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Effects of *Shen Cao* Granules on Chemotherapy-Induced Thrombocytopenia in Gastrointestinal Cancer Patients: A Randomized Controlled Trial

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Abstract

Background: To observe clinical effects of Shen Cao granules on thrombocytopenia in patients with gastrointestinal cancer undergoing chemotherapy. **Patients and Methods:** Patients under a FOLFIRI chemotherapy regimen (n = 92) were randomly divided into study and control groups (n = 46 for each group) and were given 10 g of Shen Cao granules and a placebo, respectively, once daily on chemotherapy treatment days. Platelet counts were measured every other day and any adverse reaction recorded during the study and at follow-up. **Results:** The incidence of thrombocytopenia (grades II-IV) in the study group was significantly decreased, and the length of hospitalization significantly reduced compared with the control group (11.21 ± 2.46 vs 15.34 ± 3.68 days, $P < .05$). The minimum numbers of post-chemotherapy platelets and the values of platelet counts 21 days after chemotherapy were significantly increased ([100.65 ± 63.16] × 10^9/L vs [60.21 ±37.22] × 10^9/L, $P < .05$; [267.81 ± 81.32] × 10^9/L vs [146.42 ± 70.54] × 10^9/L, $P < .001$), and the duration of thrombocytopenia and treatment with recombinant human interleukin-11 was significantly decreased in the Shen Cao treatment compared with the control group. No serious adverse events were observed. **Conclusions:** Shen Cao granules were effective in decreasing chemotherapy-induced thrombocytopenia, shortened the duration of thrombocytopenia, and reduced the length of hospital stay and costs.

Keywords

Shen Cao granules, cancer chemotherapy, thrombocytopenia

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Introduction

Cancer is the leading cause of death in China. It has been estimated that in China about 4 292 000 patients with invasive cancer were newly diagnosed and that about 2 814 000 were expected to die from cancer in 2015.[1] The bone marrow of patients undergoing chemotherapy is usually affected by chemotherapeutic drugs producing thrombocytopenia, referred to as abnormally low platelet counts in the circulating blood.[2,3] It usually takes time for cancer patients with severe thrombocytopenia to recover platelet levels to normal values, which may necessitate a reduction of chemotherapeutic drug doses or even discontinuation of chemotherapy. Severe thrombocytopenia may also increase the risk of life-threatening bleeding and complications due to infections.

Platelet transfusion is the standard treatment for thrombocytopenia, but it is associated with risks such as alloimmunization, transmission of infection, transfusion reactions, and platelet refractoriness.[4] Interleukin-11 (IL-11) is a member of a family of human growth factors and has been demonstrated to improve platelet recovery for chemotherapy-induced thrombocytopenia.[5,6] IL-11 treatment increases peripheral platelet counts, which is associated with increased bone marrow cellularity, increased cell numbers, and the cycling of immature erythroid and myeloid precursors.[7] Studies have demonstrated that recombinant human

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IL-11 (rhIL-11) could increase the blood platelet count, reduce the duration of thrombocytopenia, and promote recovery of severe thrombocytopenia to normal platelet levels.[8,9] However, the procedure of IL-11 treatment is costly, and its clinical application is also limited due to its side effects such as fatigue, myalgia/arthralgia, ache, headache, palpitation, edema, fever or anaphylaxis, infection, and lung injury.[10-12] Therefore, seeking an efficient and cost-effective approach has become one of the most important topics in clinical research into effective treatments for cancer.

Traditional Chinese medicine (TCM) has a long history in treating malignancies and holds that cancer patient experience dysfunction of viscera, deficiency of vital energy (*qi*), hyperactivity of pathogen, and weakness of body resistibility, which can cause a pale complexion, general fatigue, lassitude, dizziness, tinnitus, pale tongue with whitish fur, and a deep and weak pulse. Chemotherapeutic drugs are believed to be offensive against healthy *qi* and their toxicity can harm viscera functions, resulting in malfunctions of the stomach, spleen, and kidney. Compared with the hot nature and saliva-inhibiting properties of chemotherapeutic drugs, TCM puts a high premium on reinforcing and adjusting *qi*, promoting saliva secretion and nourishing the blood.[13]

Shen Cao granules were self-developed in our department and were designed for nourishing *Yin*, heat-clearance, hemostasis, reinforcing the essence of marrow and vital energy. They have been used in our clinic for the past 10 years.

In the current randomized controlled trial study, patients with gastrointestinal cancer were treated with FOLFIRI chemotherapy with Shen Cao granules or placebo. The clinical effects of Shen Cao granules in decreasing chemotherapy-induced thrombocytopenia, shortening the duration of thrombocytopenia, reducing the length of stay in hospital, and costs were compared with the placebo.

Subjects and Methods

Subjects

The randomized controlled trial was conducted in the Department of Oncology, Yantai Hospital of Chinese Medicine in Shandong Province, from January 2013 to August 2015. Patients were enrolled if they (1) were diagnosed with a solid malignant gastrointestinal tumor by histopathological or cytological examination; (2) needed the same regimen of chemotherapy for at least 2 cycles; (3) were aged 18 to 70 years; (4) had an Eastern Cooperative Oncology Group score of 0 to 2; (5) had normal functions of bone marrow, heart, liver, kidney, and lungs; (6) had ≥3 months of expected survival time; and (7) could provide informed consent and maintain compliance with follow-up investigations. Patients were excluded if they were pregnant, had other diseases such as active tuberculosis, serious infectious disease, mental disorders, uncontrolled hematological system diseases, or active brain metastasis. As a result, a total of 92 patients (55 men and 37 women) were recruited and randomly allocated into the treatment group (Shen Cao group) and a control group (n = 46 for each) without specific TCM diagnoses. Randomization was done by an independent researcher via random numbers generated in Microsoft Excel. To make sure that the risk of bias remained low, patients were registered in the database by means of a patient ID code so that assessors were blinded. Both the study staff and the patients were blinded to which group the patients were allocated. A Chinese medicine, termed "Shen Cao" in Chinese in the form of granules, and a corresponding placebo was given to patients in the treatment and control groups, respectively. Informed written consent was obtained from each patient and the study was approved by the Department of Science and Technology, Shandong Province. The trial was registered in Chinese Clinical Trial Registry (No. 2014GSF119019).

Treatments

Chemotherapy. All participants in both the treatment and control groups were given the same dose of the FOLFIRI chemotherapy regimen for 2 cycles (14 days per cycle), consisting of irinotecan (80 mg/m^2 dissolved in 250 mL of 0.9% NaCl intravenous [IV] for 90 minutes on the first day), leucovorin (200 mg in 0.9% 250 mL NaCl IV for 120 minutes on the first and second days), and fluorouracil (400 mg/m^2 IV on the first day and then 1200 mg/m^2 for 46-48 hours per cycle every 2 weeks).

TCM Formula. A package of 10 g Shen Cao granules (Beijing Tcmages Pharmaceutical Co, Ltd, Beijing, China) and placebo granules (Beijing Tcmages Pharmaceutical Co, Ltd), with identical appearance and packing as Shen Cao granules, was provided once daily and after being dissolved in 100-mL hot water, taken orally half an hour after breakfast from the first day until the end of chemotherapy. The company used the infrared fingerprint technology in Chinese Materia Medica and applied it in the study of the "full composition" processing of 598 commonly used types of herbal granules. They resolved the problem of equivalence of effect between herbal granules and herbal decoctions when decocted singly or together. The company used an innovative full composition industrial process that combines traditional herb processing methods with the most advanced granule extraction, concentration, and drying techniques. The full composition granules have maintained the taste and efficacy of Chinese herbal medicine. It is applied to the dispensing of TCM clinic prescription and adapts to the traditional TCM syndrome differentiation and treatment. Beijing

Tcmages Pharmaceutical Co Ltd established an integrated set of production process and quality standards for TCM herbal granules, established the first quality management system within the industry, and formulated quality standards for unprocessed Chinese Materia Medica, for materia medica prepared for decoction, and for herbal granules. It has also identified the most appropriate way for each materia medica to be cooked, either individually or together, so as to ensure that its granule extract is equivalent in effect to that when used in a combined decoction.

Toxic pollutants have been controlled according to the International Organization for Standardization.[14]

Shen Cao granules were composed of the herbs *Adenophora stricta* (Shashen), *Dendrobium nobile* (Shihu), *Agrimonia pilosa* (Xianhecao), *Lithospermum erythrorhizon* (Zicao), *Eclipta prostrata* (Hanliancao), *Lycium chinense* (Gouqi), and *Carapax Testudinis* (Guiban) in a ratio of 1:1:2:1:1:1:1. There were no known interactions of any of the Shen Cao ingredients versus the 3-FOLFIRI chemotherapies.

Placebo granules were made from a mixture of dextrine and caramel.

rhIL-11 was subcutaneously injected once daily at a dose of 1.5 mg to patients whose platelet counts were $<50 \times 10^9$/L and stopped when platelet levels reached $\geq 75 \times 10^9$/L. Platelet transfusion was performed when the platelet count was $<20 \times 10^9$/L and granulocyte colony-stimulating factor (CSF) was used for leukopenia. Granulocyte-macrophage CSF was prohibited for leukopenia.

Measurement and Assessment

The degrees of thrombocytopenia were subdivided into grade 0 (platelet count $\geq 100 \times 10^9$/L), grade I ($75\text{-}99 \times 10^9$/L), grade II ($50\text{-}74 \times 10^9$/L), grade III ($25\text{-}49 \times 10^9$/L), and grade IV ($<25 \times 10^9$/L) according to the acute/subacute reaction criteria for anticancer drugs defined by the National Cancer Institute.[15] Comparison of the case numbers of thrombocytopenia, minimum values of platelets, platelet counts on the 21st day after chemotherapy, duration of thrombocytopenia, days required for grade IV platelet recovery to $\geq 75 \times 10^9$/L, application of rhIL-11, hospitalization, and the total cost for increasing platelet counts between Shen Cao granules and placebo was assessed after 2 cycles of FOLFIRI chemotherapy. Follow-up started from the beginning of chemotherapy until the end of the study or patient death. The final follow-up was conducted during August 2015.

Statistical Analysis

All statistical analyses were conducted using SPSS Statistics for Windows (Version 17.0; SPSS Inc, Chicago, IL). All descriptive data were tested for a normal distribution prior to analysis and were presented as mean ± standard deviation. Categorical variables were expressed as numbers and were compared by using the χ^2 or χ^2 trend test or Fisher's exact test. All results were considered statistically significant if $P < .05$.

Results

Patient Characteristics

Initially, 121 patients were screened from which 44 cases were excluded. After allocation, 3 patients in the Shen Cao group and 4 patients in the control group were excluded during follow-up. Finally, a total of 92 patients (55 men and 37 women) were analyzed (46 patients in each group; Figure 1). As shown in Table 1, no significant differences were found between the 2 groups in terms of sex, height, weight, age, Karnofsky Performance Score,[16] type and TNM stage of cancer, minimum platelet count, or baseline degree of thrombocytopenia as well as previous therapies ($P > .05$).

Table 2 shows the alterations in the degree of thrombocytopenia after 2 cycles of chemotherapy between the study group and the control group, analyzed by a rank sum test. The case numbers of grades II, III, and IV thrombocytopenia were significantly fewer in the study group compared with the control group ($P < .05$, $P < .001$, and $P < .001$, respectively). The number of patients with lower grade (grades 0 and I) thrombocytopenia in the study group was significantly higher than in the control group ($P < .05$).

In addition, the minimum platelet count after 2 cycles of chemotherapy and the platelet count on day 21 of chemotherapy in the study group was significantly higher than in the control group ($[100.65 \pm 63.16] \times 10^9$/L vs $[60.21 \pm 37.22] \times 10^9$/L, $P < .05$; $[267.81 \pm 81.32] \times 10^9$/L vs $[146.42 \pm 70.54] \times 10^9$/L, $P < .001$, respectively). Approximately 57.6% and 84.2% of increased minimum platelet counts and platelet counts on day 21 after chemotherapy were observed in the Shen Cao group compared with the control group.

The changes in duration of each degree of thrombocytopenia after 2 cycles of chemotherapy in the control and study groups are shown in Table 3. Significantly decreased durations of platelet counts at grades I to IV were observed in the Shen Cao group compared with the placebo group (1.6 ± 1.8 vs 5.8 ± 4.2, $P < .001$; 0.8 ± 1.4 vs 3.6 ± 4.6, $P < .001$; 1.2 ± 0.8 vs 5.8 ± 2.3, $P < .001$; 5.6 ± 4.2 vs 10.4 ± 2.5, $P < .001$, respectively).

Furthermore, it took a significantly shorter time for grade IV platelet counts to recover to $\geq 75 \times 10^9$/L in the study group compared with the control group (5.5 ± 3.5 days vs 9.0 ± 1.3 days, $P < .05$). As expected, the average hospitalization period of patients in the Shen Cao group was significantly shorter than the control group (11.21 ± 2.46 days vs 15.34 ± 3.68 days, $P < .05$). The longest hospital

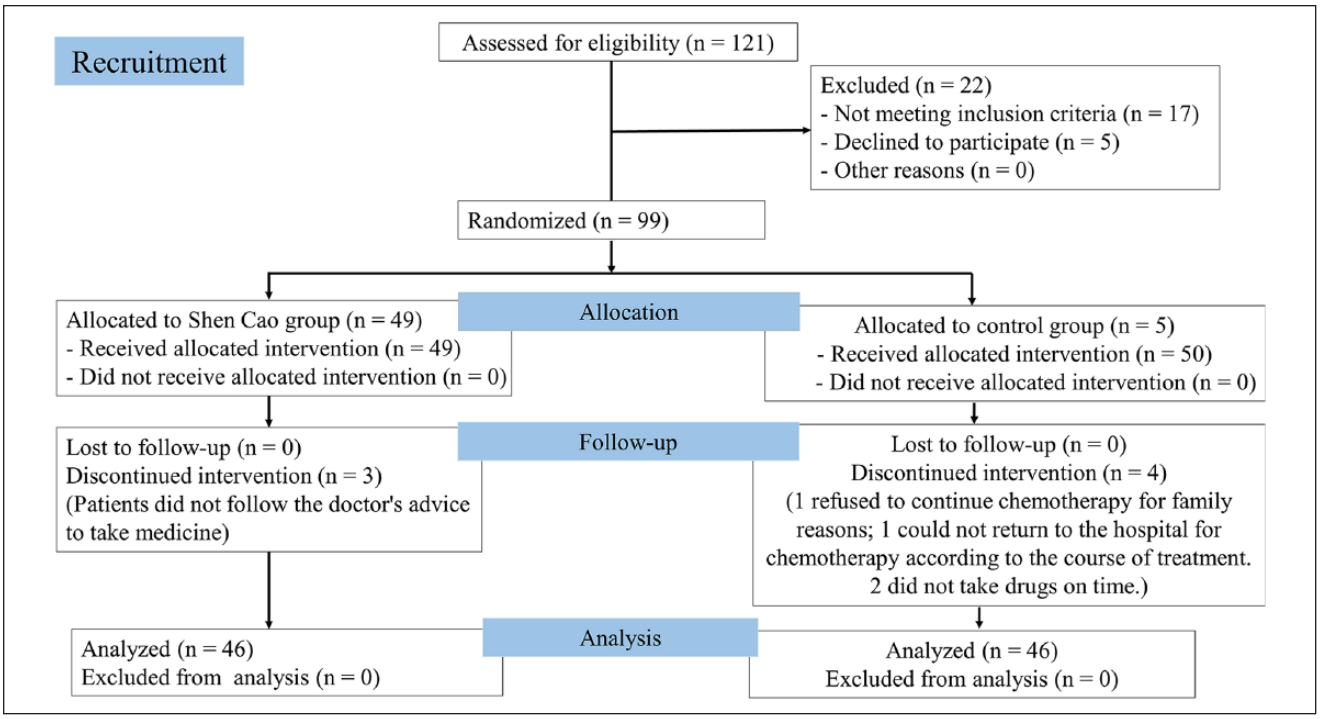

Figure 1. Flowchart of the present study.

stays in the study and control groups were 15 and 23 days, respectively.

Finally, the treatment with rhIL-11 for grade III and IV thrombocytopenia and the average cost for each patient in the study and control groups was calculated and compared. There were 5 cases who were treated with rhIL-11 in the Shen Cao group compared with 18 cases in the control group. The total cost for IL-11 and the average cost for each individual in the study group (4910.0 and 226.7 RMB, respectively) compared with the control group (50 420.0 and 1095.7 RMB, respectively) were 9.74% (4910.0/50420.0) and 20.1% (226.7/1.095.7) times reduced. Moreover, as shown in Table 4, adverse reactions, including bone marrow depression, nausea and vomiting, diarrhea, mucositis, hepatic, and renal dysfunction, were observed in both the study and control groups. However, there were significantly fewer cases of nonserious adverse events beside renal dysfunction in the Shen Cao group compared with the control group, suggesting that Shen Cao granule could effectively decrease side effects during the period of chemotherapy and follow-up. No serious adverse events were reported during the study period.

Discussion

A low platelet count (thrombocytopenia) is a common symptom and a primary concern for cancer patients receiving chemotherapy. Chemotherapeutic drugs not only destroy cancer cells, but also damage normal bone marrow hematopoietic stem cells and the hematopoietic-inductive microenvironment, resulting in bone marrow depression, thrombocytopenia, and neutropenia. Although granulocyte-macrophage CSF effectively controls neutropenia, there are no definitive treatments for thrombocytopenia caused by anticancer drugs such as paraplatin, gemcitabine, and taxinol.[17,18] When patients develop thrombocytopenia, the dose of chemotherapeutic drugs may have to be reduced and the time schedule of chemotherapy may have to be shortened or even ceased.[19,20] Current treatments for thrombocytopenia include platelet transfusion, plasmapheresis, cytokines, and the combination of TCM and Western medicine.[21]

In our study, rhIL-11 was given to patients only when their platelet levels were $<50 \times 10^9$/L and treatment continued until the platelet count reached $\geq 75 \times 10^9$/L. There were obviously fewer cases of thrombocytopenia in the Shen Cao group who received injections of rhIL-11 compared with placebo group (5 vs 18). There were lower costs for rhIL-11 treatment and average costs for hospitalization in the Shen Cao group. Moreover, the patients in the Shen Cao group exhibited significantly decreased cases of grades II to IV thrombocytopenia, an increased minimum platelet count after 2 cycles of chemotherapy, and on day 21 after chemotherapy, a decreased duration of grades I to IV platelet count, suggesting that Shen Cao granules could efficiently improve chemotherapy-induced thrombocytopenia in patients with gastrointestinal cancer.

Table 1. Patient Characteristics in the Study and Control Group.

	Control Group (n = 46)	Study Group (n = 46)	*P*
Male	28	27	1.000
Female	18	19	
Height (cm)	167.33 ± 6.21	168.45 ± 5.37	.357
Weight (kg)	60.31 ± 4.86	59.22 ± 4.68	.276
Age (years)	61.29 ± 3.33	62.37 ± 4.01	.163
KPS	80 ± 5.03	80 ± 6.12	1.000
Minimum platelet count	(138.69 ± 43.17) × 10^9/L	(142.01 ± 57.32) × 10^9/L	.7544
Cancer type			.803
Gastric cancer	23	24	
Intestinal cancer	23	22	
Colon	15	15	
Rectal	8	7	
TNM stage (intestinal cancer)			.647
I	0	0	
II	5	6	
III	13	12	
IV	5	4	
TNM stage (gastric cancer)			.586
I	2	3	
II	15	16	
III	6	5	
IV	0	0	
Thrombocytopenia			.335
Grade 0	42	39	
Grade I	4	7	-
Grade II	0	0	-
Grade III	0	0	-
Grade IV	0	0	
Previous therapies			.908
Operation	27	29	
Radiotherapy	10	9	
Systemic therapy lines	25	24	
Chemotherapy	21	20	
Chemotherapy plus antibodies	4	4	
TKI	0	0	
Postoperative adjuvant therapies	27	29	
Palliative treatments	19	17	

Abbreviations: KPS, Karnofsky Performance Score; TKI, tyrosine kinase inhibitor.

Table 2. Comparison of Thrombocytopenia Grades Between the Study and Control Groups.

Group	n	Grade 0	Grade I	Grade II	Grade III	Grade IV
Control	46	2	15	11	10	8
Study	46	10	24	7	4	1
P		<.05	<.05	<.05	<.001	<.001

From the perspective of TCM, the pathogenesis of cancer includes *qi*-stagnancy and blood stasis, phlegmatic hygrosis, intrinsic noxious heat, and weakness of healthy *qi*. Chemotherapeutic drugs could worsen the deficiency of body fluid (*Yin* fluid) due to their noxious heat effects and the dysfunction of viscera during treatment. Patients undergoing chemotherapy often experience mouth sores, discomfort of the main 5 internal organs (heart, liver, spleen, lungs, and

Table 3. Comparison of Thrombocytopenia Duration (Days) Between the Study and Control Groups.

Group	Grade I	Grade II	Grade III	Grade IV
Control	5.8 ± 4.2	3.6 ± 4.6	5.8 ± 2.3	10.4 ± 2.5
Study	1.6 ± 1.8	0.8 ± 1.4	1.2 ± 0.8	5.6 ± 4.2
P	<.001	<.001	<.001	<.001

Table 4. Comparison of Adverse Events Between the Study Group and the Control Group.

Nonserious Adverse Effects	Control Group (n = 46)	Study Group (n = 46)	*P*
Bone marrow depression	44	36	.0269
Nausea and Vomiting	35	11	<.001
Diarrhea	23	9	.0041
Mucositis	9	1	.0152
Hepatic dysfunction	25	13	.0193
Renal dysfunction	16	7	.0527

kidneys), and red tongue with reduced coating, which is considered to be caused by the deficiency of *Yin* fluid and blood stasis in cancer patients. Therefore, the principal of TCM to treat cancer patients receiving chemotherapy is based on nourishing *Yin* fluid and enriching the blood. The Shen Cao granules included the following functions: *Adenophora stricta, Dendrobium nobile*, and *Lycium chinense* could nourish *Yin* and generate body fluid[22,23]; *Carapax Testudinis* has the function of replenishing vital essence and marrow[24]; *Agrimonia pilosa*,[25] *Lithospermum erythrorhizon*,[26] and *Eclipta prostrata*[27,28] could enrich blood and staunch bleeding (Supplemental Table 1). A combination of these herbs in appropriate proportions is expected to tonify the liver and kidney, nourish body fluid, and minimize noxious heat.

It should be noted that in our study Shen Cao was combined with other standard methods of treating thrombocytopenia, such as rhIL-11, platelet transfusion, and granulocyte CSF, at severely reduced platelet levels. Further study is needed to address whether Shen Cao granules alone will be effective in treating chemotherapy-induced thrombocytopenia. Limitations of the present study have been the small sample size, which can be enlarged for further studies, which also will include the effect of Shen Cao granules on other chemotherapy-induced thrombocytopenias. In addition, basic research will be carried out to further optimize the drug formula and dosage.

In summary, the current study demonstrated that Shen Cao granules were effective in decreasing the incidence of thrombocytopenia in gastrointestinal cancer patients, shortened hospital stays, and were an economical method for treating chemotherapy-induced thrombocytopenia. There was a lower incidence of adverse effects in the Shen Cao treatment group compared with the placebo group, and no serious adverse events during the study and follow-up period were detected. Shen Cao granules should be investigated further in clinics for the prevention and treatment of chemotherapy-induced thrombocytopenia.

Authors' Note

The trial was registered in Chinese Clinical Trial Registry (No. 2014GSF119019).

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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