

# Clinical effect of Changweishu on gastrointestinal dysfunction in patients with sepsis

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## Abstract

**Objective:** To investigate Changweishu's clinical effect on gastrointestinal dysfunction in patients with sepsis.

**Methods:** Fifty patients with gastrointestinal dysfunction and sepsis were randomly divided into treatment and control groups. The control group patients received routine Western medicine treatments (meropenem, noradrenaline, glutamine glue, *Bifidobacterium lactis* triple-strain tablet), and the treatment group patients received routine Western medicine treatment combined with Changweishu. Treatments in both groups lasted 7 days. Changes in APACHE II score, gastrointestinal dysfunction score, serum levels of diamine oxidase (DAO), D-lactic acid, inflammatory factors (tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, and high-mobility group box 1 (HMGB-1)), and the incidence of multiple organ dysfunction syndrome (MODS) and mortality were observed.

**Results:** After treatment, APACHE II score, gastrointestinal dysfunction score, and DAO, D-lactic acid, TNF- $\alpha$ , IL-6, and HMGB-1 levels decreased significantly in both groups, but the decrease was more significant in the treatment group than in the control group. The incidence of MODS and mortality were significantly lower in the treatment group than in the control group.

**Conclusion:** The addition of Changweishu to routine Western treatments can improve gastrointestinal function in patients with sepsis and gastrointestinal dysfunction, as well as decreasing the incidence of MODS and mortality and improving patient prognosis.

## Keywords

Changweishu, sepsis, gastrointestinal dysfunction, tumor necrosis factor A, interleukin-6, high mobility group protein 1, diamine oxidase, D-lactic acid

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## Introduction

Sepsis is a fatal organ dysfunction caused by the host response to infection. Sepsis is common in patients in intensive care and is the leading cause of death, with a high mortality rate.<sup>1</sup> The annual incidence of severe sepsis worldwide is more than 18 million, with an annual increase in rate of 1% to 5% and mortality of at least 25%.<sup>2</sup> Research has revealed that “the gut is not only the target organ of sepsis, but also the exciting organ of injuries”; damage to gastrointestinal function enables intestinal bacteria and endotoxins to travel into the blood circulation through the mesenteric lymph nodes, inducing a systemic inflammatory response and evoking multiple organ dysfunction.<sup>3</sup> Protecting the gastrointestinal tract is therefore a key goal in the prevention and treatment of sepsis.<sup>3,4</sup> Western medicine treatments for gastrointestinal dysfunction mainly include the prevention and correction of intestinal flora disorders, the administration of prokinetic agents for the gut, and the immediate recovery of intestinal nutrition. However, these treatments do not necessarily have satisfactory therapeutic effects.<sup>5</sup> Traditional Chinese medicine has achieved good results in improving gastrointestinal function in the treatment of sepsis.<sup>5,6</sup> This study aimed to investigate the clinical effect of Changweishu on gastrointestinal dysfunction in patients with sepsis, and to observe its effects on tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, high-mobility group box 1 (HMGB-1), diamine oxidase (DAO), and D-lactic acid.

## Methods

This study was conducted in accordance with the Declaration of Helsinki and with the approval of the Ethics Committee of Hebei Provincial Hospital of Traditional Chinese Medicine (Approval number:

20151217-1). Written informed consent was obtained from all the participants.

## Patient selection

The diagnostic criteria for sepsis were based on the Third International Consensus Definition of Sepsis and Septic Shock proposed in 2016.<sup>7</sup> The diagnostic criteria for gastrointestinal dysfunction were based on the revised edition (2015) of the 1995 Lushan Conference: Multiple Organ Dysfunction Syndrome Staging and Scoring Criteria for Severity.<sup>8</sup> The inclusion criteria were: patients aged 18 to 60 years; diagnosis of sepsis according to the above criteria; and diagnosis of gastrointestinal dysfunction according to the above criteria. The exclusion criteria were: pregnant or lactating women; damage to the gastrointestinal tract due to trauma, previous gastrointestinal surgery, or primary gastrointestinal disease; and primary severe liver or renal insufficiency. All patients were recruited into the present study under informed consent.

## Source and grouping of cases

Patients with sepsis and gastrointestinal dysfunction who were admitted to the Emergency Department of Hebei Provincial Hospital of Traditional Chinese Medicine from September 2013 to June 2015 were enrolled into this study. According to a random number table, with a two-tailed  $\alpha=0.05$  and power of 75%, we needed to recruit 25 patients per group. Considering a compliance rate of 75%, we therefore asked 50 patients to participate in this study and divided them randomly into two groups: a control group and treatment group ( $n=25$  each).

## Treatments

The treatment regimen in the control group was based on the 2012 Guidelines for Severe Sepsis and Septic Shock,<sup>9</sup> and the

regimen in the treatment group comprised routine Western medicine (meropenem transfusion every 8 hours; Shenzhen Haibin Pharmaceutical Co., Ltd., Shenzhen, China; noradrenaline 0.1 to 2  $\mu\text{g kg/minute}$ ; Shanghai Wellhope Pharmaceutical Co., Ltd., Shanghai, China; glutamine 10 g/day; China Resources Shuanghe Pharmaceutical Co., Ltd., Shijiazhuang City, China) combined with one decoction per day of the prepared traditional Chinese medicine compound, Changweishu (Traditional Chinese Medicine Hebei Lerentang Co., Ltd., Shijiazhuang, Hebei Province, China). The compound was prepared by decocting and concentrating to reduce the volume to 150 mL, and was administered warm twice daily, once in the morning and again in the evening, or via nasal feeding. The composition of Changweishu was as follows: Chuanjun 9 g, Pugongying 20 g, *Ophiopogon japonicus* 15 g, Qingpi 15 g, Chinese Angelica 15 g, Red Paeony Root 12 g, White Paeony Root 12 g, Chuanxiong 9 g, Hairyvein Agrimony 20 g, Kawatsure 6 g, prepared Rhizoma Pinellize without adjuvant 6 g, Trichosanthes Kirilowi 15 g, Garden Burnet Root 20 g, and *Poria cocos* 10 g. Treatments in both groups were continued for 7 days.

### Outcome assessments

The observation indices included acute physiology and chronic health evaluation II (APACHE II) score, gastrointestinal dysfunction score, DAO, D-lactic acid, TNF- $\alpha$ , IL-6, HMGB-1 serum levels, and the incidence of multiple organ dysfunction syndrome (MODS) and mortality. Peripheral venous blood samples were obtained and centrifuged at 3500 rpm at 4°C for 15 minutes, and stored at -80°C until use. DAO, D-lactic acid, TNF- $\alpha$ , IL-6, and HMGB-1 were determined by enzyme linked immunosorbent assay using kits purchased from Hyperheal Biotech (Shanghai, China).

### Statistical methods

Data acquired in this study were analyzed using SPSS for Windows, Version 14.0 (SPSS Inc., Chicago, IL, USA). Results were calculated as mean  $\pm$  standard deviation. Intergroup comparisons were analyzed by one-way ANOVA and intragroup comparisons by repeated-measures ANOVA. Categorical variables were compared using parametric tests (Student's *t*-test and  $\chi^2$  test), and continuous variables were compared using the nonparametric Mann-Whitney test. A two-tailed  $P < 0.05$  was considered to be statistically significant.

## Results

### Patients

All 50 patients completed the study. There were 13 females and 12 males in the control group (mean age  $43.17 \pm 13.68$  years) and 15 female and 10 male patients in the treatment group (mean age  $41.32 \pm 13.57$  years). The average APACHE II scores were  $16.28 \pm 1.93$  and  $15.44 \pm 2.10$  points, respectively. There was no significant difference in baseline data between the two groups. There were no adverse effects in either group.

### Incidence of MODS and mortality in the two groups

The incidence of MODS was 24% in the treatment group and 48% in the control group, and the mortality rate was 12% in the treatment group and 32% in the control group. The incidence of MODS and mortality were both significantly lower in the treatment group compared with the control group ( $P < 0.05$ ) (Table 1).

### Comparison of APACHE II scores between the two groups

APACHE II scores were significantly reduced after treatment in both groups

( $P<0.05$ ), and the reduction was significantly greater in the treatment group compared with the control group ( $P<0.05$ ) (Table 2).

### Comparison of gastrointestinal dysfunction scores between the two groups

Gastrointestinal dysfunction scores were significantly reduced after treatment in both groups ( $P<0.05$ ), and this decrease was more significant in the treatment group compared with the control group ( $P<0.05$ ) (Table 3).

**Table 1.** Incidence of MODS and mortality in control and treatment groups.

Group	Number of cases	Incidence of MODS	MODS mortality rate
Treatment	25	6 (24%)	3 (12%)
Control	25	12 (48%)*	8 (32%)*

MODS, multiple organ dysfunction syndrome. \* $P<0.05$  compared with the control group.

### Comparison of serum DAO and D-lactic acid levels between the two groups

DAO and D-lactic acid levels were significantly reduced after treatment in both groups ( $P<0.05$ ), and the decreases were more significant in the treatment group compared with the control group ( $P<0.05$ ) (Table 4).

### Comparison of serum TNF- $\alpha$ , IL-6, and HMGB-1 levels between the two groups

TNF- $\alpha$ , IL-6, and HMGB-1 serum levels were all significantly reduced after treatment in both groups ( $P<0.05$ ), and the decreases were more significant in the treatment group compared with the control group ( $P<0.05$ ) (Table 5).

## Discussion

A series of physiological and pathological changes occur in the body during sepsis, which can also lead to the occurrence of MODS. Gastrointestinal dysfunction has

**Table 2.** APACHE II scores in the control and treatment groups before and after treatment.

Group	Number of cases	Before treatment	After treatment
Treatment	25	15.44 $\pm$ 2.10	6.80 $\pm$ 1.94* $\Delta$
Control	25	16.28 $\pm$ 1.93	7.92 $\pm$ 1.55*

Values given as mean  $\pm$  standard deviation. \* $P<0.05$  compared with before treatment;  $\Delta P<0.05$  compared with control group after treatment.

**Table 3.** Gastrointestinal dysfunction scores in the control and treatment groups before and after treatment.

Group	Number of cases	Before treatment	After treatment
Treatment	25	1.56 $\pm$ 0.71	0.88 $\pm$ 0.73* $\Delta$
Control	25	1.84 $\pm$ 0.75	1.32 $\pm$ 1.05*

Values given as mean  $\pm$  standard deviation. \* $P<0.05$  compared with before treatment;  $\Delta P<0.05$  compared with control group after treatment.

**Table 4.** Diamine oxidase and D-lactic acid levels in the control and treatment groups before and after treatment.

Group	Number of cases	Timing	DAO	D-lactic acid
Treatment	25	Before treatment	6.70 ± 0.34	4.63 ± 0.11
		After treatment	3.93 ± 0.40* <sup>△</sup>	1.95 ± 0.13* <sup>△</sup>
Control	25	Before treatment	6.67 ± 0.49	4.58 ± 0.16
		After treatment	5.87 ± 0.59*	2.63 ± 0.17*

DAO, diamine oxidase. Values given as mean ± standard deviation. \* $P < 0.05$  compared with before treatment; <sup>△</sup> $P < 0.05$  compared with control group after treatment.

**Table 5.** TNF- $\alpha$ , IL-6, and HMGB-I levels in the control and treatment groups before and after treatment.

Group	Number of cases	Timing	TNF- $\alpha$	IL-6	HMGB-I
Treatment	25	Before treatment	51.25 ± 2.34	13.24 ± 1.78	6.14 ± 1.42
		After treatment	5.38 ± 1.19* <sup>△</sup>	5.54 ± 1.26* <sup>△</sup>	3.69 ± 1.09* <sup>△</sup>
Control	25	Before treatment	50.3 ± 51.58	12.66 ± 1.43	6.23 ± 0.95
		After treatment	10.89 ± 1.65*	7.35 ± 1.85*	5.28 ± 1.64*

TNF- $\alpha$ , tumor necrosis factor; IL-6, interleukin; HMGB-I, high-mobility group box I. Values given as mean ± standard deviation. \* $P < 0.05$  compared with before treatment; <sup>△</sup> $P < 0.05$  compared with control group after treatment.

an adverse effect in patients, resulting in deterioration of their condition. Protecting gastrointestinal function and promoting its recovery are therefore key goals of sepsis treatment, aiming to avoid further disease aggravation and death.<sup>10,11</sup> Traditional Chinese medicine considers that gastrointestinal dysfunction during sepsis is caused by pathogen invasion. Changweishu mainly works by purging fu-organs to eliminate heat, and we examined the use of Changweishu to treat sepsis in the current study. This prescription increases blood circulation, nourishes the yin, and improves gastrointestinal dysfunction of sepsis.<sup>12</sup> Moreover, the components of the prescription can reinforce deficiency, reduce excess, and restore the balance of Qi-blood and Yin-Yang in the body, and promote gastrointestinal function recovery in patients with sepsis.<sup>12-14</sup> The current results showed that the incidence of MODS and mortality were lower in the treatment group than in the

control group, suggesting that Changweishu had a curative effect on gastrointestinal dysfunction in patients with sepsis.

APACHE II scores have been widely used for estimating disease severity and predicting mortality, and are commonly used for intensive care patients worldwide.<sup>15</sup> A higher score indicates a more serious condition and greater risk of death. In the present study, the decrease in APACHE II score was more significant in patients in the treatment group compared with the control group, suggesting that Changweishu had an additional beneficial effect to Western treatments in patients with sepsis and gastrointestinal dysfunction.

DAO and D-lactic acid are sensitive indicators for the early diagnosis of intestinal mucosal damage and permeability.<sup>16</sup> DAO is almost exclusively present in small intestinal mucosal epithelial cells, and damage to the mucosa results in the release of large amounts of DAO into the blood circulation,

thus increasing DAO blood levels. D-lactic acid is mainly derived from fermentation by intestinal microorganisms,<sup>17</sup> while the human body produces virtually no D-lactic acid and cannot metabolize it. Under normal conditions, the intestinal epithelium limits the levels of D-lactic acid in the intestinal cavity; however, blood D-lactic acid levels increase if the intestinal mucosal structure is damaged.<sup>18,19</sup> Changes in levels of DAO and D-lactic acid thus reflect changes in intestinal mucosal damage and permeability. In the present study, serum DAO and D-lactic acid levels were reduced more significantly in patients in the treatment group compared with the control group, suggesting that Changweishu plus Western medicines reduced intestinal mechanical barrier damage more than Western medicines alone.

TNF- $\alpha$  expression is closely related to the severity of sepsis, and IL-6 production, mediated by TNF- $\alpha$ , is also related to the occurrence of the systemic acute inflammatory reaction, and can be used to predict the severity and prognosis of sepsis.<sup>20</sup> As a late inflammatory factor, HMGB1 is also involved in the development of sepsis, and its existence further induces the production of TNF- $\alpha$  and IL-6, promotes the expansion of the inflammatory response, and induces uncontrolled inflammation.<sup>20</sup> The current results indicated that TNF- $\alpha$ , IL-6, and HMGB1 levels were all significantly lower after treatment, and that the reductions were greater in the treatment compared with the control group. The mechanism of improvement of gastrointestinal dysfunction may thus be related to the inhibition of inflammatory factors.

This study was limited by the relatively small number of cases and short observation time.

In summary, Changweishu can improve gastrointestinal function in patients with sepsis and gastrointestinal dysfunction, and can decrease the incidence of MODS and mortality. Changweishu may thus

represent a promising new clinical treatment for patients with gastrointestinal dysfunction and sepsis.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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