

Meta-Analysis of the Efficacy of Traditional Chinese Medicine in the Prevention and Treatment of Anticancer Drug-Induced Hand-Foot Syndrome: Postprint

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Abstract

Objective: To systematically evaluate the efficacy of Traditional Chinese Medicine (TCM) in preventing and treating anti-tumor drug-induced hand-foot syndrome (HFS).

Methods: PubMed, The Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP Chinese Science and Technology Journals Database (VIP), and WANFANG DATA were searched to include randomized controlled trials (RCTs) meeting the inclusion criteria. Two reviewers assessed the methodological quality of included studies using the Jadad scale, and meta-analysis was conducted using RevMan 5.4.1 software.

Results: A total of 18 RCTs involving 1,236 patients were included, with 626 in the treatment group and 610 in the control group. The quality scores of included literature ranged from 1 to 3 points. Meta-analysis results demonstrated that both oral Chinese medicine [OR=0.33, 95%CI(0.18, 0.61), P=0.0005] and topical Traditional Chinese Medicine [OR=0.28, 95%CI(0.22, 0.37), P<0.00001] for preventing and treating anti-tumor drug-induced HFS exhibited superior clinical efficacy compared with the control group, with statistically significant differences. Overall, Traditional Chinese Medicine [OR=0.29, 95%CI(0.23, 0.37), P<0.00001] for preventing and treating anti-tumor drug-induced HFS showed superior clinical efficacy compared with the control group, with statistically significant differences.

Conclusion: Traditional Chinese Medicine is superior to conventional Western medicine treatment and placebo in preventing the incidence of anti-tumor drug-induced hand-foot syndrome. However, the limited number and low quality of included studies compromised the strength of evidence.

Full Text

Abstract

Objective: To systematically evaluate the efficacy of traditional Chinese medicine (TCM) in preventing and treating hand-foot syndrome (HFS) caused by anti-tumor drugs.

Methods: PubMed, The Cochrane Library, CNKI, VIP, and WANFANG DATA were searched for randomized controlled trials (RCTs) meeting the inclusion criteria. Two evaluators assessed the methodological quality of included studies using the Jadad scale, and meta-analysis was performed using RevMan software.

Results: A total of patients were included, with in the treatment group and in the control group across RCTs. The quality scores of included literature were points. Meta-analysis results showed that both oral administration of traditional Chinese medicine [OR= (% CI,)] and external use of TCM [OR= (% CI,)] demonstrated superior clinical efficacy in preventing and treating HFS caused by anti-tumor drugs compared with the control group, with statistically significant differences. Overall, TCM [OR= (% CI,)] showed better clinical efficacy in preventing and treating HFS than the control group, with statistically significant differences.

Conclusion: Traditional Chinese medicine is superior to conventional Western medicine and placebo in preventing the incidence of HFS caused by anti-tumor drugs. However, the limited number and low quality of included studies affect the strength of the evidence.

Keywords: Hand and foot syndrome; Traditional Chinese Medicine; Integrated Traditional Chinese and Western Medicine; Meta analysis

Hand-foot syndrome (HFS) is a common complication during clinical anti-tumor therapy, characterized primarily by numbness, paresthesia, and pain in the hands and feet. In severe cases, patients may develop desquamation, fissuring, and hard blisters on the hands and feet. Currently used anti-tumor drugs, including fluorouracil agents (5-fluorouracil, capecitabine, S-1), doxorubicin liposome, cytarabine, docetaxel, and targeted drugs such as tyrosine kinase inhibitors, can all cause HFS. The development of HFS during anti-tumor therapy, particularly severe HFS, not only seriously affects patients' quality of life but also impacts their ability to continue anti-tumor drug treatment, thereby compromising anti-tumor efficacy. Therefore, active prevention and treatment of HFS during anti-tumor therapy has important clinical significance.

Current Western medicine approaches for preventing and treating HFS mainly involve symptomatic supportive treatment, oral or topical vitamin B, and oral COX-2 inhibitors. In recent years, both external TCM therapies and oral Chinese herbal medicine have achieved good clinical results in preventing and treat-

ing HFS during anti-tumor therapy. This study conducted a systematic review of clinical research on TCM prevention and treatment of HFS caused by anti-tumor drugs to provide evidence-based medical evidence for TCM interventions.

1. Materials and Methods

1.1 Literature Inclusion Criteria

Study type: Randomized controlled trials (RCTs), with no restrictions on blinding methods.

Study subjects: Patients with pathologically confirmed malignant tumors receiving chemotherapy or targeted anti-tumor drugs that may cause HFS.

Interventions: The treatment group received TCM interventions (including oral Chinese herbs, external TCM applications, etc.) concurrently with chemotherapy or targeted therapy. The control group received conventional HFS prevention treatment concurrently with chemotherapy or targeted therapy.

HFS grading standards: Using the National Cancer Institute (NCI) grading criteria and WHO hand-foot syndrome grading criteria.

Outcome measures: HFS incidence. “No HFS” was defined as absence of HFS-related symptoms during anti-tumor drug use, allowing normal work and daily life. “HFS occurrence” was defined as development of grade I or higher HFS-related symptoms during anti-tumor drug use. Some studies graded HFS and reported the number of cases at each grade in experimental and control groups, but this analysis did not separate statistics by grade. Some studies divided experimental groups into subgroups with different herbal concentrations or divided control groups into subgroups with different Western medicine interventions, but this study combined data from different subgroups for analysis.

1.2 Literature Exclusion Criteria

- 1) Animal experiments, case reports, reviews, and other non-RCT literature;
- 2) Duplicate publications;
- 3) Other skin diseases such as paronychia;
- 4) Intolerance to Chinese herbal medicine;
- 5) Discontinuation of anti-tumor therapy.

1.3 Literature Search Strategy

Computer searches were conducted in PubMed, The Cochrane Library, CNKI, VIP, and WANFANG DATA. Search terms included: hand-foot syndrome, HFS, traditional Chinese medicine, TCM, integrated traditional Chinese and Western medicine, randomized controlled trial, RCT, etc. To avoid omission, manual searches of relevant literature and reference lists of obtained articles were also performed. The search time frame was from database inception to .

1.4 Literature Screening, Data Extraction, and Quality Assessment

Two researchers independently screened literature according to inclusion and exclusion criteria, with disagreements resolved by a third researcher. Data extraction and entry were performed with double cross-checking. The quality of included studies was assessed using the Jadad scale, evaluating items including randomization method, blinding, baseline comparability, and description of dropouts and withdrawals.

1.5 Statistical Methods

Meta-analysis was performed using RevMan software. For dichotomous variables, odds ratio (OR) and 95% confidence interval (CI) were used as effect measures. Heterogeneity among included studies was assessed using the I^2 test ($\alpha = 0.05$) and quantified with I^2 statistics. When heterogeneity was low, a fixed-effects model was used for meta-analysis. When substantial heterogeneity existed, sources were analyzed and, after excluding significant clinical heterogeneity, a random-effects model was applied. When more than 10 studies were included, funnel plots were used to assess publication bias.

2. Results

2.1 Literature Search Results

The initial search retrieved articles. After screening, RCTs were ultimately included, with patients in the treatment group and in the control group. All studies were conducted in mainland China.

2.2 Basic Characteristics and Quality Assessment of Included Studies

Among the included studies, Jadad scale scores ranged from to points. used random number tables (score), used coin tossing (score), only mentioned “randomization” (score), described blinding implementation (single-blind, score), and mentioned dropouts and reasons (score).

Basic Characteristics and Methodological Quality Assessment of Included Studies

2.3 Analysis of HFS Incidence During Anti-tumor Therapy

This study conducted subgroup analysis according to different TCM intervention routes. studies used oral TCM intervention, including patients. No significant heterogeneity was found among studies ($P =$, $I^2 = \%$), so a fixed-effects model was used for weighted quantitative pooling. Meta-analysis results showed that in the oral TCM subgroup, the HFS incidence in the treatment group was significantly lower than in the control group [$OR = (95\% CI,)$, $P <$], indicating that oral TCM prevention of HFS caused by anti-tumor drugs has superior clinical efficacy compared with placebo and conventional Western symptomatic treatment.

studies used external TCM intervention, including patients. No significant heterogeneity was found among studies ($P =$, $I^2 = \%$), so a fixed-effects model

was used for weighted quantitative pooling. Meta-analysis results showed that in the external TCM subgroup, the HFS incidence in the treatment group was significantly lower than in the control group [OR = (95% CI,), $P <$], indicating that external TCM prevention of HFS caused by anti-tumor drugs has superior clinical efficacy compared with placebo and conventional Western symptomatic treatment.

Overall, meta-analysis results showed that the HFS incidence in the TCM treatment group for preventing and treating HFS caused by anti-tumor drugs was significantly lower than in the control group [OR = (95% CI,), $P <$], indicating that TCM prevention of HFS caused by anti-tumor drugs has superior clinical efficacy compared with placebo and conventional Western symptomatic treatment.

2.4 Publication Bias

Funnel plot analysis was performed on studies to evaluate publication bias. The results showed the funnel plot was basically symmetrical, suggesting small publication bias and relatively reliable results. [FIGURE:N] Funnel plot of HFS incidence.

3. Discussion

Current research indicates that the pathological manifestations of HFS mainly include vacuolar degeneration of basal keratinocytes, perivascular lymphocytic infiltration in hand and foot skin, keratinocyte apoptosis, and skin edema. The pathogenesis of HFS is not yet fully understood. Studies suggest that HFS may be closely related to inflammatory reactions in hand and foot blood vessels caused by anti-tumor drugs, as well as accumulation of anti-tumor drug metabolites in hand and foot skin. Additionally, mechanical pressure on hands and feet (such as from daily labor and walking) causing damage to local cutaneous small vessels is also a possible mechanism of HFS during chemotherapy. Currently, multiple anti-tumor drugs can cause HFS symptoms during use, with some drugs such as capecitabine having higher HFS incidence rates. Some patients discontinue subsequent anti-tumor therapy due to intolerable HFS symptoms, which seriously affects their anti-tumor treatment. Therefore, preventing and treating potential HFS during chemotherapy has important clinical significance.

Current Western medicine approaches for preventing and treating HFS during anti-tumor therapy mainly involve symptomatic treatment, oral or topical vitamins, and oral COX-2 inhibitors, all of which have certain limitations. For example, celecoxib, a COX-2 inhibitor used for HFS prevention, carries cardiovascular and gastrointestinal risks requiring assessment of cardiac and gastrointestinal function before clinical use. Long-term vitamin E use can cause adverse reactions such as nausea and vomiting. Therefore, exploring new effective drugs and methods for preventing and treating HFS during anti-tumor therapy is of great significance.

HFS has no corresponding records in TCM literature, but based on its clinical manifestations, it can be classified under “bi syndrome” and “toxic sores.” The *Suwen · Wuzang Sheng Cheng Pian* states: “When blood congeals in the skin, it becomes bi.” The disease location is in the hands and feet, with a root-deficiency and tip-excess nature, and the pathogenesis involves meridian obstruction. Cancer patients have imbalance of zang-fu organ qi, blood, yin, and yang, with deficient vital qi unable to withstand attack. Considering that anti-tumor drugs are all toxic substances, drug toxins damage qi and blood, lodge in meridians, and cause disease. Currently, TCM mainly considers HFS clinical patterns as three types: yang deficiency with blood stasis, heat-toxin accumulation, and blood deficiency with wind-dryness. Based on patients’ clinical manifestations, differentiating these patterns and providing corresponding oral or external TCM treatments have achieved good results.

This meta-analysis primarily analyzed the efficacy of oral Chinese herbs and external TCM therapies in preventing and treating HFS in cancer patients during anti-tumor therapy. The meta-analysis showed that both oral and external TCM could effectively prevent and treat HFS during anti-tumor therapy. Compared with conventional Western prevention measures, TCM intervention significantly reduced HFS incidence during anti-tumor therapy. Moreover, TCM intervention could reduce pain scores when HFS occurred, demonstrating important clinical value of TCM in preventing and treating HFS during anti-tumor therapy.

This meta-analysis still has certain limitations: 1) The number of included studies was small, with even fewer studies reporting pain score indicators, suggesting potential publication bias; 2) The quality of included literature was low, with all studies scoring less than points on the Jadad scale, and most failing to describe randomization methods. Due to obvious differences between herbal preparations and conventional Western prevention measures, double-blinding was difficult to achieve. Most studies did not mention case dropouts or withdrawals and related reasons. We look forward to future well-designed multicenter, large-sample, randomized, double-blind controlled studies to provide stronger evidence for the efficacy of TCM in preventing and treating HFS during anti-tumor therapy.

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