Gastrointestinal Medicine

ORIGINAL RESEARCH

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A Clinical Research on The Intervention of *Xuanfei Tongfu Decoction* on Gastrointestinal Dysfunction in Patients With Acute Lung Injury

Yakun Wang [1], Limei Yu [1], Yun Chen [1], Meiqi Zhang [1], Zhenfei Yu [1,*]

[1.] Department of Critical Care Medicine, Hangzhou Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, 310044 Hangzhou, Zhejiang, China

Keywords

Acute lung injury

Gastrointestinal function

Xuanfei Tongfu Decoction

Inflammatory index

* **Correspondence**

Zhenfei Yu

Department of Critical Care Medicine, Hangzhou Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, 310044 Hangzhou, Zhejiang, China

E-mail: wangyakun_wyk@163.com

Received: 5 March 2025

Revised: 2 April 2025

Accepted: 30 April 2025

Published: 26 May 2025

Gastrointestinal Medicine 2025; 1(1): 28-35.

Abstract

Objective: To explore the curative effect of *Xuanfei Tongfu Decoction* on gastrointestinal dysfunction in patients with acute lung injury based on the theory of "lung and large intestine are in harmony with each other". **Methods:** Fifty patients with acute lung injury treated with *Xuanfei Tongfu Decoction* combined with lactulose oral liquid in our hospital were collected as the combination group, and 50 patients of the same type treated with only lactulose oral liquid in the same department during the same period were collected as the control group. The clinical symptom scores of the two groups were compared, and the changes of gastrointestinal hormones and inflammation indexes were sorted out according to the case information, and their safety was analyzed. **Results:** After 7 days of treatment, the clinical symptom scores of both groups decreased, and the combined group was lower than the control group ($p < 0.05$). Serum motilin, gastrin and vasoactive intestinal peptide levels were increased in both groups ($p < 0.05$), while tumor necrosis factor, interleukin-6 and IL-1β levels were decreased in both groups ($p < 0.05$), and the changes in combination group were greater than those in control group ($p < 0.05$). There was no statistical significance in the occurrence of adverse reactions between the two groups ($p < 0.05$). **Conclusion:** Based on the theory of "lung and large intestine are in harmony with each other", *Xuanfei Tongfu Decoction* may have a better effect on gastrointestinal dysfunction in patients with acute lung injury, which can improve gastrointestinal function and reduce inflammatory response, and has good safety.

1 Introduction

Acute lung injury (ALI) is a clinically common respiratory system disease, directly or indirectly resulting from severe infection, trauma, etc., which causes damage to alveolar epithelial and capillary endothelial cells in the lungs, and diffuse interstitial and alveolar edema, characterized by acute respiratory dysfunction [1,2]. For Western medicine, measures such as mechanical ventilation and drug interventions with statins are primarily adopted to limit disease progression, which can reduce the incidence of inflammation at the endothelial and epithelial barriers and exert antibacterial effects [3,4]. However, the current treatment methods may have limited effects on preventing complications associated with ALI. Gastrointestinal complications, in particular, can easily lead to systemic inflammatory responses and multiple organ failure, resulting in a high mortality rate in clinical settings [5,6]. According to traditional Chinese medicine (TCM), the pathogenesis of ALI is often characterized by a deficiency of vital energy in the body and the presence of pathogenic factors, with "heat" and "toxin" as the basis of the disease, and "phlegm" and "stasis" as important pathological products and pathogenic factors [7]. The theory that "the lung and the large intestine are internally and externally related" is a classic concept in TCM, suggesting that lung deficiency may lead to disordered function of purification and dispersal, and the large intestine may affect the transduction ability. There is a close physiological and pathological connection between the two, which is of guiding importance for the treatment of lung and intestinal diseases [6]. *Xuanfei Tongfu Decoction* is based on TCM theory and combines the methods of lung dispersing and purgation to treat ALI, which can effectively improve the respiratory function of patients, protect the gastrointestinal mucosa, and alleviate clinical symptoms [8]. On this basis, this study compared the intervention effects of different treatment methods on patients with ALI, and explored the intervention effect of *Xuanfei Tongfu Decoction* based on the theory of "the lung and the large intestine are internally and externally related" on gastrointestinal dysfunction in such patients, providing reference and guidance for the clinical treatment.

2 Materials and methods

2.1 Case selection

(1) Diagnostic criteria: Western medicine diagnostic criteria: The diagnostic criteria for ALI were referenced from the "Guidelines for the diagnosis and treatment of acute lung injury/acute respiratory distress syndrome" [9]; TCM diagnostic criteria: The diagnostic criteria for the syndrome of lung heat and intestinal excess were established based on the "Diagnostic and Therapeutic Criteria for TCM Diseases and Syndromes" [10]. (2) Inclusion criteria: patients who met both Western and TCM diagnostic criteria; Chest CT or X-ray showing bilateral pulmonary infiltrates; age between 20 and 95 years. (3) Exclusion criteria: patients who have taken anticoagulant or antifibrinolytic drugs within the past 14 days; allergy to the study medications; diabetes or galactose intolerance; abdominal pain caused by gastrointestinal perforation, appendicitis, or intestinal obstruction; severe local or systemic infection; other malignant tumors; immune dysfunction; coagulation disorders; severe dysfunction of vital organs such as heart, liver, or kidneys; mental disorders with poor treatment compliance; incomplete clinical data; pregnant or breastfeeding women.

2.2 General information

50 patients with acute lung injury treated with *Xuanfei Tongfu Decoction* combined with lactulose oral liquid in our hospital from June 2021 to June 2023 were collected as the combination group, and 50 patients of the same type treated with only lactulose oral liquid in the same department during the same period were

included as the control group. There were no statistically significant differences between the two groups in terms of gender, age, body temperature, respiration, heart rate, blood pressure, and the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (P/F ratio) ($p > 0.05$, Table 1). This study was approved by the Medical Ethics Committee, and all patients signed informed consent forms.

Table 1 Comparison of general information between the two groups.

Group	Case	Sex (case)		Age (years old)	Body temperature (℃)	Breath (time/score)	Heart rate (time/score)	Blood pressure (mmHg)		*p*/*F* Ratio
		Male	Female					Systolic pressure	Diastolic pressure	
Combination group	50	27	23	63.14 ± 17.04	38.80 (38.20-38.80)	29.00 (21.50-30.00)	119.28 ± 20.84	103.00 (91.50-153.50)	62.00 (53.00-67.50)	209.00 (179.75-212.25)
Control group	50	21	29	63.70 ± 15.95	38.80 (38.10-38.80)	28.50 (23.50-32.00)	120.58 ± 16.21	103.00 (92.00-155.00)	62.00 (50.00-69.00)	209.00 (180.00-219.00)
$\chi^2/t/Z$		1.442		0.170	0.582	0.336	0.348	0.371	0.062	0.312
p		0.230		0.866	0.561	0.737	0.729	0.711	0.950	0.755

2.3 Treatment methods

The control group adopted sole treatment with lactulose oral solution (Hunan Kelun Pharmaceutical Co., Ltd., National medicine permission number (NMPN): H20093523, specification: 100 mL: 66.7 g) (15 mL/dose, twice daily at 8 a.m. and 8 p.m). The combination group received *Xuanfei Tongfu Decoction* in addition to lactulose. The formula for *Xuanfei Tongfu Decoction* included: 12 g *Radix Platycodi*, 12 g *Semen Armeniacae Amarum*, 10 g *Radix Asteris*, 20 g *Fructus Trichosanthis*, 10 g *Fructus Perillae*, 9 g *Fructus Aurantii Immaturus*, 10 g *Mangnolia officinalis*, 12 g *Radix Paeoniae Rubra*, 12 g *Pericarpium Arecae*, and 10 g *Radix et Rhizoma Rhei*. The decoction was prepared by the hospital's pharmacy, packed in 100 mL bags, and administered orally or via nasogastric tube at 100 ml per dose, twice daily at 8 a.m. and 8 p.m. The initial dose was 30-45 mL/day, and the subsequent dose was 15-25 mL/day, once daily. Both groups were treated for 7 days.

2.4 Observational indicators

5 mL of fasting peripheral venous blood was drawn from each patient in the morning, allowed to stand at room temperature for 30-60 min, and then centrifuged at 3000 r/min for 10 min. The serum was separated and stored at -20 ℃ for subsequent testing.

(1) Gastrointestinal hormones: gastrointestinal hormone levels were collected and compared before and 7 days after treatment in both groups. Serum motilin (MTL), gastrin (GAS), and vasoactive intestinal peptide (VIP) levels were measured using an Abbott fully automated biochemical analyzer. (2) Inflammatory markers: inflammatory markers were collected and compared before and 7 days after treatment for both groups. Tumor necrosis factor (TNF-α), interleukin (IL)-6, and IL-1β levels were measured using chemiluminescent immunoassay with reagent kits (Guangzhou Kangrun Biotechnology Co., Ltd). (3) Clinical symptom scores: clinical symptoms were collected before and 7 days after treatment for both groups, and the clinical symptom scores were compared. The efficacy evaluation criteria were based on the TCM syndrome score, which assessed the main symptoms (fever, cough, abundant phlegm, dyspnea, constipation) and secondary symptoms (restlessness, thirst, yellow urine, chest tightness). The symptoms were divided into four levels: normal, mild, moderate, and severe. Main symptoms were scored as 0, 2, 4, and 6 points, while secondary symptoms were scored as 0, 1, 2, and 3 points. (4) Adverse reactions: the incidence of adverse reactions such as nausea, vomiting, and rash during the treatment period was collected and compared between the two groups.

2.5 Statistical methods

SPSS 20.0 software was applied for statistical analyses. The enumeration data were described using n (%), which were compared by χ^2 test. Continuous variables were analyzed for normality using the Kruskal-Wallis test. Data meeting the normal distribution were expressed as mean ± standard deviation. Group comparisons were performed using the independent samples t-test. Data not meeting the normal distribution were expressed as quartile method [P50 (P25, P75)] and compared using the Mann-Whitney U test. A bilateral p-value < 0.05 was considered statistically significant.

3 Results

3.1 Comparison of clinical symptom scores before and after treatment in two groups

After 7 d of treatment, the clinical symptom scores in both groups decreased (p < 0.05), and the combined group was lower than the control group (p < 0.05, Table 2).

Table 2 Comparison of clinical symptom scores between two groups before and after treatment (score, P50 (P25, P75)).

Group	Case	Before treatment	After treatment
Combination group	50	32.00 (28.00-36.00)	10.00 (8.00-12.00) *[a]
Control group	50	32.78 ± 6.19	12.00 (10.00-17.25) *
Z		0.787	2.170
p		0.431	0.030

Note: compared to before treatment: *p < 0.05; compared with the control group after treatment: [a]p < 0.05.

3.2 Comparison of gastrointestinal hormone levels before and after treatment in two groups

Prior to treatment, the levels of MTL, GAS, and VIP between the two groups displayed no evident difference (p > 0.05). Following 7 days of treatment, the levels of MTL, GAS, and VIP in both groups increased (p < 0.05), and were higher in the combination group than the control group (p < 0.05, Table 3).

Table 3 Comparison of gastrointestinal hormones between two groups before and after treatment (P50 (P25, P75)).

Group	Case	MTL (ng/L)		GAS (ng/L)		VIP (pmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	50	280.33 (210.55-301.52)	366.01 (353.23-376.28) *	30.33 (28.19-34.55)	42.07 (40.07-48.19) *	61.54 (54.61-75.22)	96.35 (80.83-99.51) *
Control group	50	280.33 (266.01-308.95)	357.78 (347.33-367.30) *	31.74 (28.19-34.55)	40.57 (37.55-42.07) *	61.54 (52.50-75.22)	83.14 ± 17.76 *
Z		1.168	2.444	0.293	2.104	0.435	2.386
p		0.243	0.015	0.769	0.035	0.663	0.017

Note: compared to before treatment: * p < 0.05.

3.3 Comparison of inflammatory indexes before and after treatment in two groups

Before treatment, there was no statistically significant difference in the levels of TNF-α, IL-6, and IL-1β between the two groups ($p > 0.05$). 7 days of treatment resulted in downregulation of TNF-α, IL-6, and IL-1β in both groups ($p < 0.05$), and the downregulation was more notable in the combination group than the control group ($p < 0.05$, Table 4).

Table 4 Comparison of inflammatory markers between two groups before and after treatment (ng/L, P50 (P25, P75)).

Group	Case	TNF-α		IL-6		IL-1β	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combination group	50	40.44 (38.42-40.44)	17.57 (14.88-17.59) *	38.02 ± 2.71	16.34 (15.29-17.54) *	3.08 (2.88-3.56)	1.23 (1.01-1.34) *
Control group	50	40.44 (38.25-40.44)	17.59 (16.87-17.59) *	38.04 (35.31-40.42)	17.58 ± 3.04 *	2.97 (2.77-3.27)	1.53 ± 0.44 *
Z		0.116	2.185	0.314	2.051	1.721	4.082
P		0.907	0.029	0.753	0.040	0.085	< 0.0001

Note: compared to before treatment: * $p < 0.05$.

3.4 Comparison of adverse reactions between the two groups

The incidence of adverse reactions including nausea, vomiting, and rash in the combination group was lower than that in the control group, and there was no statistically significant difference in the incidence of adverse reactions between the two groups ($p > 0.05$, Table 5).

Table 5 Comparison of two groups of adverse reactions (case).

Group	Case	Nausea	Vomiting	Rash
Combination group	50	2	4	3
Control group	50	5	6	5
χ^2		0.614	0.444	0.136
p		0.433	0.505	0.712

4 Discussion

MTL, GAS, and VIP are important indicators for clinical evaluation of gastrointestinal function, the increase of which indicates improvement in gastrointestinal function [11]. This study suggested that the intervention of *Xuanfei Tongfu Decoction* based on the theory of "the lung and the large intestine are internally and externally related" significantly improved clinical symptoms and increased gastrointestinal hormone levels in patients. Lactulose oral solution is a commonly used medication for treating functional constipation, which can promote the release of gastrointestinal hormones, facilitate the movement of the stomach body and lesser curvature, enhance gastrointestinal motility, and alleviate clinical symptoms related to constipation [12]. In the *Xuanfei Tongfu Decoction*, *Fructus Trichosanthis* moistens the intestines and promotes bowel movements, *Fructus Aurantii Immaturus* eliminates food accumulation and promotes qi movement, and *Fructus Trichosanthis*

also relieves spleen dryness and moistens the body. Many of the herbs in the decoction have the effect of promoting gastrointestinal motility, enhancing the activity of gastrointestinal smooth muscles, and enhancing their contraction and relaxation functions. By regulating the repair of the intestinal mucosal barrier and the secretion of gastrointestinal hormones, the decoction can improve the intestinal microenvironment, thereby reducing the damage to the gastrointestinal mucosa caused by ALI and alleviating clinical symptoms [13,14]. Hence, the *Xuanfei Tongfu Decoction* based on the theory of "the lung and the large intestine are internally and externally related" may help alleviate gastrointestinal dysfunction in ALI patients and improve gastrointestinal function.

Patients with ALI have severe inflammatory reactions, with a large release of inflammatory mediators and cytokines. Damage to the gastrointestinal mucosa and insufficient blood supply can lead to weakened mucosal barrier function and aggravated inflammatory reactions [15]. TNF-α, IL-6, and IL-1β are common clinical indicators for detecting inflammatory reactions, with higher levels indicating more severe inflammatory reactions [16]. This study showed that the intervention with the *Xuanfei Tongfu Decoction* based on the theory of "the lung and the large intestine are internally and externally related" caused significant improvement in the inflammatory response. Lactulose has been shown to inhibit the NADPH oxidase 4 (NOX4)/NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome pathway, thereby reducing inflammation and improving gut microbiota structure in rats. Therefore, it is speculated that lactulose oral solution may have a similar anti-inflammatory mechanism in ALI patients, reducing inflammatory responses [17]. In the *Xuanfei Tongfu Decoction*, *Mangnolia* officinalis and *Semen Armeniacae Amarum* disperse the lung and relieve cough, while *Fructus Aurantii Immaturus* and *Fructus Trichosanthis* promote qi movement, sooth the chest, and clear heat and phlegm. These herbs together in the decoction can clear heat, unblock the bowl, cool the blood, resolve stasis, exert anti-inflammatory and antibacterial properties, and regulate the immune system, which can also inhibit the synthesis of inflammatory factors such as TNF-α and IL-6, reduce systemic inflammation, effectively improve ALI symptoms and aid in lung function recovery [18]. Therefore, the *Xuanfei Tongfu Decoction* based on the theory of "the lung and the large intestine are internally and externally related" may help reduce the inflammatory response in ALI patients.

Moreover, compared with monotherapy of lactulose oral solution, the combination of *Xuanfei Tongfu Decoction* and lactulose oral solution did not increase the risk of adverse reactions such as nausea, vomiting, or rash, indicating good safety. However, due to limited retrospective time and sample size in this study, the results may not be representative of all patients. Further trials and exploration are needed to verify the intervention effects of the *Xuanfei Tongfu Decoction* based on the theory of "the lung and the large intestine are internally and externally related" and to refine the relevant theoretical research.

In conclusion, *Xuanfei Tongfu Decoction* based on the theory of "the lung and the large intestine are internally and externally related" may have a better therapeutic effect on gastrointestinal dysfunction in ALI patients, which can improve gastrointestinal function and reduce inflammatory responses with a safe profile.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: Y.W.; Data curation: L.Y.; Formal analysis: Y.C.; Methodology: M.Z.; Writing – original draft: L.Y. and Y.C.; Writing – review and editing: Y.W. and Z.Y.; All authors have read and agreed to the published version of manuscript.

Ethics Approval and Consent to Participate

This study was approved by Medical Ethics Committee, and patients were informed and agreed.

Funding

This work was supported by the Hangzhou Medical and Health Science and Technology Program (No. A20210223); Zhejiang Province Traditional Chinese Medicine Science and Technology Project (No.2023ZL523).

Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Supplementary Materials

Not applicable.

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