

Additional traditional Chinese medicine on gastrointestinal dysfunction in patients with sepsis: A systematic review and meta-analysis

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Abstract: To evaluate the clinical effect and safety of western medicine plus Traditional Chinese medicine for sepsis with gastrointestinal dysfunction. We searched CNKI (January 1979 to June 2014), VIP (January 1989 to June 2014), CBM (1978 to 2014), Wan Fang DATA (January 1990 to June 2014), PubMed (1978 to June 2014), The Cochrane Library (Issue 5, 2014), Embase (1974 to June 2014), and other relevant databases and journals to identify randomized controlled trials (RCTs) on western medicine plus Traditional Chinese medicine versus western medicine only for sepsis with gastrointestinal dysfunction. The methodological quality was assessed and the data was extracted according to the Cochrane Reviewer's Handbook and related methods. Meta-analyses were performed by RevMan 5.1.0 software. Five eligible studies included 278 patients. The results of meta-analyses showed that western medicine plus Traditional Chinese medicine therapy can improve the APACHEII score, the peristaltic sound score and SIRS score, improve abdominal distension, decreased white blood cell count, reduce DAO in sepsis patients with gastrointestinal dysfunction. 3 studies reported adverse reactions, there was no significant difference between two groups. Western medicine plus Traditional Chinese medicine can improve gastrointestinal dysfunction in sepsis.

Keywords Traditional chinese medicine; sepsis; gastrointestinal dysfunction; systematic review.

INTRODUCTION

Sepsis is systemic inflammatory response syndrome (SIRS) because of microbial infection of the body (Cavaillon, 2011). The occurrence of it is due to a variety of injury caused by the release of inflammatory mediators or ischemia reperfusion injury, which can destroy intestinal mucosal barrier function, induce to the translocation of bacteria, endotoxin and various kinds of metabolites, as result of the enterogenous bacteremia, eventually lead to or exacerbate sepsis and MODS. Thus the cost of hospitalization and mortality increase greatly. How to prevent and cure function barrier of gastrointestinal damage, and improve the gastrointestinal function as soon as possible become an important content of study on prevention and treatment of sepsis. In china, during the clinical treatment of sepsis, oral Chinese medicine, enema with TCM, acupuncture, acupoint application and other traditional methods are applied to treat gastrointestinal dysfunction of sepsis and certain effect have been obtained. This research aims at the Systematic Review and meta-analysis of the safety and efficacy of Traditional Chinese medicine for gastrointestinal dysfunction in patients with sepsis, which is based on literature and provides a reference for the clinical application.

MATERIALS AND METHODS

The object of study Meet the diagnostic criteria for sepsis

(Critically, 2007), and in accordance with the diagnostic criteria of intestinal dysfunction (Bone, 1992; Wang *et al*, 1995; Zhang *et al*, 2004).

Intervention The control group received routine treatment in accordance with the' guidelines for the treatment of sepsis in SSC' (Delliger *et al*, 2008) for gastrointestinal dysfunction, such as enteral nutrition support, PPI to decrease gastric acid and gastric mucosal protection, increasing of the beneficial intestinal flora, promoting gastric dynamics, treatment group: combined with TCM based on the treatment in control group.

Exclusion criteria

The object of research is not gastrointestinal dysfunction in patients with sepsis, self-controlled study, comparative study of the pure western medicine intervention, non randomized controlled studies and inappropriate statistical methods of literature; pharmacological experiment, expert review and summary etc.

Evaluation index

Gastrointestinal dysfunction score, SIRS score, APACHEII score, bowel sound score, CRP, PCT, LPS, HMGB1, TNF-a, IL-10, DAO, white blood cell, serum albumin, Plasma diamine oxidas, intestinal dysfunction recovery time, hospitalization survival rate, 28 day survival rate, adverse events and safety index.

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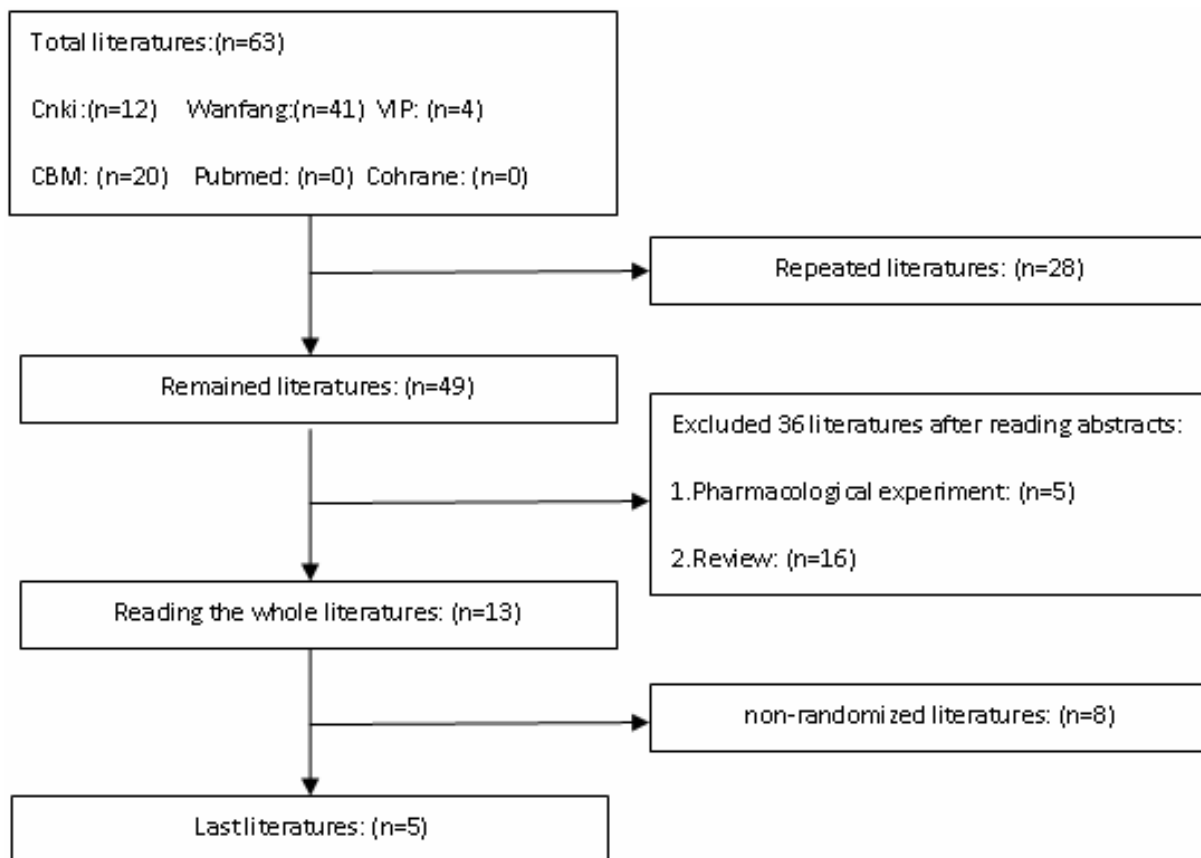


Fig.1: The main characteristics of the included studies

Search strategy

Searching database including CNKI (CNKI, 1979.01 to 2014.06), Chinese science and technology journal database (VIP, 1989.01~2014.06), Chinese biomedical literature database disc (CBM, 1978~2014), the Chinese biomedical literature database (sinomed), Wanfang database (1990.01~2014.06), PubMed (1978~2014.06), The Cochrane Library (Issue 5, 2014), and Embase (1974~2014.06). Chinese search strategies: topic=sepsis, gastrointestinal dysfunction, English search strategies: Title/Abstract=sepsis, intestinal dysfunction etc. retrieval strategy can be seen in Retrieval strategy.

Searching <Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care>, <Journal of Emergency in Traditional Chinese Medicine> and other related magazines manually, and tracking references, search of grey literature.

Document selection. Two researchers search literatures independently, and read the title and abstract, for full-text retrieval and evaluation to documents which meet the inclusion and exclusion criteria, decide through consulting experts when different opinion.

Study quality assessment. According to the evaluation standard (Higgins. 2011) of Cochrane Reviewer's

Handbook 5.1.0 (Higgins. 2011), assessing the quality of every RCT from allocation sequence, allocation concealment, blind method, data loss and intentional analysis. Each item is divided into 'yes', 'no', 'unclear'. 3 grades in judgment. 'Yes' refers to the method described clearly and correctly, or data integrity, or no selective reporting bias and other biases, indicating the possibility of bias is low, 'no' refers to the improper use of methods, or use of allocation concealment, or incomplete data, or the existence of selective reporting bias and other biases, indicating the possibility of bias high; 'unclear' means not described in this paper, the situation is unknown, show that the bias degree of probability is not clear. Deciding through discussion or consultation from the third when different opinion.

Data extraction. Formulating of document information extraction table' and 'assessment of methodological quality table' (two excel working table). One researcher extract and input data, the other one check. Data extraction including study type, patient characteristics, treatment method the measurement results etc. All items (Higgins, 2011) in the quality assessment tool for the Cochrane method on another worksheet. The extraction of the information obtained from the other two researchers will be checked carefully and decided by the third one when different opinion.

Table 1: The evaluation index

First author and year of publication	Number of patient T/C	Sex male/female	Age (year)	Treatment of TCM	Drug combination	w-up	Evaluation index	Side effects
Shi Bian (Shi, 2012)	28/30	T: 21/7 C: 27/3	T: 47.59±3.23 C: 46.48±2.84	Xiaotantongfu free decoction, oral, 40g/time, 2 times / day	Treat infections nutritional support, conventional treatment in accordance with the guide of SSC in sepsis treatment, treatment of gastrointestinal function injury: Mosapride Citrate Tablets + Famotidine For Injection +Bifido bacterium triple viable capsule	7□	Gastrointestinal dysfunction score, SIRS score, improvement of borbo-rygmus , abdominal distension, defecation, and gastrointestinal function	1 cases of the treatment group reduced stool frequency increased, and improved after reduction
YaoKun (Yao, 2012)	30/30	T: 18/12 C: 17/13	T: 50.60±12.96 C: 50.00±14.25	Dachengqi enema, 400ml/ time, 1 times/ day	Refer to “International guideline for management of severe sepsis and septic shock: 2008”	7□	APACHEII score CRP the drop of WBC	A few mild diarrhea, which did not affect the treatment
XieDongping (Xie, 2010)	21/21	T: 16/5 C: 17/4	T: 70.48±8.80 C: 74.81±9.26	Dachengqi enema, 400ml/ time, 1time s/day Electro acupuncture at bilateral Zusanli , 2 / day: Dachengqi, oral,200ml / time, 1 times / day	Refer to “International guideline for management of severe sepsis and septic shock: 2008”, and nutritional support	5□	Gastrointestinal dysfunction score, SIRS score, APACHEII score, CRP, DAO, prealbumin, TNF-a, IL-10,28 day survival rate, survival rate	3 cases of diarrhea, even loose stool watrey, more than5 times / day, which was relieved by discontinuation of oral medicine and enema
Zhang Xiaoxuan (Zhang et al, 2011)	30/30	T: 17/13 C: 11/19	T: 63.47±13.56 C: 62.34±14.41	Wuzhuyu powder and clove powder attached Shenque point, 6 hours per time, 1 times / day	Treatment of infection, fluid resuscitation, vasoactive drug, nutritional support	7□	Gastrointestinal dysfunction score, gurgling sound score	Not mentioned
SuYujie (Su et al, 2013)	29/29	T: 15/14 C: 19/10	T: 61.35±12.32 C: 60.34±13.21	Ruyisan attached Shenque point, 12 hours /times, 1 times / day	Refer to “Surviving Sepsis Campaign: 2003”and”Guideline of integrative medicine for sepsis: 2011	5□	Gastrointestinal dysfunction score, gurgling sound score	Some patients with skin pruritus. Using gold Wanhong cream (hospital preparation to wear the skin before treating, in order to reduce the stimulation of the drugs

T: Treatment group C: Control group

Outcomes and measurements. Using the RevMan 5.1.0 software (Review.2011) provided by Cochrane network to analysis the data, count data using relative risk (RR), measurement data using weighted mean difference (WMD), both with 95% confidence interval (CI). The heterogeneity was measured by χ^2 statistic. Level of significance set for $\alpha=0.1$. Using the fixed effects model for no heterogeneity measurement ($P<0.1$ or $I^2<50\%$) if $P<0.1$ or $I^2>50\%$, by using random effects model for significant heterogeneity. Test results were listed in the forest plot.

RESULT

Study selection

The search retrieved 63 references, among which 28 duplicates were repeated. Of the 49 remaining articles, 36 were excluded based on title and abstract. Full-text was obtained for the remaining 13 articles. Of these, 8 were non-randomized trials.

Characteristics

The clinical situation. 5 RCT included 278 patients,

Table 2: The quality of the included studies

Included studies	Stochastic method	Allocation concealment	Blind method	Intentional analysis	Quality grade
Hi Bian 2012 (Shi, 2012)	Random seed	Y	Double-blind	Y	B
Yao Kun 2005 (Yao, 2012)	Random figure	N	N	Y	C
Xie Dongping 2010 (Xie, 2010)	Simple random	Y	N	Y	C
Zhang Xiaoxuan 2011 (Zhang <i>et al</i> , 2011)	Random figure	N	N	N	C
Su Yujie 2013 Su <i>et al</i> , 2011 (Su <i>et al</i> . 2013)	Random figure	N	N	N	C

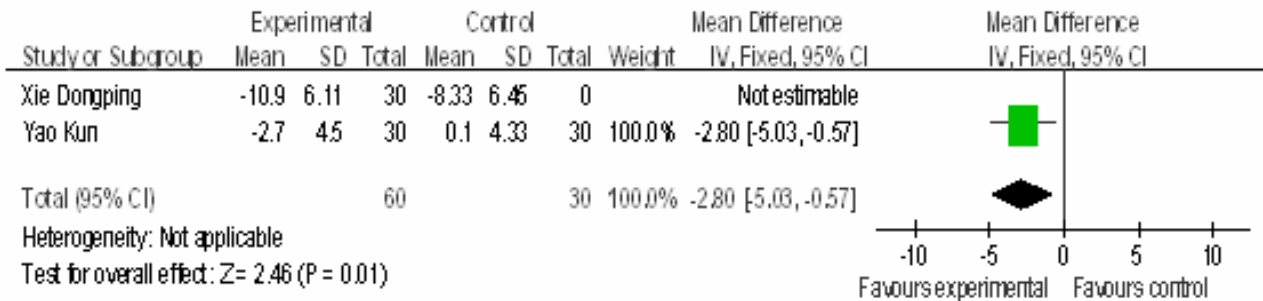


Fig. 2: Chinese medicine intervention effect on sepsis and gastrointestinal dysfunction in patients with APAC- HEII score

including 198 cases of male (71.22%), 80 cases of female (28.78%); It is 17-84 years old, The primary diseases were multiple injury¹¹, infection of the respiratory system (Bone *et al*, 1992; Zhao *et al*, 2008; Cavaillon, 2011), digestive system (Zhang *et al*, 2011; Shi 2012), urinary system (Zhao *et al*, 2008) and other system (Zhang *et al*, 2011; Shi, 2012; Yao, 2012), abdominal operation (Shi, 2012), two literatures (Xie, 2010; Shi, 2012) did not mention the primary disease. (table 1)

Treatment. IN the 5 RCT, control group with conventional western medicine treatment, referred to the guidelines for treatment of sepsis and gastrointestinal dysfunction therapy. Treatment group were treated by TCM on regular conventional western medicine, Xiaotantongfu free decoction (Shi, 2012), oral, 40g/ time, 2 times / day, for 7 days; Dachengqi (Xie, 2010; Yao, 2012) enema, 400ml/ time, 1 times/day, for 7 days; Electro acupuncture at bilateral Zusanli (Xie, 2010), 2/ day, for 5 days; Dachengqi (Xie, 2010), oral, 200ml /time, 1 times / day, for 5 days; Wuzhuyu powder and clove powder attached Shenque point (Zhang *et al*, 2011), 6 hours per time, 1 times / day, for 7 days; Ruyisan attached Shenque point (Su *et al*,2013), 12 hours /times,1 times/ day, for 5 days.

The evaluation index (table 1). The literature were evaluated by gastrointestinal dysfunction score referred to 3 (Xie, 2010; Zhang *et al*, 2011; Shi, 2012), by APACHEII score referred to 2 (Xie, 2010; Yao, 2012), by gurgling sound score referred to 2 (Zhang *et al*, 2011; Su

et al, 2013), by SIRS score referred to 2 (Xie, 2010; Shi, 2012), by CRP referred to 2 (Xie, 2010; Yao, 2012), by the improvement of borborygmus, abdominal distension, defecation, and gastrointestinal function referred to 1 (Shi, 2012) by the improvement of gastrointestinal dysfunction score referred to 1(Su *et al*, 2013). by the drop of WBC referred to 1 (Yao,2012), by DAO, prealbumin, TNF-a , IL-10, 28 day survival rate, survival rate, mortality referred to 1(Xie,2010) .

Article quality

Therapeutic evaluation

APACHEII score. There were 2 studies (Xie, 2010; Yao, 2012) on the basis of APACHEII score changing before and after the treatment. Result had no statistical heterogeneity (P=0.99, I²=0%), and used fixed effects model for Meta analysis. The results showed: Conventional western medicine and traditional Chinese medicine intervention can make the APACHEII scores of gastrointestinal dysfunction in patients with sepsis decreased significantly [RR=-2.59, 95%CI (-4.42, -0.76), P=0.005] (fig. 2).

CRP. There were 2 studies (Xie, 2010; Yao, 2012) on the basis of CRP changing before and after the treatment. Result had no statistical heterogeneity (P=0.39, I²=0%), and used fixed effects model for Meta analysis. The results showed: conventional western medicine and traditional Chinese medicine intervention can make the CRP of gastrointestinal dysfunction in patients with sepsis decreased significantly [RR=-17.5, 95% CI (-31.12-3.89), P=0.01] (fig. 3).

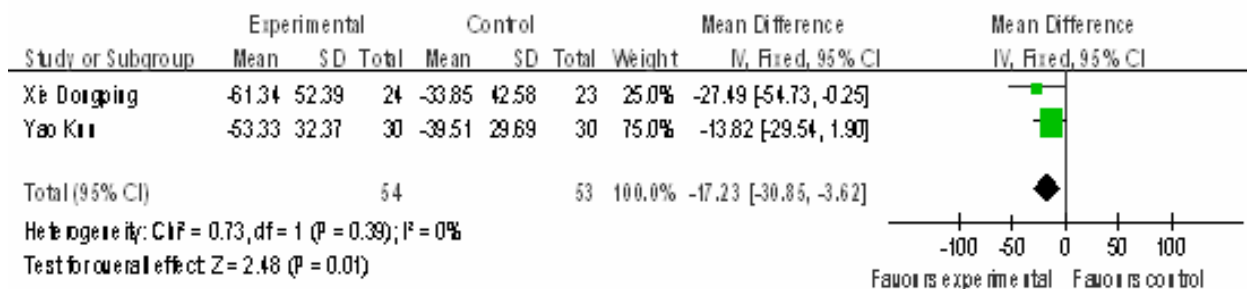


Fig. 3: Chinese medicine intervention effect on sepsis and gastrointestinal dysfunction in patients with CRP

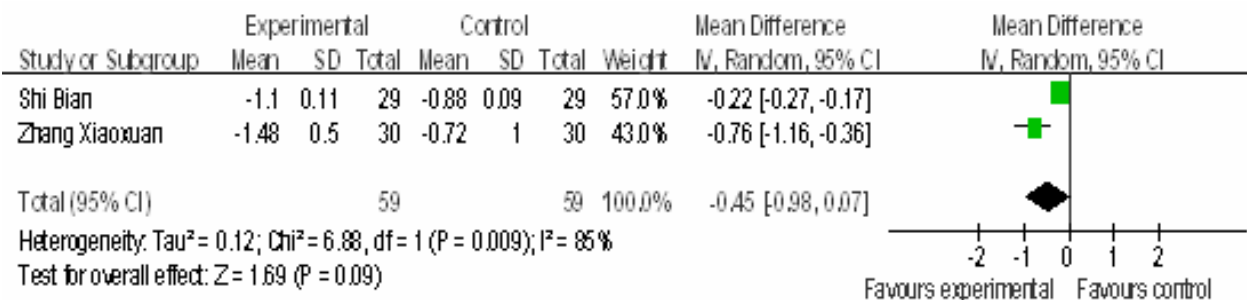


Fig. 4: Chinese medicine intervention effect on sepsis and gastrointestinal dysfunction in patients with Gastrointestinal dysfunction score

Gastrointestinal dysfunction score. There were 4 studies (Xie, 2010; Zhang *et al*, 2011; Shi, 2012; Su *et al*, 2013) on the basis of gastrointestinal dysfunction score changing before and after the treatment. Result had statistical heterogeneity ($P=0.009, I^2=85\%$), and used random effects model for Meta analysis. The results showed: Conventional western medicine and traditional Chinese medicine intervention can make the gastrointestinal dysfunction score of gastrointestinal dysfunction in patients with sepsis decreased significantly. ($RR=-0.45, 95\%CI (-0.98,0.07), P=0.09$) (fig. 4). Xie Dongping (Xie, 2010) treated patients with Dachengqi Tang oraling, enema and bilateral Zusanli acupuncture for 5 days. All patients in the treatment group achieved the purpose of treatment. Intestinal dysfunction score was 0 points. While there were still 6 cases of the control group did not, statistical difference was significant ($p<0.05$). Su Yujie (Su *et al*, 2013) obtained that the treatment group was better than control group by comparing two groups. Four articles results indicated that the gastrointestinal function of Chinese medicine intervention in patients with sepsis improved, but because of the different specific evaluation method, it showed no obvious improvement from taking the first two experiments. Why? It might because that the study was on a relatively small sample, and could not reflect the true situation, or gastrointestinal dysfunction score standard was not accurately to reflect the changes of gastrointestinal function.

Gurgling sound score. There were 2 studies (Zhang *et al*, 2011; Su *et al*, 2013) included. Zhang Xiaoxuan (Zhang *et al*, 2011) treated the control group with routine

method and treated the experimental group with wine-Wu Zhuyu and wine-clove to attach umbilicus for 7 days, experimental group was better than control group ($P<0.05$) while the gurgling sound score of two-group decreased ($P<0.05$). Su Yujie15 treated the experimental group with Ruyi San sticking Shenque acupoint for 5 days, the effect of the treatment group was better than control group ($P<0.05$).

SIRS score. There were 2 studies (Xie, 2010; Shi, 2012) included. Shi Bian11 treated patients with Xiaotantongfufang combined with conventional western medicine, There was no significant difference ($p>0.01$) of SIRS score between two groups, Xiaotantongfu on SIRS score of patients with sepsis were significantly improved. There was significant difference between the two groups ($p<0.01$). Xie Dongping (Xie, 2010) treated patients with Dachengqi Tang oraling, enema and bilateral Zusanli acupuncture, compared with control group, no statistical significance ($P>0.05$).

Others. Shi Bian (Shi, 2012) judged the effectiveness of traditional Chinese medicine therapy through the improvement of gurgling sound, abdominal distension, defecation and gastrointestinal function. Among them, the improvement of gurgling sound, abdominal distension, and gastrointestinal function were more than those in the control group, it had significant difference ($P<0.05$). There were no significant difference of defecation ($P>0.05$). Xie Dongping (Xie, 2010) used DAO, prealbumin, TNF- α , IL-10 as well as clinical symptoms as evaluation index. The results showed that DAO levels of treatment group decreased significantly ($P<0.05$) than

control group, There were no significant difference between the treatment group and the control group at prealbumin, TNF-a and IL-10 ($P>0.05$). Yao Kun (Yao, 2012) compared WBC of treatment group with the control group. The results suggested that WBC of the two groups after treatment were decreased. In treatment group, it was a significant difference before and after treatment. ($P<0.01$) and it was not in the control group.

Overall mortality. Xie Dong Ping (Xie, 2010) mentioned the mortality during hospitalization and mortality of 28 days, the result showed that it was exactly same between two groups. He compared the survival rate of hospitalized patients in the two groups. There were 2 cases died in treatment group and 3 cases in control group, which was no significant difference ($P>0.05$).

Adverse events. Shi Bian (Shi, 2012) mentioned that one patient appeared the increase of defecate frequency, more than 3 times/day. The symptom alleviated after stopping the medicine, He did not indicate the section. Yao Kun (Yao, 2012) observed that a little mild diarrhea. It didn't affect treatment. Xie Dongping (Xie, 2010) used glycerine enema to control group when necessary in intestinal dysfunction. There was no adverse reaction associated with enema. While 3 cases of treatment group with diarrhea, showed yellow loose stools, even for dilute sample, more than 5 times / day. It could be alleviated when stopping oral medicine and enema. The statistical analysis showed there was no significant difference in the incidence of adverse reaction of two groups of patients.

DISCUSSION

In foreign countries, there are a lot of basic and clinical researches of intestinal dysfunction in sepsis, but the overall mortality rate remain high. In Chinese, traditional Chinese medicine has no specific gastrointestinal dysfunction in sepsis diagnosis, "Treatise on Febrile Diseases" is considered to be the earliest monograph on sepsis treatment. The method of TCM such as flowing qi and blood, ascending the clear things, descending the turbid things, adjusting the movement of qi and so on are used in prevention and treatment of sepsis with gastrointestinal dysfunction during modern time.

But because of the restriction of studies' quality and evaluation index, there are still some following problems. The studies included only observed clinical indexes of patients during treatment, without long-term follow-up observation and end events, so the long-term efficacy and safety of evaluation of additional traditional Chinese medicine still can't be assessed. In the actual clinical research of traditional Chinese medicine in the treatment of sepsis with gastrointestinal dysfunction, there is still a lack of systematic and rigorous scientific design and higher level of Evidence of evidence based medicine, which is one of the reasons why the effect of traditional

Chinese medicine has not been accepted better for the international medical community. The further research needs to be particularly concerned about this. Because there is no uniform evaluation standard can reflect the severity of sepsis with gastrointestinal dysfunction accurately, objectively and simply, evaluation standard of diagnosis and evaluation index used in these studies are different, so it is difficult to compare different kinds of TCM treatments. Above all, these factors all can affect the evaluation of the therapeutic effect and safety of TCM in the treatment of sepsis with gastrointestinal dysfunction. But it provides the thought and method may be effective for the treatment of sepsis with gastrointestinal dysfunction and also has laid the foundation for the higher quality study in future.

CONCLUSION

1 Effect of TCM. The meta-analysis of five studies included suggested that additional TCM on gastrointestinal dysfunction in patients with sepsis could improve APACHEII score, gurgling sound score, SIRS score, abdominal distension, decreased WBC and DAO. It had no obvious statistical difference compared with the control group on the intestinal dysfunction score, improvement of stool frequency, prealbumin, TNF-a, IL-10. There are 3 research (Critically. 2007; Zhao *et al.* 2008; Cavaillon. 2011) reported adverse reactions, there was no significant difference between two groups.

The quality of included studies

Methodological value of the article the 5 studies included were all randomized controlled trials, Four studies (Zhang *et al.*, 2011; Shi, 2012; Yao, 2012; Su *et al.*, 2013) were grouped according to the random number table method. One study (Xie, 2010) was according to the simple random method, did not illustrate the specific method of grouping. Two studies (Shi, 2012; Xie, 2010) studies described allocation concealment. One research (Shi, 2012) mentioned blind method. All studies did not mention the follow-up, we cannot rule out selection bias, measurement bias, implement bias and so on.

Choice of evaluation index There is still no unified evaluation index for gastrointestinal dysfunction in sepsis. Every experiment had taken different evaluation index, which caused the difficulty and uncertainty of systemic review.

The results of this study indicate that additional Traditional Chinese medicine can play a positive role in improving the APACHEII score, the peristaltic sound score, SIRS score, abdominal distension, decreasing white blood cell, reducing DAO of sepsis patients with gastrointestinal dysfunction.

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