; (III) electrolyte disturbance (serum potassium <3.5 or >5.5 mmol/L); (IV) severe hepatic and renal impairment; (V) severe hypotension and tachycardia including ventricular tachycardia or ventricular fibrillation (9).

Study procedures

Patients were randomly assigned into a levosimendan group (n=100) and a control group (n=100) using random numbers in a randomized block design. Random numbers were generated by Statistic Package for Social Science (SPSS) version 17.0 software (SPSS Inc., Chicago, USA).

After diagnosed with Takotsubo syndrome and assigned into the two groups, the control group underwent regular treatment, and the levosimendan group was administrated with levosimendan (Qilu Pharmaceutical, Jinan, China; Specifications: 5 mL, 12.5 mg) at continuously intravenous infusion of 0.1 $\mu\text{g}/\text{kg}/\text{min}$ without loading dose for 24 hours in addition to regular treatment (1,10). Drug use was a standardized process. All patients received coronary angiography and left ventriculography. They all had continuous strict electrocardiographic and hemodynamic monitoring. Left ventricular ejection fraction (LVEF) was measured using Simpson's method through standard echocardiography. The blood sample was drawn from all patients and then analyzed in the Department of Biochemistry. Serum NT-proBNP levels were measured by NT-proBNP Flex Reagent Cartridge (PBNP/LPBN) produced by Siemens Healthcare Diagnostics Inc (Deerfield, USA) on the Dimension RxL Max (Siemens Healthcare Global, Erlangen, Germany). Serum creatinine levels were measured by enzymatic assay (Roche Diagnostics GmbH) on the Hitachi 7600 autoanalyzer (Hitachi, Tokyo, Japan). All patients were followed up on the 30 and 180 days after treatment (1,11). All patients were not re-hospitalized after discharge from hospital. They received follow-up and reexamination in the Outpatient Department in our hospital.

Statistical analyses

Continuous variables with normal distribution were reported using mean and standard deviation, and the difference between the two groups was compared using Student's *t*-test. Continuous variables with abnormal distribution were reported using median and interquartile range, and the difference between the two groups was compared using Mann-Whitney U test. Categorical variables were reported with number and percentage, and the difference between the two groups was compared with Chi-square test. All analyses were carried out by SPSS version 17.0 software (SPSS Inc., Chicago, USA), and P value <0.05 was accepted as statistically significant.

Results

Age of all patients was 71 [66–85] years, and there were 138 females (69%). Baseline characteristics between the two groups had no significant difference before treatment ($P>0.05$ for all; *Table 1*). Comparison between the two groups on the 30 and 180 days after treatment is shown in

Table 1 Baseline characteristics of elderly patients with Takotsubo syndrome in the levosimendan and control group

Characteristics	Levosimendan group (n=100)	Control group (n=100)	P
Age (year)	72 [68–76]	71 [68–77]	0.498
Females, n (%)	71 (71.0)	67 (67.0)	0.541
Hypertension, n (%)	21 (21.0)	17 (17.0)	0.471
Diabetes mellitus, n (%)	11 (11.0)	13 (13.0)	0.663
SBP (mmHg)	136 [120–145]	129 [121–140]	0.389
DBP (mmHg)	70 [64–72]	68 [64–74]	0.573
Heart rate (time/minute)	93 [89–103]	97 [90–102]	0.232
NYHA class, n [%]			1.000
IV	100 [100]	100 [100]	
LVEF [%]	29 [27–31]	29 [25–32]	0.473
NT-proBNP (pg/mL)	2,040.8 (1,543.2–3,856.1)	2,358.5 (1,760.8–3,539.8)	0.398
Serum creatinine ($\mu\text{mol/L}$)	79.0 (71.0–98.5)	85.6 (75.9–92.5)	0.353
ACEI/ARB, n (%)	29 (29.0)	23 (23.0)	0.333
Beta-blockers, n (%)	0	0	1.000
Diuretics, n (%)	83 (83.0)	87 (87.0)	0.428

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotension receptor blocker; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Table 2. In the levosimendan group, LVEF was significantly higher, and New York Heart Association (NYHA) class and serum NT-proBNP levels were significantly lower, than those in the control group ($P < 0.05$ for all). Systolic blood pressure, diastolic blood pressure, heart rate and serum creatinine levels had no significant difference between the two groups ($P > 0.05$ for all). Other kinds of side effects were not found in the two groups. Compared with the control group, mortality was significantly lower in the levosimendan group ($P < 0.05$). All patients died of circulatory failure.

Discussion

Takotsubo syndrome has a low global incidence (1). The treatment of Takotsubo syndrome in elderly patients should be taken into special consideration (1). As advised by the current position statement from the Heart Failure Association of European Society of Cardiology, inotropes, including dobutamine and dopamine, should be forbidden in patients with Takotsubo syndrome, as further activation of catecholamine receptors or other molecular pathways might aggravate their condition (12,13). Levosimendan is one of the limited options that

is left, but there have been rare case reports and series to observe the application of levosimendan in patients with Takotsubo syndrome, and prospective studies to probe the efficacy and safety of levosimendan are still necessary, especially in Chinese elderly patients (1). The current study found that levosimendan improved cardiac function and reduced mortality in elderly patients, which suggests that levosimendan is effective in treating Takotsubo syndrome in Chinese elderly patients. Meanwhile, these elderly patients in the current study exhibited no distinction of blood pressure, heart rate and renal function with the treatment of levosimendan or not, which suggests that levosimendan is safe in treating Takotsubo syndrome in Chinese elderly patients. Therefore, levosimendan is very appropriate for Chinese elderly patients with Takotsubo syndrome.

Levosimendan is a new type of Ca^{2+} sensitizer that can improve cardiac function without severely affecting stable hemodynamics and renal function (3,4). Levosimendan has provided beneficial cardioprotective and hemodynamic effects in cardiac surgery field and patients with septic shock (4,14,15). However, there has hardly been any prospective studies analyzing the application of levosimendan in patients with Takotsubo syndrome. The current study

Table 2 Efficacy and safety of elderly patients with Takotsubo syndrome in the levosimendan and control group

Characteristics	Levosimendan group (n=100)	Control group (n=100)	P
30 days			
NYHA class, n (%)			0.041
II	68 (68.7)	48 (52.2)	
III	29 (29.3)	38 (41.3)	
IV	2 (2.0)	6 (6.5)	
LVEF [%]	47 [44–55]	47 [41–51]	0.035
NT-proBNP (pg/mL)	759.3 (545.5–1,116.9)	897.6 (660.8–1,118.2)	0.044
Serum creatinine (μmol/L)	83.6 (73.6–103.0)	88.3 (71.1–99.0)	0.596
SBP (mmHg)	124 [121–132]	125 [114–136]	0.852
DBP (mmHg)	61 [58–65]	61 [59–64]	0.848
Heart rate (time/minute)	79 [75–84]	77 [74–81]	0.135
Mortality, n (%)	1 (1.0)	8 (8.0)	0.041
180 days			
NYHA class, n (%)			0.042
I	68 (68.7)	50 (54.3)	
II	31 (31.3)	42 (45.7)	
LVEF [%]	49 [47–57]	49 [47–53]	0.040
NT-proBNP (pg/mL)	476.7 (245.5–664.6)	542.5 (360.8–748.7)	0.032
Serum creatinine (μmol/L)	83.0 (73.7–101.0)	86.3 (69.1–97.7)	0.669
SBP (mmHg)	119 [117–130]	121 [110–132]	0.871
DBP (mmHg)	59 [55–64]	62 [56–64]	0.563
Heart rate (time/minute)	72 [68–77]	71 [67–77]	0.249
Mortality, n (%)	1 (1.0)	8 (8.0)	0.041

DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

proved favorable efficacy and safety of levosimendan in Chinese elderly patients with Takotsubo syndrome. It is not surprising that levosimendan has beneficial effects on the elderly patients with cardiac troponin C insensitive to Ca^{2+} . Levosimendan can be combined with cardiac troponin C for the greater sensitivity to Ca^{2+} , leading to myocardial contraction even at the same or lower Ca^{2+} concentration (16,17).

Conclusions

The current study demonstrated that levosimendan showed reliable efficacy and safety in Chinese elderly patients with

Takotsubo syndrome, supporting the idea that levosimendan has the potential to be an essential drug applied for patients with Takotsubo syndrome.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol has been approved by Ethics Committee of Chinese People's Liberation Army General Hospital (Beijing, China; ID: 301hn11201601) and it conforms to the Helsinki Declaration. Each participant provided written informed consent to be included in the study.

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