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JTCM 中医杂志 Journal of Traditional Chinese Medicine

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J Tradit Chin Med 2016 December 15; 36(6): 706-710
ISSN 0255-2922

CLINICAL STUDY

Protective effect of Xuebijing injection on myocardial injury in patients with sepsis: a randomized clinical trial

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Supported by Key Medical Research Subject of Hebei Province (the Protective Effect and Mechanism of Xuebijing Injection on Cardiac Function in Patients With Sepsis, No. ZD20140379)

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Accepted: October 15, 2015

Abstract

OBJECTIVE: To investigate the protective effect and possible mechanism of Xuebijing Injection on myocardial injury in patients with sepsis, and to evaluate its prognostic implications.

METHODS: Patients with septic myocardial injury were recruited, and were randomly divided into two groups: treatment group and control group. All patients in two groups received conventional cluster treatment, the patients in treatment group additional received Xuebijing injection dissolved in 0.9% sodium chloride injection, and the patients in control group received the same amount of 0.9% sodium chloride injection. At the beginning of treatment and 3, 7 and 10-day after treatment, laboratory indicators of cardiac troponin Ⅰ (cTnI), N-terminal proB-type natriuretic peptide (NT-proBNP) and procalcitonin (PCT) were respectively tested in venous blood. The patient's length of stay in Intensive Care Unit (ICU) and the mortality in 28 days were recorded.

RESULTS: At 3, 7 and 10-day after treatment, the improvements of cTnI, NT-proBNP and PCT in treatment group were better than those in control group, and the differences were statistically significant ($P < 0.05$). The mortality of treatment group in 28 days was not significantly different from that of control group ($P > 0.05$). The ICU length of stay of treatment group was shorter than that of control group ($P > 0.05$).

CONCLUSION: Xuebijing injection could improve the levels of cTnI, NT-proBNP and PCT in patients with septic myocardial injury .and it had a protective effect on myocardial injury.

Key words: Sepsis; Myocardial reperfusion injury; Cardiac troponin Ⅰ; Pro-brain natriuretic peptide (1-76); Procalcitonin; Randomized clinical trials; Xuebijing injection

INTRODUCTION

Sepsis usually progress quickly, severe sepsis and septic shock are the main cause of death in noncardiac critically patients.[1] About 50% of patients with sepsis appeared varying degrees of myocardial depression, and the mortality can be as high as 70% to 90%.[2] The research reported that the myocardial organic damage

had existed in early sepsis, and low blood pressure, arrhythmias and heart failure easily appeared in these patients.[3] Therefore, it is an important significant to timely administer effective medicine to patients with septic myocardial injury.

The traditional medicine in treatment of infectious diseases has a long history. Xuebijing injection is anintravenous solution prepared with a formula from Traditional Chinese Medicine (TCM). The formula consists of Chishao (*Radix Paeoniae Rubra*), Danggui (*Radix Angelicae Sinensis*), Chuanxiong (*Rhizoma Chuanxiong*), Honghua (*Flos Carthami*), and Danshen (*Radix Salviae Miltiorrhizae*), so it with the efficacy of activating blood circulation to remove blood stasis, cooling the blood and clearing the toxic heat.[4] Xuebijing injection is initially used for treatment of severe acute respiratory syndrome (SARS), which caused by coronavirus. But today it is widely used in kinds of critically ill patients, including endotoxemia, circulatory and respiratory failure, multiple organ dysfunction and so on.[5,6]

We used Xuebijing injection in patients with septic myocardial injury, to observe its effect on the level of cardiac troponin Ⅰ (cTnI), N-terminal proB-type natriuretic peptide (NT-proBNP) and procalcitonin (PCT), to explore its protective effect on myocardial injury in patients.

METHODS

Participants

From January 2011 to December 2013, a total of 74 patients with septic myocardial injury were elected in Intensive Care Unit of The Second Hospital of Tangshan and People's Hospital of Tangshan. Age of patients ranged form 18 to 71 years old.

Inclusion criteria

All patients were diagnosed according to the sepsis diagnostic criteria recommended by the International Sepsis conference in December 2001.[7] The age of patients was not less than 18 years old.

Exclusion criteria

Patients with cancer, blood diseases, rheumatic diseases and acquired immune deficiency syndrome had been ruled out before the election, other patient with a history of previous cardiac surgery, myocardial infarction, heart failure, coronary heart disease or cardiomyopathy had been ruled out too. In addition, the patient who had occurred chest compressions, defibrillation ordirect current cardioversion before 7 days election were ruled out.

This study was approved by the ethics committee of The Second Hospital of Tangshan and People's Hospital of Tangshan, and all treatment obtained informed consent from patients or their families and signed agreement.

Design

This study was a randomized, double-blind, and placebo-controlled trial. The proportion of two samples was 1∶1. According to formula the minimum sample size was calculated, in which α take 0.05 (two-sided) and β take 0.10 (one-sided). A minimum of 32 patients in each group would be needed. A total of 74 patients were estimated for the study considering the exclusion of patients who failed to participate in follow-up and those who drop out of the trial.

Random and blinding

According to the admission order of Intensive Care Unit (ICU), each patient obtained a serial number, the serial numbers were divided into two groups by a statistical software SPSS 17.0 (SPSS software Inc., Chicago, IL, USA). The distribution ratio of two groups was 1∶1. Outcome measures were performed by an independent researchist, who was not informed of the treatment sequence or what treatment the patients would received. Therefore, the researchers and participants were unaware of the kind of injection given to each participant. When treatment drug (Xuebijing injection)or control drug (0.9% sodium chloride injection)was using, an opaque bag on the outside (blinding).

Interventions

All patients in two groups received conventional cluster treatment in accordance with international guidelines criteria.[8] The conventional cluster treatment included the treatment of primary disease, blood and fluids transfusion, protective mechanical ventilation, analgesic, sedative, anti-inflammatory, anti-infective medications, nutritional support, water and electrolyte balance maintaining, and so on. The patients in treatment group additional received Xuebijing injection (Tianjin Chase Sun Pharmaceutical Co., Ltd., Tianjin, China). The application was that 50 mL Xuebijing injection dissolved in 100 mL 0.9% sodium chloride injection was administered by intravenous infusion, 2 times/day, starting from the day of diagnosis was confirmed and the treatment of the Xuebijing injection lasted for 10 days. The patients in control group additional received the same amount of 0.9% sodium chloride injection.

Outcome measures

At the beginning of treatment and 3, 7 and 10-day after treatment, laboratory indicators of cTnI, NT-proBNP and PCT were respectively tested in venous blood. The patient's length of stay in ICU and the mortality in 28 days were recorded. The detection reagent of cTnI, NT-proBNP and PCT provided by Getein Biotechnology Co., Ltd., (Nanjing, China). All outcome measures were collected by the same investigator for continuity and to aid in maintaining a standard procedure.

Safety assessments included investigator inquiries about the occurrence of adverse events (dizziness, palpitation, nausea, diarrhea and skin allergies). Routine inspections of blood, urine, stool, and liver/kidney function tests were taken before and after treatment.

Statistical analysis

Statistical software SPSS 17.0 (SPSS software Inc., Chicago, IL, USA) was used to analyze data. Measurement data was presented as mean ± standard deviation ($\bar{x}$ ± *s*). Student's *t* test was performed to test the difference between the two groups. $P < 0.05$ was the significant level.

RESULTS

Comparison of Basic characteristics

Seventy-four patients with septic myocardial injury were elected. Because patients or their families did not agree to participate in the research, two patients were excluded. According to the admission order of ICU, each patient obtained a serial number, and then the serial number was divided into treatment group (36 cases) and control group (36 cases) by computer-generated randomly. Two patients in treatment group dropped out, because patients had poor compliance, and would not coordinate outcome measures. One patient in control group gave up because the patient was not satisfied with treatment. The flow diagram of this study design was depicted in Figure 1.

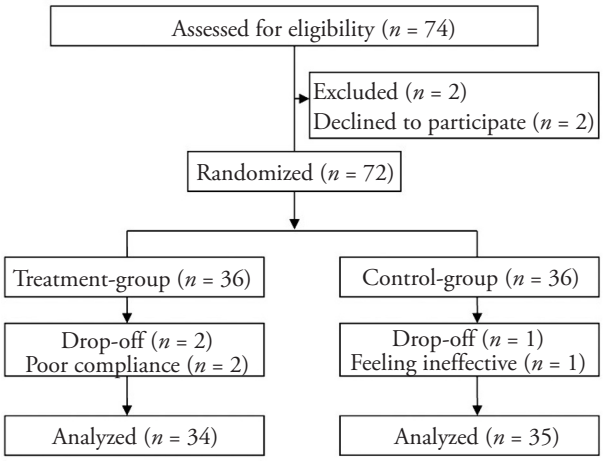

Figure 1 Flow diagram of this randomized trial

At the beginning of treatment, there were no statistically significant differences between the two groups in terms of gender, age, primary lesion, past history and acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ). The mortality in 28 days respectively were 14.71% and 22.85%, the mortality in treatment group was lower than that in control group, but the difference was not statistically significant. The length of stay in ICU of treatment group was less than that of control group, and the difference was statistically significant (Table 1). There were no adverse events recorded from the study medication.

cTnI

At the beginning of treatment (0 day), there was no statistically significant difference between the two groups in term of cTnI (t_0 = 0.083, $P > 0.05$). At 3, 7 and 10-day after treatment, the levels of cTnI in treatment group were lower than those of control group, and the differences were statistically significant (t_3 = 3.385, t_7 = 4.429, t_{10} = 5.090, $P < 0.05$) (Figure 2).

NT-proBNP

At the beginning of treatment (0 day), there was no statistically significant difference between the two groups in term of NT-proBNP (t_0 = 0.290, $P > 0.05$). At 3, 7 and 10-day after treatment, the levels of NT-proBNP in treatment group were lower than those of control group, and the differences were statistically significant (t_3 = 3.037, t_7 = 3.286, t_{10} = 5.954, $P < 0.05$) (Figure 3).

PCT

At the beginning of treatment (0 day), there was no statistically significant difference between the two groups in term of PCT (t_0 = 0.178, $P > 0.05$). At 3, 7 and 10-day after treatment, the levels of PCT in treatment group were lower than those of control group, and the differences were statistically significant (t_3 = 2.831, t_7 = 3.452, t_{10} = 3.180, $P < 0.05$) (Figure 4).

Table 1 Comparison of basic characteristics of the two groups ($\bar{x}$ ± *s*)

Variables		Treatment group (*n* = 34)	Control group (*n* = 35)	χ^2/ *t* value	*P* value
Male/female (*n*)		23/11	20/15	0.81	0.37
Age (years)		47.8±15.5	48.2±13.1	0.11	0.91
APACHE Ⅱ (score)		22.9±4.4	21.4±4.8	1.28	0.22
Past history [*n* (%)]	Hypertension	7 (20.6)	5 (14.3)	0.48	0.49
	Glycuresis	3 (8.8)	4 (11.4)	-	1.00
Primary lesion (*n*)	Lung	14	12	0.87	0. 83
	Enterocoelia	8	11		
	Urinary system	2	3		
	Others	10	9		
Mortality in 28 days [*n* (%)]		5 (14.7)	8 (22.9)	0.75	0.39
Stay in ICU (days)		11.5±2.9	13.8±2.6	3.52	<0.001

Notes: ICU: intensive care unit, APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ.

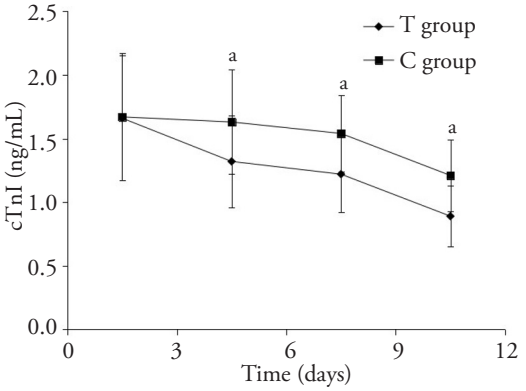

Figure 2 Comparison of cardiac troponin Ⅰ between treatment group and control group

All patients in two groups received conventional cluster treatment. The patients in treatment group additional received Xuebijing injection, 50 mL Xuebijing injection dissolved in 100 mL 0.9% sodium chloride injection was administered by intravenous infusion, 2 times/day, 10 days. The patients in control group additional received the same amount of 0.9% sodium chloride injection. Compared with control group, $^{a}P < 0.05$.

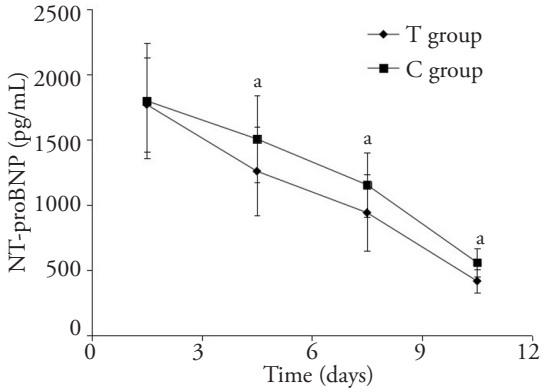

Figure 3 Comparison of N-terminal proB-type natriuretic peptide between treatment group and control group

All patients in two groups received conventional cluster treatment. The patients in treatment group additional received Xuebijing injection, 50 mL Xuebijing injection dissolved in 100 mL 0.9% sodium chloride injection was administered by intravenous infusion, 2 times/day, 10 days. The patients in control group additional received the same amount of 0.9% sodium chloride injection. Compared with control group, $^{a}P < 0.05$.

DISCUSSION

In this study, we investigated the effect of Xuebijing Injection on myocardial injury in patients with sepsis in terms of cTnI, NT-proBNP, PCT, ICU length of stay, and mortality in 28 days. cTnI is a structural protein on striated muscle, and only exists in myocardial cells. It can influence the activity of atpase through binding to calcium ions to regulate interaction of actin and myosin, and induce myocardial contraction and relaxation. B-type natriuretic peptide (BNP) is a neuropeptide hormone secreted by ventricular myocytes, with role of promote sodium, diuresis and expand blood vessels. When ventricular myocytes endure stretch, proBNP is rapidly released into the blood, and cleaved into same molar amount of biologically active BNP and inactive NTproBNP.[9] PCT is a glycoprotein, which is very low in healthy human blood, so it is hardly detected. PCT is an ideal indicator of inflammation, which is the best marker for clinical diagnosis of sepsis.[10,11] PCT significantly increases in severe bacterial infections, while it does not increase during local infection, viral infection, chronic non-specific inflammation, cancer fever or autoimmune disease. Comparison with other inflammatory markers.

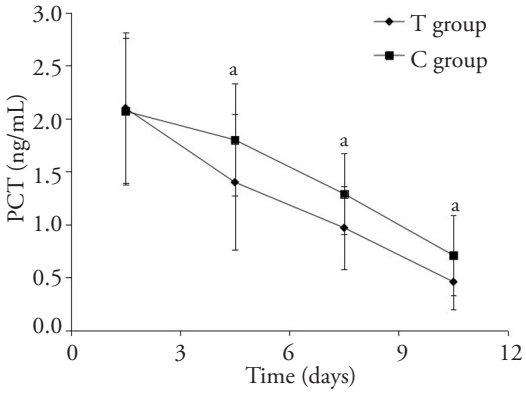

Figure 4 Comparison of procalcitonin between treatment group and control group

All patients in two groups received conventional cluster treatment. The patients in treatment group additional received Xuebijing injection, 50 mL Xuebijing injection dissolved in 100 mL 0.9% sodium chloride injection was administered by intravenous infusion, 2 times/day, 10 days. The patients in control group additional received the same amount of 0.9% sodium chloride injection. Compared with control group, $^{a}P < 0.05$.

Clinical studies suggest that Xuebijing injection had effects of antagonizing endotoxin, adjusting immune response, antagonizing inflammatory cytokines, improving microcirculation and protecting endothelial cells.[12] In this study, at 3, 7 and 10-day after treatment, the levels of cTnI, NT-proBNP and PCT in treatment group improved better than those of control group, and the differences were statistically significant ($P < 0.05$), and the change trends of three markers were similar. Those results illustrated Xuebijing injection had a protective effect on septic myocardial injury. At the same time, it could improve prognosis in patients with sepsis. In addition, the length of stay in ICU of treatment group was shorter than that of control group, and the difference was statistically significant. In conclusion, Xuebijing injection improved prognosis in patients with sepsis.

An important limitation is that this study was a two-center controlled trial study, so a multicenter controlled trial is needed to further confirm the effects of Xuebijing injection in septic myocardial injury. In addition, this study is a preliminary study, it is necessary to extend the time of observation for accurately evaluate the effects of Xuebijing injection in future research.

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