Effects of Xinkeshu combined with levosimendan on perioperative heart failure in oldest-old patients with hip fractures

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Abstract

OBJECTIVE: To investigate the clinical effects of Xinkeshu combined with levosimendan on perioperative heart failure in oldest-old patients with hip fractures.

METHODS: Oldest-old patients over 80 years old with perioperative heart failure and hip fractures were randomly divided into the control and observation groups, with 50 patients in each group. All patients in both groups were treated with conventional anti-heart failure therapy and levosimendan, whereas patients in the observation group additionally received Xinkeshu tablets. Clinical manifestations; left ventricular ejection fraction (LVEF); left ventricular end-diastolic dimension (LVEDD); left ventricular end-systolic dimension (LVESD); B-type natriuretic peptide (BNP), superoxide dismutase (SOD), malondialdehyde (MDA), nitric oxide (NO), and endothelin-1 (ET-1) levels; and self-rating anxiety scale (SAS) and self-rating depression scale (SDS) scores were compared between before and after treatment to evaluate the curative effects of Xinkeshu combined with levosimendan.

RESULTS: After treatment, the efficacy rate was significantly higher in the observation group than in the control group. LVEF and the levels of SOD and NO were higher in the observation group than in the control group after treatment. However, LVEDD; LVESD; BNP, MDA, and ET-1 levels; and the SAS and SDS scores were lower after treatment in the observation group than in the control group.

CONCLUSION: Levosimendan combined with Xinkeshu can improve cardiac function, alleviate oxidative stress, and relieve anxiety and depression in oldest-old patients with perioperative heart failure and hip fracture.

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Keywords: Aged, 80 and over; Hip fractures; Perioperative period; Heart failure; Levosimendan; Xinkeshu

INTRODUCTION

With the aging of the population, concerns about the health problems of oldest-old people are increasing. As a frail group in society, oldest-old people experience a decline in physical functioning as well as decreases in balance and response ability. This results in certain life difficulties, which may lead to fall and hip fracture. Surgery is the preferred treatment for hip fracture. However, several factors after fractures such as pain, infection, and anesthesia impose an additional burden on the heart, which can ultimately induce heart failure and increase perioperative risk. According to previous studies, perioperative heart failure is a high risk factor for poor prognoses. Therefore, we should pay attention to the treatment of perioperative heart failure in oldest-old patients with hip fractures.
Traditional Chinese Medicine (TCM) has long been used to treat heart failure. With in-depth study, the etiology, pathogenesis, TCM symptom pattern identification, and types of heart failure have been clarified, and abundant experience concerning treatment has been accumulated. According to the principle of TCM symptom pattern identification, the combination of TCM and Western Medicine in the treatment of heart failure has obvious synergistic effects, fewer adverse reactions, and other beneficial features. Xinkeshu and levosimendan as monotherapies both have good therapeutic effects against heart failure. Nevertheless, relatively few studies have examined the clinical effects of their combined use in the treatment of perioperative heart failure in oldest-old patients. In this study, we investigated the effect of Xinkeshu combined with levosimendan on perioperative heart failure in oldest-old patients with hip fractures.

**METHODS**

**Study design**

This randomized, controlled clinical study was conducted from April 2018 to June 2019, in the Third Hospital of Hebei Medical University. One hundred oldest-old patients with perioperative heart failure after hip fracture were randomly divided into control (50 patients) and observation groups (50 cases) using a computer-generated randomization sequence. All patients in both groups were treated with levosimendan and conventional anti-heart failure therapy, and the patients in the observation group were also treated with Xinkeshu. The study was approved by the ethics committee of our hospital, and written consent was obtained from each patient.

**Inclusion and exclusion criteria**

The inclusion criteria were as follows: (a) age of at least 80 years; (b) diagnosis of hip fracture using imaging; (c) matching the diagnostic criteria of Chinese guidelines for the diagnosis and management of heart failure; (d) surgical treatment for hip fracture; and (e) provision of written informed consent. The exclusion criteria were as follows: (a) presence of other fractures; (b) presence of mechanical obstructive diseases that significantly affect ventricular filling or ejection function; (c) liver or kidney dysfunction; (d) allergy to the examined treatments; (e) a history of malignant tumors; and (f) severe mental disorders.

**Treatments**

All patients in both groups were treated with levosimendan and conventional anti-heart failure therapy, including diuretics, digitalis, and angiotensin-converting enzyme inhibitors, in addition to oxygen inhalation and bed rest. Levosimendan was infused via a micro-pump before surgery (Qilu Pharmaceutical Co., Ltd., Jinan, China, NMPN: H20100043), at a dose of 0.05 μg·kg⁻¹·min⁻¹. The dose could be adjusted according to the patient condition and continued for up to 24 h. In the process of injection, electrocardio-monitoring was used to observe the patients’ clinical symptoms, blood pressure, and heart rate. The patients in the observation group were also treated with two Xinkeshu tablets (Shandong Wohua Pharmaceutical Co., Ltd., Weifang, China, NMPN: Z20023128, Specification: 0.62 g per tablet) orally three times a day. Patients with hypertension and diabetes were treated with routine drugs.

**Assessment**

Left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), and left ventricular end-systolic dimension (LVESD) were measured and calculated using a color Doppler ultrasound diagnostic instrument before and after treatment (1 week after surgery). The self-rating anxiety scale (SAS) and self-rating depression scale (SDS) were used to evaluate patients’ mood, and standard scores were recorded before and after treatment. Blood samples were collected on an empty stomach to measure plasma B-type natriuretic peptide (BNP), superoxide dismutase (SOD), malondialdehyde (MDA), nitric oxide (NO), and endothelin-1 (ET-1) levels before and after treatment. SOD and MDA levels were measured using xanthine oxidation and thiobarbituric acid tests, respectively. NO levels were measured using the nitrate reduction method. ET-1 levels were measured via radioimmunoassay. The surgical steps were strictly in accordance with the instructions of the kit. The curative effect was assessed after treatment (1 week after surgery). The relief of clinical symptoms and improvement of cardiac function indicated treatment efficacy. Ineffectiveness was identified by a lack of significant improvement of worsening of clinical symptoms.

**Statistical analysis**

Data were analyzed using SPSS 21.0 (IBM Corp., Released 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY, USA). Data were presented as the mean ± standard deviation or percentage. A t-test, paired t-test, or c² test was conducted to test the differences between groups. Significance was indicated by $P < 0.05$.

**RESULTS**

One hundred patients were eventually analyzed. The control group included 18 men and 32 women, and the mean age was (86.1 ± 3.3) years (range, 80-96 years. In this group, 23 patients were diagnosed with femoral neck fractures, and 27 patients had femoral intertrochanteric fractures. The observation group included 17 men and 33 women, and the mean age was (85.6 ± 3.4) years (range, 80-95 years. In total, 24 patients were diagnosed with femoral neck fractures, and...
26 patients had femoral intertrochanteric fractures. The baseline characteristics of the patients are presented in Table 1.

Comparison of cardiac function between the groups
Before treatment, there were no significant differences in LVEF, LVEDD, LVESD, and BNP levels between the two groups (Table 2). After treatment, LVEDD, LVESD, and BNP levels were significantly lower in both groups, whereas LVEF was significantly higher (all \( P < 0.05 \), Table 2). LVEDD, LVESD, and BNP levels were significantly lower in the observation group than in the control group, whereas LVEF was significantly higher in the observation group (all \( P < 0.05 \), Table 2).

Comparison of SAS and SDS scores between groups
Before treatment, SAS and SDS scores were not significantly different between the two groups (Table 3). The SAS and SDS scores were significantly lower in both groups after treatment (both \( P < 0.05 \), Table 3). SAS and SDS scores were significantly lower in the observation group than in the control group (both \( P < 0.05 \), Table 3).

Comparison of plasma SOD, MDA, NO, and ET-1 levels between the groups
Before treatment, there were no significant differences in SOD, MDA, NO, and ET-1 levels between the two groups (Table 4). After treatment, SOD and NO levels were significantly higher in both groups, whereas MDA and ET-1 levels were significantly lower (all \( P < 0.05 \), Table 4). After treatment, SOD and NO levels were significantly higher in the observation group than in the control group, whereas MDA and ET-1 levels were significantly lower in the observation group (all \( P < 0.05 \), Table 4).

Table 1 Baseline characteristics of the patients (**x ± s**)

<table>
<thead>
<tr>
<th>Item</th>
<th>Control group (n = 50)</th>
<th>Observation group (n = 50)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>86.1 ± 3.3</td>
<td>85.6 ± 3.4</td>
<td>0.463</td>
</tr>
<tr>
<td>Male/female</td>
<td>36/14</td>
<td>34/16</td>
<td>0.663</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 ± 2.2</td>
<td>24.4 ± 2.3</td>
<td>0.189</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>19 (38)</td>
<td>20 (40)</td>
<td>0.838</td>
</tr>
<tr>
<td>Diabetes [n (%)]</td>
<td>12 (24)</td>
<td>11 (22)</td>
<td>0.812</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72.5 ± 9.6</td>
<td>71.3 ± 10.1</td>
<td>0.544</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>135.4 ± 15.2</td>
<td>136.8 ± 14.3</td>
<td>0.637</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>70.3 ± 8.2</td>
<td>71.1 ± 7.8</td>
<td>0.646</td>
</tr>
</tbody>
</table>

Notes: observation group: patients were treated with conventional anti-heart failure therapy and levosimendan; the conventional anti-heart failure therapy was continued until the seventh day after operation; levosimendan was infused via a micro-pump before surgery at a dose of 0.05 μg·kg⁻¹·min⁻¹, and continued for up to 24 h. Control group: patients were treated with conventional anti-heart failure therapy, levosimendan and Xinkeshu tablets (1.24 g each time, three times a day). BMI: body mass index.

Table 2 Comparison of cardiac function between the groups (**x ± s**)

<table>
<thead>
<tr>
<th>Item</th>
<th>Control group (n = 50)</th>
<th>Observation Group (n = 50)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>44.1 ± 2.3</td>
<td>50.3 ± 4.0°</td>
<td>43.9 ± 2.4</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>51.7 ± 2.9</td>
<td>47.2 ± 3.0°</td>
<td>52.4 ± 3.3</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>40.2 ± 2.6</td>
<td>35.1 ± 2.7°</td>
<td>40.7 ± 2.6</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>705.2 ± 121.3</td>
<td>346.4 ± 136.8°</td>
<td>713.1 ± 103.4</td>
</tr>
</tbody>
</table>

Notes: observation group: patients were treated with conventional anti-heart failure therapy and levosimendan; the conventional anti-heart failure therapy was continued until the seventh day after operation; levosimendan was infused via a micro-pump before surgery at a dose of 0.05 μg·kg⁻¹·min⁻¹, and continued for up to 24 h. Control group: patients were treated with conventional anti-heart failure therapy, levosimendan and Xinkeshu tablets (1.24 g each time, three times a day). LVEF: Left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; BNP: B-type natriuretic peptide. \( P < 0.05 \), compared with itself at baseline; \( P < 0.05 \), compared with the control group.
DISCUSSION

A number of studies have identified crucial roles of oxidative stress and vascular endothelial dysfunction in the development of heart failure.\textsuperscript{10} Severe post-traumatic stress reaction occurs after hip fracture in oldest-old people. Under the triple hit of physical stress, psychological stress, and iatrogenic stress, post-traumatic stress reaction may induce myocardial ischemia, myocardial stunning, and stress cardiomyopathy, which manifest as heart failure. The specific mechanism may be as follows: after fracture, the stress response occurs mainly based on the neuroendocrine reaction, which excites the sympathetic nerve, induces the release of large amounts of catecholamines, accelerates the production of oxygen radicals, ultimately injures cardiomyocytes, and causes myocardial stunning.\textsuperscript{11,12} Meanwhile, catecholamines induce coronary vasospasm, arteriolar constriction, and impaired endothelial function.\textsuperscript{13} According to TCM, the basic pathological mechanism of heart failure is mainly heart-Qi deficiency and heart-Yang deficiency. In the face of heart-Qi deficiency, blood circulation cannot be promoted, resulting in blood stasis and insufficient systemic perfusion.\textsuperscript{14} Based on the aforementioned mechanisms, the myocardial contractility of patients with heart failure decreases, resulting in decreased cardiac output and insufficient peripheral organ perfusion, which manifest as hypotension, tachycardia, oliguria, and fatigue. Oldest-old people often have multiple diseases, complex conditions, and poor tolerance, which complicate the treatment of perioperative heart failure. Based on the mechanism of perioperative heart failure in oldest-old patients with hip fracture, efforts should be made to enhance myocardial contractility, activate blood circulation, and remove blood stasis. As a new-generation positive inotropic drug, levosimendan can enhance myocardial contractility without increasing myocardial oxygen consumption, dilate blood vessels, and protect the myocardium by activating ATP-sensitive K+ channels.\textsuperscript{15,16} Xinkeshu tablets are composed of five pure botanical drugs, including Dangshen (Radix Salviae Miltiorrhiza), Sanqi (Poncirus trifoliata), Muxiang (Radix Paeoniae Alba), Gegen (Fructus Crataegus Pinnatifida), and Xuanbeijing (Radix Paeoniae Alba). The main effective components are tanninone, nortic acid, and costuslacone, which can promote blood circulation, remove blood stasis, dilate coronary arteries, improve cardiac microcirculation, and antagonize oxygen radicals.\textsuperscript{17} The results illustrated that the efficacy rate and LVEF after treatment were significantly higher in the observation group than in the control group, suggesting that Xinkeshu combined with levosimendan can enhance the treatment effect for perioperative heart failure in oldest-old patients with hip fracture and improve cardiac function. SOD and MDA are indicators of oxidative stress, and they can indirectly reflect the degree of oxidative stress and participate in the development of heart failure. Lu et al.\textsuperscript{18} found that Xinkeshu could improve SOD activity in serum and myocardial tissue, reduce MDA levels, effectively scavenge oxygen radicals, and protect rabbits against myocardial ischemia reperfusion injury and myocardial stunning caused by the ligation of left anterior descending coronary artery. NO and ET-1 are vasoactive substances produced by vacu-
lar endothelial cells. Reduced plasma NO levels and elevated ET-1 levels are important markers of vascular endothelial dysfunction. Relevant studies found that Xinkeshu can improve vascular endothelial function in patients with coronary heart disease or coronary microcirculation disorders.20 Levosimendan dilates coronary and peripheral vessels, alleviates myocardial ischemia, and reduces oxygen free radical production.21,22 The results demonstrated that SOD and NO levels were significantly higher in the observation group than in the control group, whereas MDA and ET-1 levels were significantly lower, suggesting that Xinkeshu combined with levosimendan could further alleviate oxidative stress and improve vascular endothelial function in the perioperative period.

After treatment, SAS and SDS scores were significantly lower in the observation group than in the control group. We believe that the psychological endurance of oldest-old people is reduced, and they are prone to anxiety, fear, and mood fluctuation because of environmental changes, pain, and worries about surgery and the prognosis during hospitalization. Salvia miltiorrhiza, Panax notoginseng, Radix Aucklandiae, and Hawthorn in Xinkeshu can act on the liver and gallbladder meridians related to mood to further improve the adverse conditions.23

In conclusion, levosimendan combined with Xinkeshu can improve cardiac function, alleviate oxidative stress, and relieve anxiety and depression in oldest-old patients with perioperative heart failure and hip fractures. However, this study had several limitations. First, the number of samples was small. Second, only a 1-week study was conducted without a long-term evaluation of prognosis. Furthermore, the mechanism of perioperative heart failure was not studied in depth. Further multicenter randomized controlled trials with larger sample sizes are needed in the future.

REFERENCES