

Reducing postsurgical exudate in breast cancer patients by using San Huang decoction to ameliorate inflammatory status: a prospective clinical trial

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ABSTRACT

Background Reducing inflammatory factors in wound exudate is a promising treatment approach for healing wounds in postsurgical breast cancer patients. Traditional Chinese Medicine (TCM) treatments have been shown to be beneficial and safe for optimal regulation of oxidative stress during the postoperative period. In the present clinical trial, we evaluated the effectiveness of a promising Chinese herbal formula, San Huang decoction [SHD (Radix astragali, Radix et rhizoma rhei, and Rhizoma curcuma longa, 3:1:1; supplemental Table 1)], on wound inflammatory response after mastectomy.

Methods The study randomized 30 patients with breast cancer who fulfilled the inclusion and exclusion criteria to either a treatment ($n = 15$) or a control group ($n = 15$). Patients in the treatment group received liquid SHD, taken twice daily with or without food. Treatment was given for 1 day before surgery and for 7 days postoperatively. Participants in the control group received a placebo on the same schedule as the treatment group. Outcomes measured in every subject included clinical TCM and wound inflammation symptom scores, daily and total amounts of drainage fluid, and levels of inflammatory factors in the exudate [tumour necrosis factor α (TNF- α), interleukins 6 (IL-6), 8 (IL-8), and 2R (IL-2R), human C-reactive protein (CRP)] at 2 hours and on days 1, 3, and 7 postoperatively.

Results The total amount of drainage fluid over 7 days was significantly lower in the treatment group (572.20 ± 93.95 mL) than in the control group (700.40 ± 107.38 mL). The TCM symptom score was also lower in treatment group (day 7: 1.87 ± 0.83 vs. 4.80 ± 3.61 , $p = 0.049$), as was the inflammatory symptom score (day 7: 0.67 ± 0.72 vs. 3.67 ± 2.50 , $p = 0.001$). Levels of TNF- α , IL-6, IL-8, IL-2R, and CRP in drainage fluid were significantly lower with SHD treatment.

Conclusions Perioperative treatment with SHD effectively lessened postoperative exudate and ameliorated inflammatory symptoms in patients who underwent surgery for breast cancer.

Key Words Breast cancer surgery, complementary medicine, exudate, flaps, inflammation, inflammatory factors, San Huang decoction, Traditional Chinese Medicine, TCM

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INTRODUCTION

Breast cancer is one of the most common malignant tumours in women and poses a serious threat to women's health¹. As treatment concepts have changed and advanced, treatments have become more comprehensive, with the removal of cancerous tissue by surgery remaining

one of the most important measures^{1,2}. However, surgery inevitably causes tissue trauma, setting off the body's inflammatory, proliferation, and repair processes, which can lead to complications such as wound pain, skin flap ischemia, necrosis, and subcutaneous effusion.

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Recent research has suggested that, by causing tissue damage, surgery triggers immune cells to produce inflammatory cytokines such as interleukins 2 (IL-2), 6 (IL-6), and 8 (IL-8), tumour necrosis factor α (TNF- α), and C-reactive protein (CRP), among others^{3,4}. Inflammation has been found to possibly be related to tumour metastasis: for instance, inflammatory cells are more abundant in invasive metastases of breast cancer⁴. Surgery induces an acute inflammatory response that could negatively affect clinical outcomes in breast cancer⁵. Elevated inflammatory mediators including vascular endothelial growth factor C, TNF- α , and IL-1 β are associated with increased rates of breast cancer recurrence and metastasis after surgery⁶. Inflammatory biomarkers and scores might be important prognostic indicators in breast cancer during the perioperative period.

How to reduce inflammation in patients after surgery for breast cancer has been a question in both Western and Traditional Chinese medicine (TCM)^{7,8}. Appropriate measures have included reasonable post-operative exercise⁹ to reduce body mass index, diminish inflammation, and improve prognosis¹⁰. A previous study showed that STAT3 inhibitors act to decrease the inflammation in breast cancer cells treated with wound exudate¹¹. Optimal regulation of the inflammatory state caused by surgery, with a view to improving the control of tumour metastasis, might be an effective approach. A unique advantage of TCM is that it addresses multiple targets and has multilevel regulatory activity⁸.

After breast surgery, the surgical wound commonly produces exudate, in that the wound in the breast tissue elicits an inflammatory wound-healing response, with subcutaneous accumulation of serous fluid¹². Decreasing the exudate shortens the extubation time after surgery for breast cancer patients and has a beneficial effect on patient quality of life. Analysis of exudates shows that the fluid contains inflammatory factors; classically, inflammation is considered to be the first phase of wound repair¹³. Most exudate research has focused on the association of exudates with increased infection or with effect on cosmesis^{14,15}; little research has considered the potential regulation of the exudate itself to favour control over a microenvironment that promotes oncogenic growth.

San Huang decoction (SHD) is a herbal medicine composed of Radix astragali, Radix et rhizoma rhei, and Rhizoma curcuma longa. This traditional TCM formula might have a suppressive effect on tumour growth. In an earlier study¹⁶, we found that SHD was likely to inhibit the growth of breast cancer cells by regulating inflammatory factor and Aurora kinase pathways. Radix astragali has been proved to be able to lower the level of inflammatory factors such as IL-6 *in vivo*¹⁷. In other studies, Rhizoma curcuma longa was also seen to potentially have an anti-cancer effect, and Radix et rhizoma rhei was shown to regulate inflammatory factors in breast cancer patients^{18–20}.

The present study focused on clinical observations of the effect of SHD on the inflammatory response in the wound left by breast cancer surgery, as demonstrated by changes in the wound during the perioperative period. The aim of the study was to evaluate the effect of SHD

on inflammatory status and recovery during the period after breast cancer surgery.

METHODS

Study Protocol

The research protocol was approved by the institutional review board of Human Research in the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine. From January 2015 to December 2015, patients from the Breast Disease Department of Jiangsu Provincial Hospital of TCM were identified, screened, and enrolled in the study, after informed consent had been obtained. Participants were recruited from a population of patients undergoing routine follow-up at the clinic during the perioperative period.

Inclusion Criteria

Patients were invited to participate in the study if they fulfilled both of the following inclusion criteria:

- a diagnosis of breast cancer with planned modified radical surgery, and
- an age of 30–70 years.

Informed consent documents were explained to potential participants, who signed them after reaching a clear understanding of their contents.

Exclusion Criteria

Patients were excluded if

- they were undergoing surgery other than modified radical surgery,
- they had clinical stage IV breast cancer (according to the TNM staging system²¹), a serious disease of the internal organs, or
- they were using oral anticoagulation or anti-inflammatory medications such as aspirin and steroids.

If patients wanted to withdraw consent, if they failed to adhere to the research protocol, or if serious adverse events occurred, the individual's participation was suspended, and withdrawal was recorded.

Sample Size

Based on an earlier study, we had baseline data from case report forms for Chinese breast cancer patients²². Although that study was published in a Chinese journal, we consider it to be the most relevant data. To account for a potential drop-out rate of up to 20% at 7 days, we planned to randomize 35 patients.

Randomization and Blinding

The inclusion and exclusion criteria were met by 30 patients, who were then randomly and equally allocated to group A (experimental) or group B (control). Randomization was accomplished through an interactive Web-based response system managed by Endpoint Clinical (San Francisco, CA, U.S.A.), which allows for unblinding if necessary for patient safety. All patients, study site personnel, raters, and contract research organization staff were blinded to group assignment.

Treatment Technique

Preparation of the SHD Extract

Radix astragali (TCM name: *Huang qi*), 30 g; Radix et rhizoma rhei (TCM name: *Da huang*), 10 g; and Rhizoma curcuma longa (TCM name: *Jiang huang*), 10 g, were acquired from Jiangsu Province Hospital of TCM (Nanjing, P.R.C.). The total weight of the crude herbs was 50 g. The herbs were blended in 500 mL of double-distilled water (1:10, weight to volume) for 1 hour and heated to 100°C for 2 hours. After continuous boiling for 2 hours, the remainder of the sample was concentrated to 200 mL. This final 200 mL decoction was taken orally in two divided doses (equating to 200 mL SHD daily for an average adult with a body weight of 60 kg). The preparation steps were completed using a tisane device in Jiangsu Province Hospital.

Perioperative Procedures and SHD Administration

All patients received an intravenous drip of cefazolin sodium (2.0 g) for 30 minutes before surgery, a continued intravenous drip of cefazolin sodium (2.0 g) for 1 hour during surgery, and an intravenous drip of omeprazole (42.6 mg) to suppress stomach acid. The total amount of fluid infused was 1500 mL, which included dextrose (750 mL), salt (750 mL), vitamin C (2.0 g), vitamin B complex (0.2 g), and potassium chloride (1.0 g). A liquid diet was required for 6 hours after surgery, and normal oral intake was permitted by 12 hours after surgery.

Participants in the treatment group received 200 mL liquid SHD, which was taken orally as a split dose twice daily, in the morning and afternoon. Participants in the control group received a placebo (200 mL sodium chloride liquid) on the same schedule. Both liquids were supplied in non-transparent plastic bags. Because all patients drank their liquid from plastic bags with the same appearance, they were partly blinded to their group allocation (the liquids had different tastes). Otherwise, all patients received the same basic treatments. The SHD or placebo was given for 1 day preoperatively and 7 days postoperatively.

Collection of Baseline Values

Age, lymph node metastasis, and TNM stage were collected from the postoperative pathology report. Baseline levels of inflammatory factors were evaluated in serum samples collected from each subject 1 day before surgery.

Collection of Wound Drainage Fluid

Underarm drainage fluid (5 mL) was collected at 2 hours and on days 1, 3, and 7 postoperatively. The drainage bag was changed after each collection. Each fluid sample was centrifuged, and the supernatant was collected and stored at -80°C to allow for standardized examination.

Outcome Measures

Primary Outcomes

The amount of fluid drained on days 1, 3, and 7 postoperatively and the total volume of fluid drained over the period of 7 days were recorded.

Clinical symptom scores were based on *chi* deficiency and blood stasis according to the four diagnoses in TCM

(based on the GB/T 16751.2-1997 standard) and the TCM symptom scale, as tested by the Delphi method. The criteria used (moderately pale complexion; fatigue; shortness of breath; slow speech, low voice; spontaneous sweating; palpitations; insomnia; dizziness; chest tightness and chest pain; local and sharp pain, such as caused by a needle; a partial purplish spot on the surgical flap; numbness; a purplish or pale gray tongue, with teeth marks or ecchymosis; sinking-fine or stringy-acerbic pulse) could potentially total to 16 points (positivity for an item scored 1 point, and negativity for an item scored 0 points).

Wound inflammation symptoms took into account the surgical wound, the condition of the skin flap, and the inflammatory status of the drainage fluid^{23,24} (Table 1).

Secondary Outcomes

Inflammatory factors in the drainage fluid were measured. Levels of TNF- α , IL-6, IL-8, IL-2R, and CRP were evaluated using ELISA kits. The ELISA kits for TNF- α , IL-6, IL-8, and IL-2R were purchased from Beijing 4A Biotech Co., Ltd. (Beijing, P.R.C.: catalog nos. 20150109, 20150110, 20150111, and 20150113 respectively). The ELISA kit for CRP was purchased from Shanghai Mibio Bio-tech Co., Ltd. (Shanghai, P.R.C.: catalog no. ml 027874).

ELISA

To each well in a 96-well plate, 300 μ L of wash buffer was added for 30 seconds before aspiration. Then, 50 μ L of assay buffer (1 \times) was added to each well. In the blank wells, 50 μ L double-diluted standard and 50 μ L standard diluent were added in duplicate. In the other wells, 50 μ L sample was added, followed by 50 μ L diluted detection antibody. The plate was then covered with an adhesive strip and incubated at room temperature (18°C–25°C) for 2 hours on a microplate shaker set at 300 rpm. The liquid was then aspirated from each well, and the wells were washed 6 times by filling each well with 300 μ L wash buffer (1 \times). After the final wash, 100 μ L of diluted streptavidin–horseradish peroxidase was added to each well, and the plate was covered with a fresh adhesive strip. The plate was then incubated at room temperature (18°C–25°C) for 45 minutes on a microplate shaker set at 300 rpm. Finally, 100 μ L of substrate solution was added to each well, and the plate was incubated for 5–30 minutes at room temperature, protected against light. Then, 100 μ L of stop solution was added to each well. The color in the well changed from blue to yellow. If the color in the well was green or did not appear uniform, the plate

TABLE 1 Wound inflammation symptom scores

Symptom	Score			
	0	1	2	3
Incision pain score	None	Mild	Moderate	Severe
Degree of incision pain	None	Occasional	Mild	Constant
Flap color	Normal	Reddish	Cerise	Violet
Extent of flap swelling	None	<4 cm ²	4–8 cm ²	>8 cm ²
Flap swelling score	None	Mild	Moderate	Severe
Color of drainage fluid	Yellowy	Reddish	Cerise	Violet

was gently tapped to ensure thorough mixing. Then, within 30 minutes, the optical density was determined using a microplate reader set to 450 nm.

The detection time for ELISA of blood samples (baseline inflammatory factors in serum) was 1 day before surgery. Other ELISA analyses (inflammatory factors in exudate) were performed at 2 hours and on days 1, 3, 7 postoperatively for every subject.

Safety Assessment

To assess treatment safety and risk, adverse events occurring in participants were recorded and analyzed. For risk assessment, the total number of adverse events and the rate of events occurring more than once in the patients were determined. Independent observers who did not participate in this study determined whether a relationship existed between each adverse event and SHD application.

Statistical Analysis

The statistical analyses were performed using the SPSS Statistics software application (version 17.0: SPSS, Chicago, IL, U.S.A.). Continuous variables are expressed as medians with standard deviation. Groups were compared using the *t*-test or Student *t*-test, as appropriate based on the data distribution. Categorical variables are expressed as percentages. Groups were compared using the chi-square or Fisher exact test, as appropriate based on the expected counts. Patient characteristics and history were compared between the groups, and descriptive statistics are used to describe the trial results. The Student *t*-test was applied to compare the scores based on wound inflammation symptoms, the scores based on TCM symptoms, and the scores based on postoperative inflammatory symptoms at every time point in the treatment and control groups. Similar analyses were performed for other outcomes. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Participant Recruitment and Characteristics

From January 2015 to December 2015, 35 patients were assessed for eligibility, and 30 were enrolled as study participants. Figure 1 depicts the flow chart for the trial. All patients underwent modified radical mastectomy, and 73.3% of the participants in each group were found to have positive lymph nodes. Of all participants, 86.3% were diagnosed with invasive ductal or invasive lobular carcinoma, with 67.7% having a TNM stage in the range IIA–IIC. At baseline, no significant differences between treatment groups were observed in terms of age, TNM stage, and level of inflammatory factors before surgery (Table II).

Volume of Drainage Fluid

During the first 3 days after the operation, the daily volume of drainage fluid in both groups was more than 100 mL; it decreased significantly thereafter. In the treatment group, the total volume of drainage fluid was about 572.2 mL; it was 700.24 mL in the control group—a statistically significant difference ($p = 0.001$). On postoperative day 7, the volume of drainage fluid in the treatment group had declined to 55.4 mL; the volume in the control group

was 73.27 mL ($p = 0.012$). Table III presents the details of those results.

Evaluation of TCM Symptom Scores

Both groups of patients had a sleepless, weary, and pale complexion before the operation, which, according to TCM theory, is considered part of *chi* deficiency syndrome. On postoperative day 1, the average symptom scores in both groups were high at 5.20 and not statistically significantly different ($p > 0.05$). On postoperative day 3, the average score in the treatment group had fallen to 3.27, with a considerable reduction in symptoms of sleeplessness, fatigue, and lilac tongue. In contrast, the average score in the control group had increased to 6.53, indicating worsened TCM status. The difference between the groups was statistically significant ($p = 0.002$). On postoperative day 7, the average score in the treatment group had fallen further to 1.87, with only mild lassitude. In the control group the average score was 4.80, with symptoms of a pale and dark complexion, weakness, laziness to speak, insomnia, and a lilac tongue, accompanied by indentations or ecchymosis. The difference between the groups was significant at $p = 0.049$ (Table IV).

Evaluation of Wound Inflammation Scores

On postoperative day 1, the patients in both groups had moderate incision pain, a reddish flap, mild-to-moderate swelling of the skin, with part of the flap showing a red-purple colour, and the presence of dark pink drainage fluid. Average scores were 6.47 in treatment group and 5.73 in control group, a nonsignificant difference ($p = 0.388$). By day 3 after surgery, the average score in the treatment group had substantially declined to 3.47, with symptoms of occasional incision pain and the presence of light-coloured drainage fluid. However, the average score in the control group was 5.33, which did not represent a considerable reduction in symptoms. The difference was statistically significant ($p = 0.020$). By day 7 after surgery, the score in the treatment group had declined to 0.67, which indicated that inflammatory symptoms had nearly disappeared. Meanwhile, the score in the control group had decreased only to 3.67, with mild incision pain, light swelling of the flap, and drainage fluid of a carnation or light yellow color. The difference was statistically significant at $p < 0.01$. Table V shows details of those scores.

Levels of Inflammatory Factors in Drainage Fluid

To examine changes from baseline in the presence of inflammatory factors in the wound drainage fluid, the levels of the various inflammatory factors were compared with the levels measured in exudate at 2 hours after the operation. No statistically significant differences were observed ($p > 0.05$). On postoperative day 1, the levels of inflammatory factors in the drainage fluid had increased significantly in both groups. Specifically, levels of TNF- α and IL-8 were elevated up to 4 times their baseline value, and levels of CRP, IL-2R, and IL-6 were elevated up to 2 times their baseline values; however, the differences between the groups were nonsignificant. From baseline to day 3, levels of CRP, IL-2R, IL-6, and IL-8 in the treatment group had declined to half their day 1 levels; moreover, the level

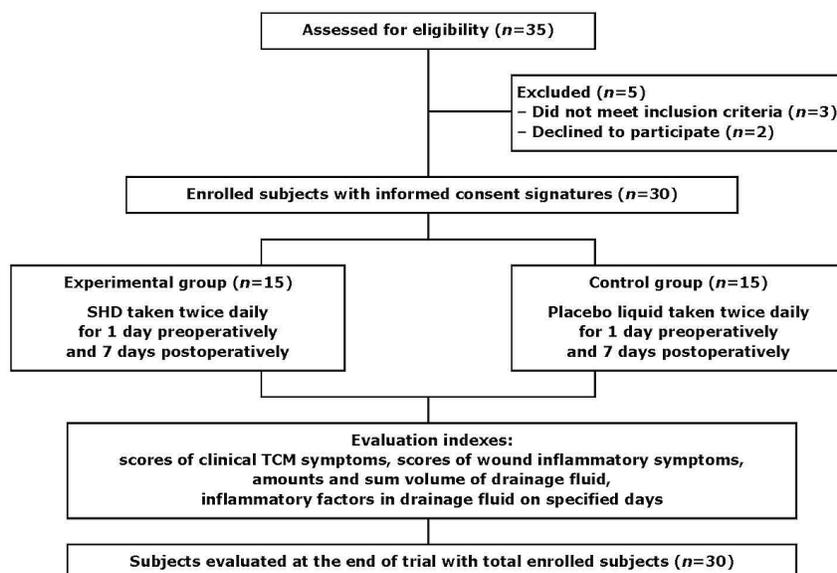


FIGURE 1 Participant flow through the trial. SHD = San Huang decoction; TCM = Traditional Chinese Medicine.

TABLE II Baseline characteristics of the study patients

Characteristic	Patient group		p Value
	Treatment	Control	
Mean age (years)	52.8±6.7	51.87±8.91	0.183
Lymph node metastasis			
None	4	4	
1–3	6	7	
>3	5	4	
TNM stage (n)			1.000
I	3	3	
IIA	5	5	
IIB	5	5	
IIIA	2	2	
Mean laboratory values			
CRP (mg/L)	3.62±1.43	3.66±1.34	0.929 ^a
IL-6 (pg/L)	7.91±3.78	7.45±4.12	0.749 ^a
TNF-α (pg/L)	10.09±6.60	10.45±7.90	0.895 ^a

CRP = C-reactive protein; IL-6 = interleukin 6; TNFα = transforming growth factor α.

of TNF-α had declined to an average of 711.32 pg/L from 901.47 pg/L. In the control group, the levels of IL-2R and IL-6 were found to have declined only slightly, and the levels of other factors (CRP, TNF-α) remained slightly increased. Statistically significant differences between the two groups were evident. On postoperative day 7, the levels of CRP, IL-6, and IL-2R had declined to less than the levels observed at 2 hours after the operation, which means that patients in the treatment group had nearly recovered from the acute inflammatory status of the operation. Levels of TNF-α had declined to about half the levels noted at 3 days after the operation, and levels of IL-8 had declined to 3.25 pg/L. In

TABLE III Volume of postoperative drainage fluid

Patient group	Drainage (mL) by postoperative day			
	Day 1	Day 3	Day 7	TOTAL
Treatment	166.87±52.73	114.67±48.27	55.40±36.52	572.20±93.95
Control	149.80±62.15	117.33±39.09	73.27±31.56	700.40±107.38
	p=0.424	p=0.289	p=0.012	p=0.001

TABLE IV Traditional Chinese Medicine symptom scores

Patient group	Score by postoperative day			
	Day 0 ^a	Day 1	Day 3	Day 7
Treatment (n=15)	2.80±1.37	5.20±2.48	3.27±1.16	1.87±0.83
Control (n=15)	2.60±1.68	5.13±2.83	6.53±3.46	4.80±3.61
	p=0.724	p=0.946	p=0.002	p=0.049

^a Before surgery.

the control group, the level of each of the inflammatory factors at day 7 was compared with the level observed at 2 hours after the operation, and all were significantly high ($p < 0.05$) except for IL-2R ($p = 0.198$). Additionally, the difference between the two groups was highly statistically significant ($p < 0.001$). Table VI shows the detailed results.

Safety Assessment

Adverse events were recorded for all patients who participated in the trial. No patient in either group experienced an adverse event. The decoction used in the study was an oral medication. No patients had an abnormal routine blood test or an abnormal liver or kidney function test before or after the operation (supplemental Tables 2 and 3).

DISCUSSION

According to TCM theory, the essential cause of breast cancer is an imbalance in the body, with long-term insults from external pathogenic factors and inadequate endogenous resistance, followed by *chi* stagnation and blood stasis, and consequently tumour formation inside the breast. Surgery further enhances those conditions, producing a microenvironment that is beneficial for wound healing, but also for tumour growth, because the production of inflammatory factors is stimulated. According to TCM, the effects of the three herbal components of SHD (Radix astragali, Radix et Rhizoma rhei, and Rhizoma curcuma longa) are to enhance *chi* and eliminate blood stagnation²⁵⁻²⁷; the combined functions of those components would be to effectively

restore the human microenvironment balance, benefiting postoperative wound healing and helping to control breast cancer recurrence.

To date, breast cancer surgery has been an indispensable and irreplaceable treatment for complete cure of the disease. However, when the target tissues are removed, the results also include wound pain, purple blood stasis in the skin flap, and release of inflammatory factors. After breast surgery, the process of wound healing starts immediately, involving the three overlapping phases of inflammation, proliferation, and remodelling²⁸. The inflammation phase is essential for wound healing; however, prolongation of the inflammatory environment can also contribute to tumour initiation, promotion, angiogenesis, and metastasis because of elevated levels of IL-6 and CRP, which are correlated with worse overall survival²⁹. Controlling the inflammatory status of patients postoperatively is therefore of great importance not only to benefit wound healing, but also to inhibit tumour growth. Unfortunately, effective measures for regulating the perioperative microenvironment to control tumour recurrence and tissue repair are still lacking.

According to TCM theory, when target tissues are removed, vessels and collateral channels are also destroyed, which leads to a type of *chi* deficiency and blood stasis status manifested in certain clinical symptoms. Those symptoms include a pale white complexion; fatigue; slowness of speech; sharp pain localized in the skin flap; a purplish or

TABLE V Postoperative inflammatory symptom scores

Patient group	Score by postoperative day		
	Day 1	Day 3	Day 7
Treatment (n=15)	6.47±2.33	3.47±1.92	0.67±0.72
Control (n=15)	5.73±2.25	5.33±2.23	3.67±2.50
	p=0.388	p=0.020	p=0.001

^a Before surgery.

TABLE VI Inflammatory factors in postoperative drainage fluid

Factor and patient group ^a	Value by postoperative interval				p Value ^b
	Hour 2	Day 1	Day 3	Day 7	
CRP (mg/L)					
Treatment	99.84±54.86	215.71±56.08	141.46±55.74	71.49±26.63	0.004
Control	110.18±65.23	217.72±32.36	238.85±29.84	212.96±30.10	
	p=0.772	p=0.941	p=0.040	p=0.001	
IL-6 (pg/L)					
Treatment	2.53±0.57	4.52±0.95	2.80±0.78	1.98±0.69	0.013
Control	2.46±0.68	4.52±1.02	3.49±0.65	3.20±0.60	
	p=0.780	p=0.984	p=0.013	p=0.000	
IL-8 (pg/L)					
Treatment	0.90±0.65	4.18±0.72	3.95±0.78	3.25±0.85	0.001
Control	0.99±1.23	4.31±0.88	4.55±0.82	4.09±0.74	
	p=0.797	p=0.664	p=0.049	p=0.007	
IL-2 receptor (pg/L)					
Treatment	106.07±55.47	247.66±146.02	79.02±47.46	68.27±40.73	0.198
Control	103.18±53.51	274.38±133.63	175.86±69.41	157.91±62.24	
	p=0.886	p=0.994	p=0.001	p=0.001	
TNF α (pg/L)					
Treatment	261.61±87.76	901.47±197.24	711.32±195.92	429.58±130.97	0.005
Control	221.36±69.95	819.19±306.50	863.67±203.45	690.53±225.09	
	p=0.176	p=0.389	p=0.046	p=0.001	

^a Each group included 15 patients.

^b Comparing day 7 with the control group value at hour 2 after surgery.

CRP = C-reactive protein; IL-6 = interleukin 6; IL-8 = interleukin 8; TNF α = transforming growth factor α .

pale gray tongue, with teeth marks or ecchymosis; and a sinking-fine or stringy-acerbic pulse. The same symptoms also indicate that the patients are in an acute inflammatory state postoperatively, which is reportedly an independent factor promoting breast cancer progression and poor clinical outcome³. Patients should therefore benefit from appropriate regulation of their inflammatory status, which could possibly control postoperative wound healing and even the progression of breast cancer.

Based on the guidelines of TCM theory, we adopted a therapy that, to reduce the inflammatory status produced by surgical treatment in patients with breast cancer, tonifies *chi* and invigorates the circulation of blood during the perioperative period. We found that all symptoms caused by an inflammatory response can be effectively reduced with SHD treatment, which leads to rapid recovery after surgery. A randomized controlled trial in which SHD was used topically on wounds reported that TCM methods can effectively reinforce deficiency and promote tissue regeneration³⁰. That trial proved that TCM treatment for tonifying *chi* and enhancing blood circulation could effectively improve wound healing. We used traditional Chinese herbs given orally, an approach that can be conveniently adopted by patients undergoing breast cancer surgery.

Our research showed that use of SHD was significantly associated with reduced wound pain, swelling, and volume of wound exudate, and also with improved color of the exudate by reducing the levels of inflammatory factors in the wound exudate. The amount of exudate has also been reported to be reduced by surgical fixation of the flap, which would require additional surgical processes such as sutures, and could affect patient comfort³¹. Our method, in which SHD was taken orally, has the advantage of convenience, while still reducing the levels of inflammatory factors in the exudate.

Our study also quantified TCM symptoms by using scores to objectively evaluate the changes after surgery. The results show that SHD can completely ameliorate postoperative discomfort and eliminate the local inflammatory response within 1 week. A Delphi study showed that patients with breast cancer manifested *chi* and blood deficiency postoperatively³², which accords with our finding that such patients manifest *chi* deficiency and blood stagnation. We also evaluated the improvement in systemic *chi* and blood status under TCM theory guidelines by scoring the local inflammatory response in terms of the inflammatory factor content of the wound exudate.

Because inflammation has a marked influence on tumour relapse and prognosis³³, as well as on overall survival³⁴, we measured the levels of inflammatory factors within the wound exudate to assess the potential effects of SHD on the wound microenvironment in patients during the perioperative period. Inflammatory factors such as CRP, IL-6, and TNF- α stimulate tumour cell proliferation and invasion³⁵. Interleukin 8, also known as CXC chemokine 8, is the earliest discovered cytokine; it is chemotactic and activating for neutrophils and plays an important role in the process of inflammation. Previous studies have shown that elevated IL-8 levels are closely related to the proliferation, survival, and movement of breast tumour cells and to angiogenesis, and that IL-8 participates in the

processes of tumorigenesis, progression, and metastasis³⁶. Wound drainage fluid resulting from acute tissue trauma, with significantly high levels of inflammatory cytokines (TNF- α , IL-6, IL-8, and IL-10), has been reported to hamper wound healing³⁷. However, relatively few studies have focused on the inflammatory factor content of wound drainage fluid. Wound healing in rabbits was reported to be improved when IL-8 levels are lowered³⁸. Moreover, changes in inflammatory cytokines are seen earlier in wound exudate than in serum, which directly reflects the inflammatory state of the wound³⁹.

Inhibition of the secretion of inflammatory cytokines such as IL-6 and IL-10 in the wound is therefore conducive to postoperative recovery⁴⁰. Interleukin 2 is a cytokine signalling molecule that regulates the activity of leucocytes for the immune system. It is a link between organism infection and rejection⁴¹. When initial T cells are stimulated by antigens, IL-2 also promotes those cells to differentiate into effector T cells and memory T cells, thereby helping the body fight infection⁴¹. The effective binding of soluble IL-2 receptor and IL-2 is an important part of the normal immunoregulation of IL-2-dependent lymphocyte function. Some studies have suggested that an increase in the level of IL-2 can reflect the degree of inhibition of immune function in the body⁴².

We found that abnormal levels of inflammatory factors in wound exudate could last for 1 week under common postoperative treatment conditions. Levels of those inflammatory factors could be substantially reduced by SHD taken orally, reaching normal levels within 1 week, in accordance with the amelioration of local inflammation as suggested by TCM theory. In contrast, levels of inflammatory factors in a control group that did not receive SHD were still higher at 7 days after surgery than they had been at 2 hours after surgery.

Adjustment of the inflammatory and stress states of bodily fluids by our SHD was associated with a reduction in postoperative drainage fluid. Our trial makes a good start toward bridging the gap between Western medicine and TCM, focusing on controlling postoperative inflammation. The inflammatory environment is closely related to tumour proliferation. Controlling inflammation could play a positive role in controlling tumour recurrence and metastasis. Several clinical trials have reported that TCM methods applied systemically or topically (or both) can improve wound healing⁴³. However, earlier reports observed only clinical symptoms and did not investigate changes in factors that might be involved in the healing process. By also investigating changes in inflammatory factors present in wound exudate, our study sheds light on the mechanism by which TCM exerts clinical effects on breast cancer recovery during the perioperative period. Studies in the future could perhaps consider the relationship between SHD and the recurrence and metastasis of breast cancer.

With respect to the safety of SHD, clinical observation shows that it was very safe. Neither patient group experienced side effects. After a slight increase on postoperative day 1, the percentage of neutrophils returned to normal by postoperative day 7. Other routine tests of blood and of liver and renal function were within their reference

ranges, indicating that SHD did not cause severe allergic reactions or obvious hepatorenal toxicity.

Limitation of TCM Treatment

The first shortcoming of our experiment is the issue of blinding. We could achieve complete blinding in the random allocation, but for Chinese medicines taken orally, complete patient blinding seems unworkable. The packaging used for our control group was the same as for the treatment group (a special opaque packaging bag for Chinese herbal medicine). The control group received 200 mL physiologic saline (provided by the pharmacy department of Jiangsu Province Hospital of Traditional Chinese Medicine), whose colour, when the liquid was consumed through an opaque tube, is not easy to distinguish. But Chinese medicine has a bitter taste and physiologic saline is salty, and so the smell and taste of two liquids have certain differences. Our patients were not exactly the same in terms of admission time and ward location. They all volunteered to join the trial, and before it began, they all expressed their willingness to follow the protocol and not to exchange their trial medications.

A second shortcoming is that follow-up was not long. Prolonging the follow-up would have been helpful for observation of the effect of SHD on extubation time and survival time.

A third shortcoming is that the sample size was small. Further research should focus on the effect of the exudate on normal breast tissue and on breast cancer cells in culture to ascertain its effects on proliferation, invasion, and migration of tumour cells, as well as on immune regulation. Given that Chinese herbs depend on sourcing, it is difficult to promote their use.

CONCLUSIONS

The results of our prospective clinical study provide some evidence that administration of SHD during the perioperative period can decrease wound exudate and regulate inflammatory symptoms. However, given the small sample size and short observation period, our results reflect only the functionality of SHD for improving inflammation. No direct clinical evidence for the effect of SHD on breast cancer has been studied. In future, we intend to enlarge our research sample to analyze differences in the rate of disease-free survival in the experimental and control groups, and to acquire direct evidence of the effect of SHD on breast cancer.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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