

Tripterygium wilfordii Hook F Treatment for Idiopathic Refractory Nephrotic Syndrome in Adults: A Meta-Analysis

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Key Words

Nephrotic syndrome · Refractory nephrotic syndrome · Idiopathic refractory nephrotic syndrome, meta-analysis · Immunosuppressive agents · *Tripterygium wilfordii* Hook F

Abstract

Tripterygium wilfordii Hook F (TwHF) is a Chinese herbal medicine with immunosuppressive effects and an established history of use in the treatment of inflammatory and autoimmune diseases. We have carried out a meta-analysis of randomized controlled trials (RCTs) and quasi-RCTs which assessed the effectiveness of TwHF in the treatment for idiopathic refractory nephrotic syndrome (IRNS). After reading the full text, only three RCTs or quasi-RCTs meeting our inclusion criteria were selected. Our meta-analysis indicated that TwHF has beneficial effects on the remission of IRNS. There was no significant publication bias in the meta-analysis studies. However, studies with a larger sample size and including patients with both a mild and severe histopathological change involvement separately are needed to assess the effects of TwHF in IRNS patients before exact conclusions can be drawn.

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Introduction

Idiopathic refractory nephrotic syndrome (IRNS) is composed of idiopathic steroid-resistant nephrotic syndrome and frequently relapsing nephrotic syndrome including idiopathic steroid-dependent nephrotic syndrome. At present there is a lack of safe and effective drugs for IRNS and currently the primary drugs for IRNS are steroids, alkylating agents, and cyclosporin. Nevertheless, many side effects have affected their use. Corticosteroids such as prednisone can stop the protein leak but it frequently recurs and further corticosteroids can have adverse effects of poor growth, cataracts, osteoporosis and high blood pressure. Patients who fail to respond may be treated with immunosuppressive agents such as cyclophosphamide (CTX), chlorambucil or cyclosporin, or with non-immunosuppressive agents such as ACE inhibitors.

Tripterygium wilfordii Hook F (TwHF), a vine-like plant which grows in Southeast China, is one of the most studied herbs in Chinese medicine for the treatment of immunogenetic diseases such as systemic lupus erythematosus. TwHF has been found to inhibit interleukin-2, interferon-1, and PGE₂, and prednisone requirements in systemic lupus erythematosus were reduced by 50% in subjects taking TwHF [1]. TwHF contains bioactive compounds that possess immunosuppressive agents. These

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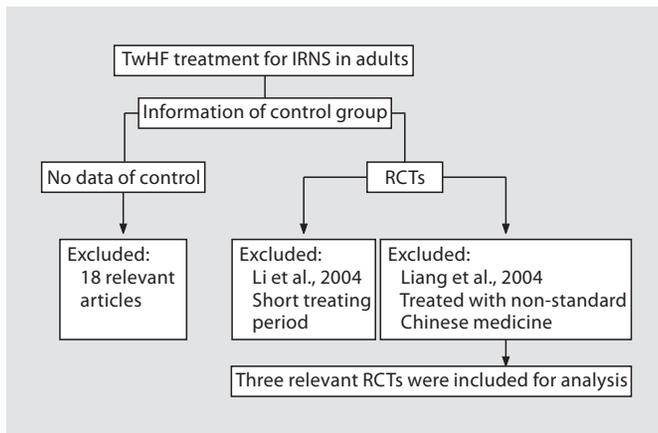


Fig. 1. Flow diagram for inclusion and exclusion of studies.

compounds are considered to be potential drugs for the treatment of IRNS. Wong et al. [2] found that the ^{14}C - β -hydroxyl- and γ -butyrolactone moieties of the triptolide molecule play a pivotal role in its anti-inflammatory properties and cytotoxicity, and are responsible for the antiproliferative activity.

Ji et al. [3] reported the clinical trial of TwHF in human kidney transplantation in China, and found that the TwHF was effective preventing renal allograft rejection and increased long-term renal allograft survival among adult cadaveric renal transplant recipients. TwHF has been used for years to treat IRNS in China; however, the effects and safety of the agent have not been systematically reviewed. To assess the benefits and harms of TwHF in treating IRNS in adults, either as sole agents or in addition to other drug therapies, we carried out a meta-analysis of randomized controlled trials (RCTs) or quasi-RCTs testing the effectiveness of TwHF for the treatment of IRNS which includes publications up to April 2008.

Methods

Identification of Eligible Studies

We searched the Cochrane Library, MEDLINE, EMBASE, Chinese Biomedicine Database (CBM), CNKI, VIP and reference lists of articles without language restriction. The most recent search was dated April 2008. All RCTs and quasi-RCTs assessing the use of TwHF in treating IRNS in adults, either as sole agents or in addition to other drug therapies, were included. The search terms were: refractory nephrotic syndrome, steroid-resistant nephrotic syndrome, steroid-dependent nephrotic syndrome, relapsing nephrotic syndrome, *T. wilfordii*, *Tripterygium*, thunder god vine, lei gong teng, and seven-step vine.

Inclusion and Exclusion Criteria

Studies in any language were screened against the following inclusion criteria: (a) human subjects, (b) use of a control group, (c) subjects randomized or quasi-randomized between treatment groups, (d) allowing assessment of the efficacy and harms of TwHF, and (e) subjects diagnosed with refractory nephrotic syndrome. Quality of reporting was assessed using the 5-point Jadad Scale. Studies were excluded if they did not clearly report the number of patients who recovered or deteriorated. All articles underwent a multilevel, systematic review by a team of two physicians. The reviews were conducted independently.

Quality Assessment of Primary Studies

We evaluated the quality of the studies which were included in the analysis with the Jadad Scale, which is the established procedure by which study methodologies are evaluated [4]. Its scale assigns 0 or 1 points to each of the following five items: (1) with or without randomization, (2) the appropriateness of the randomization methods if used, (3) with or without double-blind elements, (4) the appropriateness of double-blinding if used, and (5) the incidence of withdrawals and dropouts. Thus, the Jadad score can range from 0 to 5.

Data Extraction

Two investigators extracted standard information from an independent study. From each study, the following information was obtained: first author, journal, year of publication, demographics, study population, the number of cases, TwHF dosage, placebo or immunosuppressive agents, completely recovered cases, effective, and no effect, rate of completely recovered and total efficacy.

Statistical Analysis

Statistical analyses were performed with the Cochrane RevMan software version 4.2 (Cochrane Library, UK), and the results were expressed as odds ratio (OR) for dichotomous outcomes, with 95% confidence intervals (95% CI). Heterogeneity among the included trials was analyzed using the heterogeneity Q statistic test. If the significant Q statistic ($p < 0.05$) indicated heterogeneity across studies, the DerSimonian and Laird method in the random effects model was used for meta-analysis. Otherwise, the Mantel-Haenszel method in the fixed effect model was selected.

The potential for publication bias was examined by the funnel plot method, Begg's test for testing of publication bias was performed by Stata Statistical Software Version 8.1 (Stata Corp., College Station, Tex., USA). $p < 0.05$ was considered statistically significant.

Results

Studies Included in the Meta-Analysis

We identified 23 potentially relevant articles, but only three RCTs [5–7], enrolling a total of 150 patients who were included in the final analysis: one trial compared TwHF with placebo [6] and two with CTX [5, 7], as displayed in figure 1. These three RCTs conventionally received treatment with prednisone. The quality of the

Table 1. Summary of randomized or quasi-randomized clinical trials included in the meta-analysis

Ref.	Design	Jadad scores	Subjects	Treatment	Main results
He et al. [5]	Randomized double-blind parallel group trial	3	32 adults meeting IRNS criteria, 15 for TwHF group (M: 6, F: 9), 17 for control group (M: 7, F: 10)	1.0 mg·kg ⁻¹ ·day ⁻¹ TwHF; CTX 2.0 mg·kg ⁻¹ ·day ⁻¹ up to 6–8 g and then ceased	TwHF group: 10 completely recovered, 2 effective, 3 no effect; control group: 3 completely recovered, 6 effective, 8 no effect
Zhong et al. [6]	Randomized double-blind parallel group trial	4	58 adults meeting IRNS criteria, 32 for TwHF group (M: 18, F: 14), 26 for control group (M: 14, F: 12)	1.0–2.0 mg·kg ⁻¹ ·day ⁻¹ TwHF; control group (placebo)	TwHF group: 28 completely recovered, 3 effective, 1 no effect; control group: 22 completely recovered, 1 effective, 3 no effect; 2 menstrual disturbance in TwHF group
Xiao et al. [7]	Randomized double-blind parallel group trial	4	60 adults meeting IRNS criteria, 35 for TwHF group (M: 20, F: 15), 25 for CTX group (M: 18, F: 7)	1.5–2.0 mg·kg ⁻¹ ·day ⁻¹ TwHF for 4 weeks, then converted to 1.0 mg·kg ⁻¹ ·day ⁻¹ ; CTX 2.0 mg·kg ⁻¹ ·day ⁻¹ up to 6–8 g and then ceased	TwHF group: 30 completely recovered, 2 effective, 3 no effect, 18 side effects*; CTX group: 18 completely recovered, 2 effective, 2 no effect, 27 side effects, 1 subject stopped treatment for the increase of glutamic-pyruvic transaminase

IRNS = Idiopathic refractory nephrotic syndrome; TwHF = *Tripterygium wilfordii* Hook F; CTX = cyclophosphamide; M = male; F = female. * Side effects means the total frequencies occurred.

three RCTs was optimal and the characteristics of the studies included are listed in table 1. No studies are available demonstrating the correlation of TwHF treatment with proteinuria decrease in IRNS patients.

Effect of TwHF on Completely Recovered IRNS

Three studies assessed the completely recovered rate in a total of 150 patients, and 82 were assigned to the TwHF treatment groups, while 68 were in the control groups. 68 completely recovered subjects were seen in the TwHF treatment groups, and 43 of 68 patients in the control groups. Because heterogeneity was not significant ($p = 0.20$), the fixed effects model was used to ascertain the OR value, and a statistical analysis showed that this estimate was statistically significant ($p = 0.01$, 95% CI 1.26–6.30), as shown in figure 2.

Effect of TwHF on Total Efficacy Rate in IRNS

75 of 82 patients (total efficacy rate 91.46%) were seen in the TwHF treatment groups, and 52 of 68 patients (total efficacy rate 76.47%) were seen in the control groups. Because heterogeneity was not significant ($p = 0.95$), the

fixed effects model was used to ascertain the OR value, and a statistical analysis showed that this estimate was statistically significant ($p = 0.02$, 95% CI 1.20–8.76), as shown in figure 3.

Side Effects

Two RCTs [5, 6] did not demonstrate the side effects clearly, so we cannot evaluate the harm between the use of TwHF and CTX or placebo. It was for this reason that He [5] and Zhong et al. [6] did not report the sort of pathological IRNS patients, and we also cannot judge which sort of pathological changes more effectively responded to TwHF therapy.

Publication Bias

Funnel plots showed symmetric patterns for both the completely recovered rate and total efficacy rate as shown in figures 4 and 5. Because the sample size of these three RCTs included in this meta-analysis were all small, we conducted Begg's test to evaluate the publication bias by Stata software, and revealed no significant heterogeneity in the meta-analysis studies.

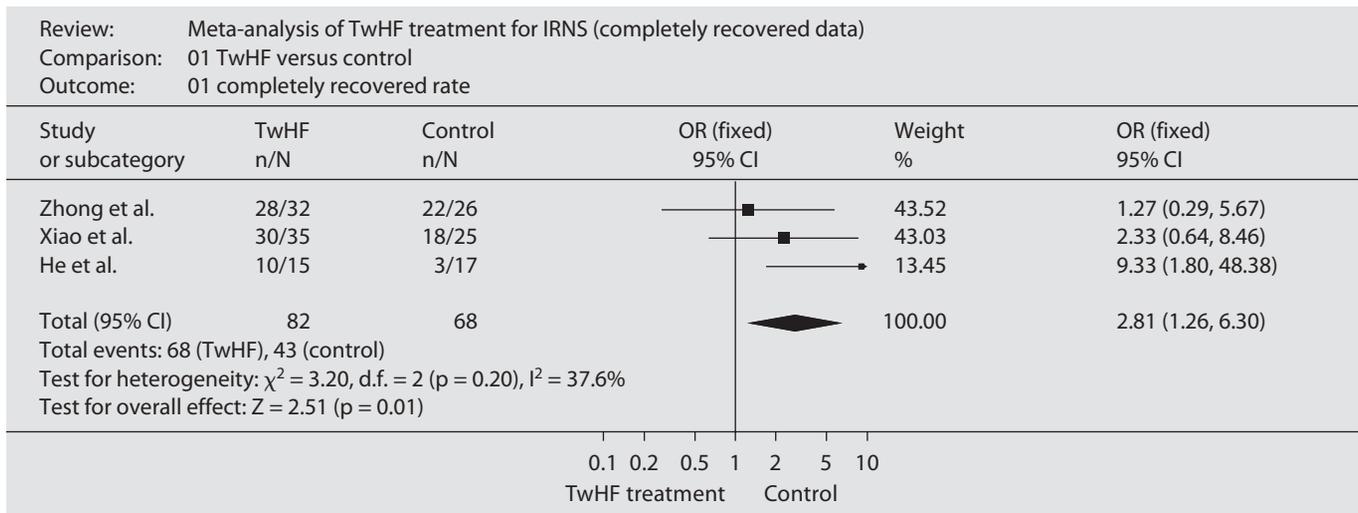


Fig. 2. Meta-analysis of TwHF treatment for IRNS (completely recovered rate).

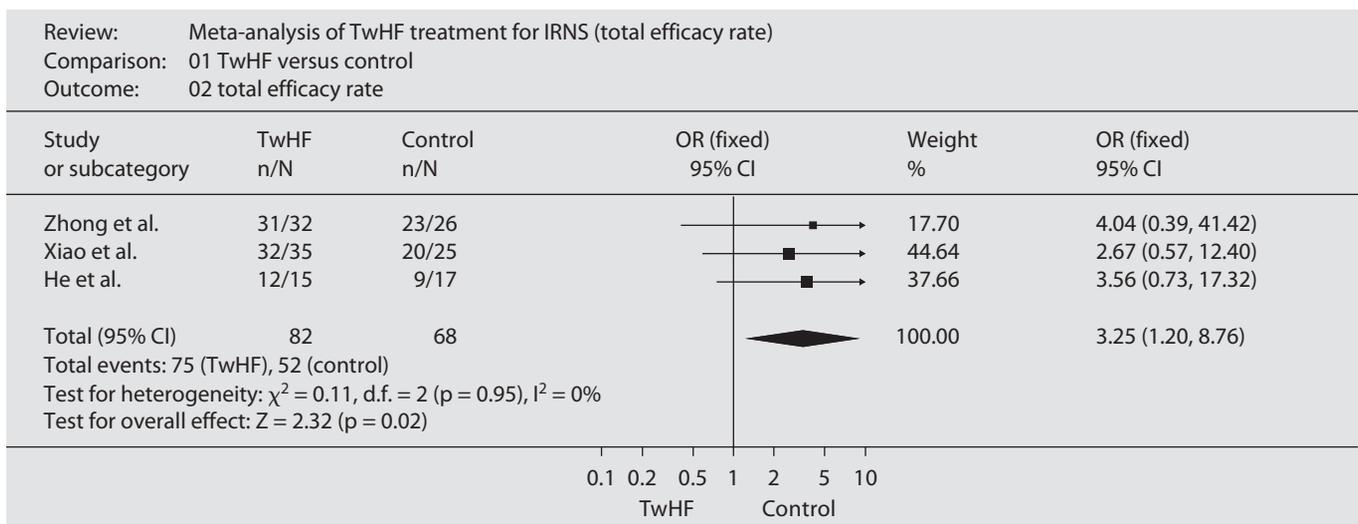


Fig. 3. Meta-analysis of TwHF treatment for IRNS (total efficacy rate).

Discussion

Heavy proteinuria, hypoalbuminemia, edema and hypercholesterolemia are the main characteristics of nephrotic syndrome. 80–90% of steroid-sensitive nephrotic syndrome patients relapsed within 1 year after standard corticosteroid therapy. About half relapse frequently and are at risk of the adverse effects of steroids. Chinese herbal medicines, such as TwHF, have gained growing interest recently and may prove to be viable treatment options [8].

TwHF may have some positive effects in treating IRNS by increasing plasma albumin and reducing blood cholesterol, Cushing's syndrome, hormone-reduced syndrome and respiratory tract infection. However, limited by the lack of high-quality clinical studies, we are unable to recommend TwHF for IRNS.

A meta-analysis can summarize the results from different studies by producing a single estimate of the major effect with enhanced precision [9]. One of the major advantages of meta-analysis is to increase sample size, which

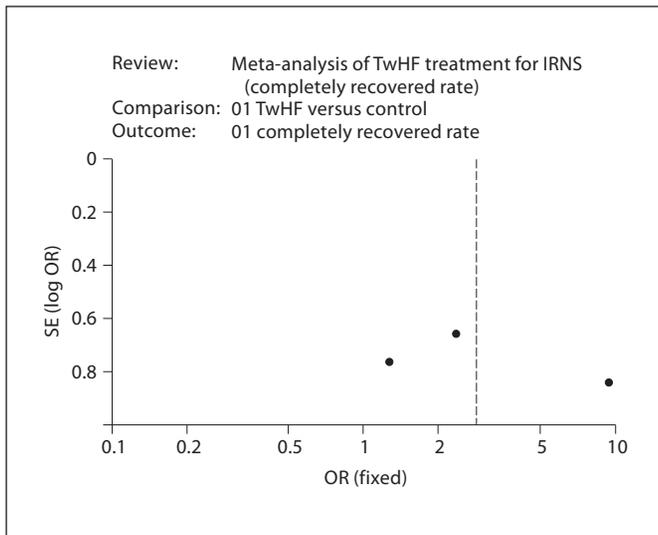


Fig. 4. Funnel plot for meta-analysis of TwHF treatment for IRNS (completely recovered rate).

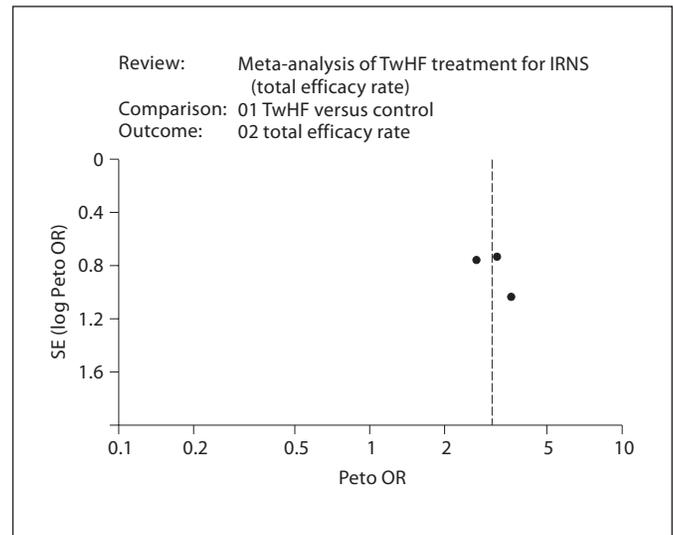


Fig. 5. Funnel plot for meta-analysis of TwHF treatment for IRNS (total efficacy rate).

may decrease the probability that random error will produce false-positive or false-negative associations [10].

In comparison to placebo or CTX, use of TwHF resulted in a significant increase of completely recovered rate (OR 2.81, 95% CI 1.26–6.30) and total efficacy rate (OR 3.25, 95% CI 1.20–8.76) at the end of the treatment period. Although we restricted our study only to RCTs, and the quality of these studies was optional, the samples involved in the meta-analysis was not enough to reach a compelling conclusion. Better designed studies are needed to reach a definitive assessment of this matter.

TwHF has been used in traditional Chinese medicine as a cancer therapy and also as an insecticide for hundreds of years. Recently, its xylem extract has been used in the clinical treatment of rheumatoid arthritis, skin disorders, male fertility control, and other inflammatory and autoimmune diseases [11–13]. Various diterpene lactone epoxide compounds isolated from TwHF have also shown anti-inflammatory and immunosuppressive activities. For example, triptolide, triptolide, triptonide, triptolide, triptolide, triptolide, and 16-hydroxytriptolide significantly inhibited the proliferation of T and B lymphocytes and demonstrated immunosuppressive activity [14, 15]. The ethyl acetate extract of TwHF and triptolide can inhibit transcription of the iNOS gene, and contributes to the anti-inflammatory effects of this traditional Chinese herbal medicine [16].

Tripterygium has also been suggested to inhibit interleukin-2 expression on T cells at the level of the purine-box/nuclear factor of activated T cells and nuclear factor- κ B transcriptional activation and induce T-cell apoptosis [17]. Additionally, triptolide can block fibroblast maturation/proliferation and inhibit transforming growth factor- β mRNA expression in vitro [18]. A safe ethyl acetate extract prepared in this way was used in two US National Institutes of Health-sponsored human clinical trials which found that ethyl acetate extract dosages up to 570 mg/day appeared to be safe and that 6 of 10 cases treated with 180 mg/day showed disease improvement [19]. Although benefits were apparent with the use of TwHF treatment, this therapy was not without side effects. Common side effects included stomach upset, diarrhea, skin rash, and change in skin pigmentation. These blights were controllable with dosage adjustment and many symptoms ceased without intervals. However, other side effects of this medicine were more serious and difficult to control, including reversible infertility in men and amenorrhea in women [20, 21].

Our meta-analysis had several limitations. First, the number of subjects included in this analysis was not necessarily high. Second, for the same reason that He [5] and Zhong et al. [6] did not report the pathological sorts of IRNS patients, we also cannot judge which sort of pathological changes more effectively responded to TwHF therapy, and finally, in all the studies, both the interven-

tion group and control group conventionally received treatment with prednisone. Studies to assess the effects of TwHF alone in patients who are not receiving other therapies are therefore needed.

In brief, current available evidence supports the use of TwHF in patients with IRNS. However, studies with larger sample sizes and including patients with both a mild and severe histopathological change involvement separately are needed before any meaningful conclusions can be drawn.

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