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Original Article

Efficacy of Zicao Ointment combined with Xiaoyan Topical Granules for the treatment of skin pruritus in hemodialysis patients based on traditional Chinese medicine theory

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Abstract: Objective: To evaluate the clinical efficacy of Zicao Ointment combined with Xiaoyan Topical Granules in treating skin pruritus among hemodialysis (HD) patients based on traditional Chinese medicine (TCM) external therapy theory. Methods: We included 175 HD patients treated at Dongguan Traditional Chinese Medicine Hospital from May 2022 to May 2025: 85 received basic treatment (control group) and 90 received Zicao Ointment plus Xiaoyan Topical Granules (research group). The outcome measures included curative efficacy, Visual Analog Scale for Itch (VASI)-based pruritus assessment, Modified Duo's Pruritus Score, Pittsburgh Sleep Quality Index (PSQI), dialysis adequacy and residual renal function (blood urea nitrogen [BUN], serum creatinine [Scr], β2-microglobulin [β2-MG]), calcium-phosphorus metabolism (serum calcium/phosphorus and parathyroid hormone), serum indices (interleukin [IL]-2/6 and C-reactive protein [CRP]), and safety (contact dermatitis, liver injury, skin irritation/burning sensation, calcium-phosphorus metabolism fluctuation abnormalities). Results: Compared to control patients, those receiving Zicao Ointment plus Xiaoyan Topical Granules had significantly higher overall efficacy, lower VASI, Modified Duo's scores, and PSQI scores at 2 and 4 weeks after treatment, and greater reductions in BUN, Scr, β2-MG, serum phosphorus, iPTH, IL-2, IL-6, and CRP at week 4 ($P<0.05$). Similar serum calcium and total incidence of adverse events were found in the two groups. Conclusion: Zicao Ointment combined with Xiaoyan Topical Granules based on TCM external therapy theory demonstrates clinical efficacy for treating skin pruritus in HD patients.

Keywords: TCM external therapy theory, Zicao Ointment, Xiaoyan (anti-inflammatory) Topical Granules, hemodialysis, skin itching

Introduction

End-stage kidney disease (ESKD) represents the final stage of progressive chronic kidney disease. Affected patients typically present with impaired renal function, systemic toxin accumulation, and symptoms such as limb edema, nausea, and anorexia [1, 2]. As the disease progresses, sepsis may develop, severely affecting patients' quality of life and prognosis [3]. Global statistics indicate 2.6 million ESKD patients currently receive renal replacement therapy such as hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation, with the figure projected to reach 5.4 million by 2030 [4]. HD is a widely used renal replacement therapy for ESKD patients. As a serious complication among such patients, skin pruritus is present in as many as 45.0%, with mild, moderate, and severe symptoms found in 34.4%, 11.4%, and 4.3%, respectively, which seriously threatens both their sleep and life quality [5]. In addition, pruritus compromises the effect maximization of HD and is closely

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related to a prolonged dialysis treatment recovery time and an increased dialysis withdrawal likelihood [6]. Antihistamines, the mainstay to treat skin pruritus in current clinical practice, have unsatisfactory curative effects [7]. To enhance the efficacy for skin pruritus management in HD patients, this study proposes a new treatment based on the traditional Chinese medicine (TCM) external therapy theory.

TCM argues that skin pruritus belongs to the "pruritus due to wind pathogen" and "pruritic dermatosis" categories. In patients on maintenance HD, the pathogenesis lies in the kidneys, with kidney-essence deficiency. Insufficient essence and blood leads to inadequate nourishment and moistening of the skin, resulting in dryness and pruritus due to endogenous wind [8]. Therefore, treatment principles for these patients emphasize dispelling wind, relieving itching, tonifying blood, and nourishing yin [9]. Zicao Ointment is an empirical TCM prescription developed by our department during 2018 to 2022. It has the effects of cooling blood and nourishing yin, diminishing inflammation and relieving itching, expelling wind and moistening dryness, and removing putrefaction and promoting granulation. It is simple to use, low-cost, safe, and not painful. The main component of Zicao Ointment is Arnebiae Radix extracted from Lithospermum erythrorhizon, a plant of the Boraginaceae family. Its active components, such as shikonin and acetylshikonin, exhibit detoxicating, eruption-promoting, blood-cooling, and circulation-promoting effects. They also possess antibacterial and anti-inflammatory properties, enhance fibroblast and endothelial cell activity, and accelerate wound healing [10, 11]. Xiaoyan (Anti-inflammatory) Topical Granules is also an empirical prescription developed based on TCM external treatment theory in our hospital, with Radix Sophorae Flavescentis, Fructus Cnidii, Radix Stemonae, Fructus Xanthii, Flos Lonicerae, Cortex Dictamni Radicis, Flos Chrysanthemi Indici, and Kochiae Fructus being its Chinese medicinal ingredients. Before use, the prescription needs to be dissolved in boiling water and cooled to room temperature before application by soaking or wet dressing to the affected area to exert the effects of clearing away heat, drying dampness, expelling wind, and relieving itching.

This study aimed to evaluate the efficacy of Zicao Ointment combined with Xiaoyan Topical Granules in treating skin pruritus in HD patients. Given the limited evidence regarding this therapeutic approach, this study may provide novel insight into TCM-based management of skin pruritus in HD patients.

Materials and methods

General information

This study was approved by the Ethics Committee of Dongguan Traditional Chinese Medicine Hospital. We retrospectively included 175 patients receiving in-center HD at Dongguan Traditional Chinese Medicine Hospital between May 2022 and May 2025. Patients were divided according to the treatment they actually received (non-randomized): 85 patients who received basic treatment constituted the control group, and 90 who received Zicao Ointment plus Xiaoyan Topical Granules constituted the research group. The groups were well-balanced in general data distributions and demonstrated clinical comparability ($P>0.05$).

Since this study was of a retrospective design, a *post-hoc* power analysis was conducted based on the efficacy of the study cohort (88.89% in the research group and 70.59% in the control group), with the effect size (rate difference) calculated to be 18.30% (standardized effect size, Cohen's $h\approx0.48$). Setting two-tailed $\alpha=0.05$ and power $(1-\beta) = 0.80$, the minimum sample size required for each group was 72 cases, calculated using the difference test formula for comparing rates between two groups. The final actual enrollment was 85 cases in the control group and 90 cases in the research group, exceeding the minimum sample size requirement.

Patient selection criteria

Inclusion criteria: being diagnosed as requiring maintenance HD [12]; meeting the TCM diagnostic criteria for blood deficiency with wind-dryness and blood stasis syndrome (defined as meeting ≥2 cardinal and ≥2 secondary symptoms for blood deficiency with wind-dryness, and ≥1 cardinal or secondary symptom for blood stasis; criteria detailed below); aged 18-80 years; on maintenance HD for more than 6 months; receiving 2-3 HD sessions per week; possessing normal communication and cognition; complete clinical data. The cardinal symptoms for blood deficiency and wind-dryness

syndrome are generalized pruritus, itching with a crawling sensation, and dry skin; the secondary symptoms are mental fatigue, dizziness, palpitations, and insomnia. For blood stasis syndrome, the main symptoms are the presence of numerous scratch marks (TCM syndrome score >2 points), accompanied by purpuric streaks; the secondary symptoms are dull complexion, purple lips, dry mouth without desire to drink, dull purple tongue with petechiae or ecchymoses, and fine and astringent pulse.

Exclusion criteria: itchy skin caused by dermatitis, eczema, or other diseases; pre-HD skin pruritus; allergies to the drugs involved in this study; pregnancy or lactation; hematopoietic or immune system diseases; or systemic diseases such as vasculitis and diabetes.

Treatment methods

Basic treatment, including dietary guidance, psychological nursing, and regular dialysis, was provided for control patients. Additionally, routine interventions for skin pruritus specifically included: (1) applying mild emollients (such as vaseline and urea ointment) to the skin every day to keep it moist; (2) avoiding hot water scalding and using neutral bath solution; (3) wearing loose cotton clothes; and (4) avoiding scratching and applying a local cold compress if necessary.

The research group was treated with Zicao Ointment + Xiaoyan Tropical Granules in addition to the aforementioned measures. Zicao Ointment was prepared in steps described below: Arnebiae Radix (30 g), Saposhnikoviae Radix (20 g), as well as 5 g each of Rhizoma Bletillae, Atractylodis Macrocephalae, white Poria, Chrysanthemum morifolium, and Radix Paeoniae Alba, were added to olive oil (750 mL), boiled, and filtered to remove the medicinal residue. The solution was then added with 50 g of solid wax and subpackaged for cooling and packaging. Application method: The application site was determined as per the doctor's advice. An appropriate posture was used to expose the patient's application site, and a rubber drawsheet of appropriate size was spread. During this process, proper measures were taken to keep warm. After cleaning the skin and confirming skin condition, the ointment was applied evenly to the affected area, with TCM massage subsequently performed to enhance drug penetration. When necessary, coverage with gauze and fixation with adhesive tape or bandage were conducted. During the medication application process, we closely observed the patient's reaction, asked if they were experiencing any discomfort, and were vigilant for any changes in the local skin and condition. After medicine application, the patient was helped to get dressed, placed in a comfortable position, and make up the bed unit. Usage of Xiaoyan Topical Granules: The medicine, comprised of Radix Sophorae Flavescentis, Fructus Cnidii, Radix Stemonae, Fructus Xanthii, Flos Lonicerae, Cortex Dictamni Radicis, Flos Chrysanthemi Indici, and Kochiae Fructus, was put into a basin, melted with boiling water, and then cooled slightly for soaking or wet dressing of the affected area. The granules were used 1-2 packs each time, 1-2 times a day, which could be adjusted according to the patient's condition. A 2-week treatment course and a 4-week observation period were implemented for both groups.

For both groups, TCM syndrome evaluation was completed by trained practitioners. In this study, two Chinese medicine practitioners independently evaluated the syndromes, with Cohen's kappa, an inter-rater reliability coefficient, of 0.632.

Outcome measures

Efficacy: Therapeutic effectiveness, assessed according to the alleviation of pruritus symptoms and skin lesions, was determined as markedly effective (disappeared pruritic symptoms or only slight itching after treatment), effective (relieved pruritic symptoms after treatment with reduced skin lesions compared to baseline), or ineffective (no post-treatment amelioration of the pruritic symptoms or skin lesions). The percentage of the sum of the markedly effective cases and the effective cases in the total number of cases is the total treatment effectiveness rate.

Visual Analog Scale for Itch (VASI) [13]. Patients were self-rated for their pruritus severity with the VASI (a 0-10-point scale) according to their subjective feelings, with 0 for no itching and 10 for the most severe itching that is unbearable. The patients marked the position of the line segment indicating their degree of

itching, followed by measurement to obtain their specific VAS scores.

Modified Duo's Pruritus Score [14]. Measurements of the degree, area, as well as duration and frequency of skin pruritus were made with the Modified Duo's Pruritus Score. The below detailed the evaluation criteria: (1) Skin pruritus degree: 1 point for itching without the need for relief through scratching; 2 points for relieved symptoms after scratching without damaging the skin; 3 points for ineffective symptoms relief after scratching, which damaged the skin; 4 points for extensive skin damage by scratching; 5 points for the presence of dysphoria symptoms; (2) Itching area: 1 point for single-site itching; 2 points for multi-site itching; 3 points for generalized pruritus; (3) Duration and frequency: 1 point was assigned for every 4 episodes of itching lasting ≤10 minutes, or for each single episode lasting >10 minutes, up to a maximum of 5 points. The above three items were evaluated twice (in the morning and afternoon), with the highest possible score being 26 points. At the same time, the degree to which itching interfered with nighttime sleep was scored. Two points were given for each itching-induced arousal, with the highest score of 14 points. Hence, the 24-hour maximum score was 40 points.

Sleep quality [15]. Patients underwent a sleep quality assessment in recent one month by the Pittsburgh Sleep Quality Index (PSQI). Eighteen items from seven major domains, namely sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disorders, hypnotics, and daytime dysfunction, were assessed with a total score ranging from 0 to 21. The higher the patient's score, the worse the sleep quality.

Dialysis adequacy and residual renal function (RRF). Before and after treatment, all the urine excreted by patients in both cohorts within 24 hours was collected for the determination of blood urea nitrogen (BUN) and serum creatinine (Scr) using an automatic biochemical analyzer. Venous blood (3 mL) sampling was performed before and after treatment, and the serum obtained via centrifugation was tested by immunoturbidimetry for β2-microglobulin (β2-MG) concentrations.

Calcium (Ca)-phosphorus (P) metabolism. Before and after treatment, we examined patients' serum Ca and P with an automatic biochemical analyzer and intact parathyroid hormone (iPTH) levels using the electrochemiluminescence method.

Serum indices. Using the enzyme-linked immunosorbent assay (ELISA) technique, we detected patients' interleukin (IL)-2, IL-6, and C-reactive protein (CRP) in the serum.

Safety. We observed and recorded the cases of adverse events such as contact dermatitis, liver injury, skin irritation/burning sensation, Ca-P metabolism fluctuation abnormalities, and calculated the total incidence rate. Abnormalities in Ca-P metabolism were defined as serum Ca, P, or Ca × P product falling outside the clinically acceptable range during treatment. By referring to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [16], the conditions can be specifically categorized as: hyperphosphatemia: serum P>1.45 mmol/L (4.5 mg/dL); hypercalcemia: serum Ca>2.55 mmol/L (10.2 mg/dL); or elevated Ca × P: Ca × P>4.52 $mmoL^2/L^2$ (55 mg^2/dL^2).

In this study, blinding was implemented for the outcome assessors and statistical analysts to minimize bias.

Statistical analysis

SPSS 26.0 was used for data processing. Continuous variables were presented as mean ± standard deviation [SD]). Inter-group and intra-group comparisons were made using independent-sample and paired t-tests, respectively. Categorical variables were presented as numbers (percentage), and inter-group comparisons were preformed using the chi-square test. A *P* value <0.05 was considered significant.

Results

Baseline data

No significant differences were observed between the two groups in terms of age, dialysis age, sex, albumin, disease type, Kt/V, or baseline values of VASI, Modified Duo's Pruritus Score, PSQI, BUN, Scr, β2-MG, serum Ca, serum P, iPTH, IL-2, IL-6, and CRP (P>0.05) (**Table 1**).

Efficacy

In the control group, 19 cases were classified as markedly effective, 41 cases as effective, and 25 cases as ineffective, whereas the cor-

Table 1. Comparison of baseline data between the control and research groups

Data	Control group (n=85)	Research group (n=90)	χ^2/t	P
Age (years)	54.67±10.07	55.54±11.44	0.533	0.595
Dialysis age (months)	29.93±7.48	30.38±7.97	0.385	0.701
Sex			0.719	0.397
Male	47 (55.29)	44 (48.89)		
Female	38 (44.71)	46 (51.11)		
Albumin (g/L)	29.04±6.83	30.82±6.26	1.799	0.074
Disease type			0.847	0.838
Diabetic nephropathy	43 (50.59)	40 (44.44)		
Hypertensive nephropathy	14 (16.47)	18 (20.00)		
Chronic glomerulonephritis	19 (22.35)	23 (25.56)		
Other primary diseases	9 (10.59)	9 (10.00)		
Kt/V	1.30±0.09	1.32±0.11	1.312	0.191
Baseline VASI (points)	7.00 (6.00, 8.00)	7.00 (6.00, 8.00)	-1.485	0.138
Baseline Modified Duo's Pruritus Score (points)	29.48±5.06	29.29±4.91	0.252	0.801
Baseline PSQI (points)	11.75±4.22	12.01±3.32	0.454	0.650
Baseline BUN (μmol/L)	41.46±10.12	42.10±11.44	0.391	0.696
Baseline Scr (μmol/L)	915.66±104.54	914.76±115.17	0.054	0.957
Baseline β2-MG (mg/L)	21.82±4.25	22.57±5.34	1.024	0.307
Baseline serum Ca (mmol/L)	2.09±0.18	2.14±0.21	1.687	0.094
Baseline serum P (mmol/L)	2.07±0.26	2.08±0.33	0.222	0.825
Baseline iPTH (pg/mL)	377.04±129.25	389.38±149.22	0.583	0.561
Baseline IL-2 (pg/mL)	2.53±0.41	2.64±0.50	1.586	0.115
Baseline IL-6 (pg/mL)	3.62±0.54	3.62±0.68	0.000	>0.999
Baseline CRP (mg/L)	7.47±1.95	7.62±2.08	0.491	0.624

Note: VASI, Visual Analog Scale for Itch; PSQI, Pittsburgh Sleep Quality Index; BUN, blood urea nitrogen; Scr, serum creatinine; β2-MG, β2-microglobulin; Ca, calcium; P, phosphorus; iPTH, intact parathyroid hormone; IL-2, interleukin-2; IL-6, interleukin-6; CRP, C-reactive protein.

Table 2. Comparison of curative effects between the control and research groups

Indicator	Control group (n=85)	Research group (n=90)	χ^2	P
Marked effectiveness	19 (22.35)	47 (52.22)		
Effectiveness	41 (48.24)	33 (36.67)		
Ineffectiveness	25 (29.41)	10 (11.11)		
Overall effectiveness	60 (70.59)	80 (88.89)	9.150	0.003

responding numbers in the research group were 47, 33, and 10 cases, respectively. The overall effective rate was significantly higher in the research group than in the control group (88.89% vs. 70.59%, P=0.003) (**Table 2**).

VASI

No significant difference was observed in baseline VASI score between the two groups (P>0.05). Following treatment, VASI scores decreased to varying degrees in both groups. Compared to the control group, the research group exhibited a significantly greater reduction in VASI scores at 2 and 4 weeks after treatment (P<0.05; **Table 3**).

Modified Duo's pruritus score

Baseline Modified Duo's Pruritus Scores were comparable between groups (P>0.05). Following treatment, the scores decreased in both groups, with significantly lower scores observed in the research group than in the control group at 2 and 4 weeks after treatment (P<0.001; **Table 4**).

PSQI

No significant difference was observed in baseline PSQI scores between the two groups (P>0.05). After treatment, PSQI scores decreased significantly in both groups, with the

Table 3. Comparison of Visual Analog Scale for Itch (VASI) scores between the control and research groups

Indicator	Control group (n=85)	Research group (n=90)	Z	P
Pre-treatment	7.00 (6.00, 8.00)	7.00 (6.00, 8.00)	-1.485	0.138
2 weeks post-treatment	6.00 (5.00, 7.00)	5.00 (4.00, 6.00)	-2.546	0.011
4 weeks post-treatment	4.00 (4.00, 5.00)	4.00 (3.00, 5.00)	-1.974	0.048

Table 4. Comparison of Modified Duo's Pruritus Score between the control and research groups

Indicator	Control group (n=85)	Research group (n=90)	t	P
Pre-treatment	29.48±5.06	29.29±4.91	0.252	0.801
2 weeks post-treatment	22.96±5.21	15.22±3.51	11.583	<0.001
4 weeks post-treatment	20.59±4.11	11.46±3.72	15.422	<0.001

Table 5. Comparison of Pittsburgh Sleep Quality Index (PSQI) scores between the control and research groups

Indicator	Control group (n=85)	Research group (n=90)	t	P
Pre-treatment	11.75±4.22	12.01±3.32	0.454	0.650
2 weeks post-treatment	10.59±3.14	8.69±3.41	3.828	<0.001
4 weeks post-treatment	7.51±2.73	5.07±1.93	6.857	<0.001

research group demonstrating significantly lower scores compared to the control group (P<0.001; **Table 5**).

Dialysis adequacy and RRF

Baseline levels of BUN, Scr, and β2-MG were comparable between the two groups (P>0.05). After treatment, all indices showed significant reductions in both groups (P<0.05). Notably, post-treatment levels of these parameters were significantly lower in the research group than in the control group (P<0.05; **Figure 1**).

Ca-P metabolism

Baseline serum Ca, P, and iPTH levels showed no significant differences between the two groups (P>0.05). Following the treatment, serum Ca levels did not change significantly within either group, and no significant difference was observed between groups (P>0.05). In contrast, serum P and iPTH levels decreased significantly after treatment in both groups (P<0.05), with greater reductions observed in the research group (P<0.05; **Figure 2**).

Serum indices

No significant differences were found in baseline IL-2, IL-6, and CRP levels between the two groups (P>0.05). After treatment, all inflammatory markers decreased significantly in both groups (P<0.05), with more pronounced reductions observed in the research group (P<0.05; **Figure 3**).

Safety

In the control group, adverse events included 2 cases of contact dermatitis, 1 case of liver injury, 3 cases of skin irritation/burning sensation, and 10 cases of Ca-P metabolism fluctuation; the corresponding case numbers in the research group were 3, 2, 5, and 8, respectively. No significant difference was observed in the overall incidence of adverse events between the two groups (P>0.05; **Table 6**).

Discussion

The pathophysiology of skin pruritus in hemodialysis (HD) patients involves accumulation of uremic toxins in the skin and activation of non-histaminergic itch pathways, related to immune dysregulation, peripheral neuropathy, and opioid imbalance [17]. This not only further adds disease complexity and causes sleep issues, but also affects the normal work and social activities of patients [18]. It is thus necessary to seek effective and safe intervention measures for skin pruritus in HD patients.

This study found that Zicao Ointment + Xiaoyan Topical Granules can significantly improve curative effects and effectively relieve itching symptoms and skin lesions in HD patients compared with simple basic treat-

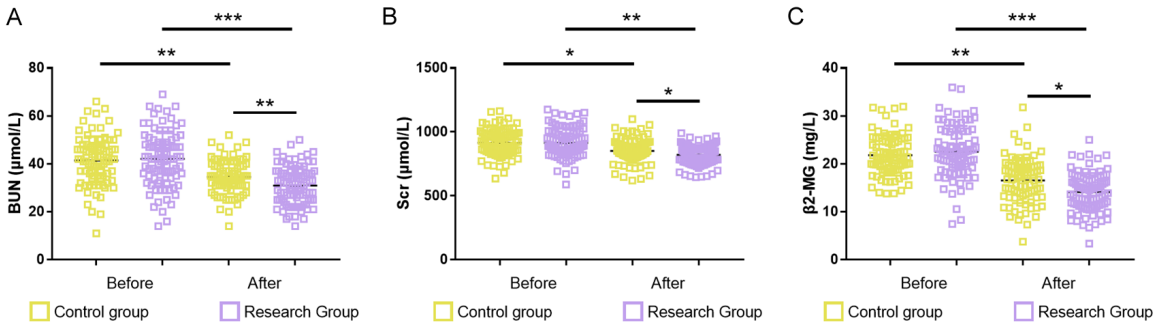

Figure 1. Comparison of renal function-related indicators before and after treatment between the two groups. A. Blood urea nitrogen (BUN). B. Serum creatinine (Scr). C. β2-microglobulin (β2-MG). Note: *P<0.05, **P<0.01, ***P<0.001.

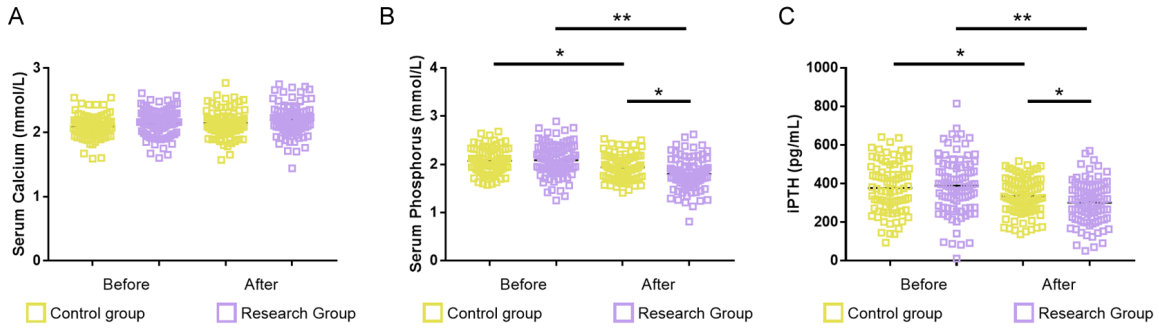

Figure 2. Comparison of calcium-phosphorus metabolism markers before and after treatment between the two groups. A. Serum calcium levels. B. Serum phosphorus levels. C. Intact parathyroid hormone (iPTH) levels. Note: *P<0.05, **P<0.01.

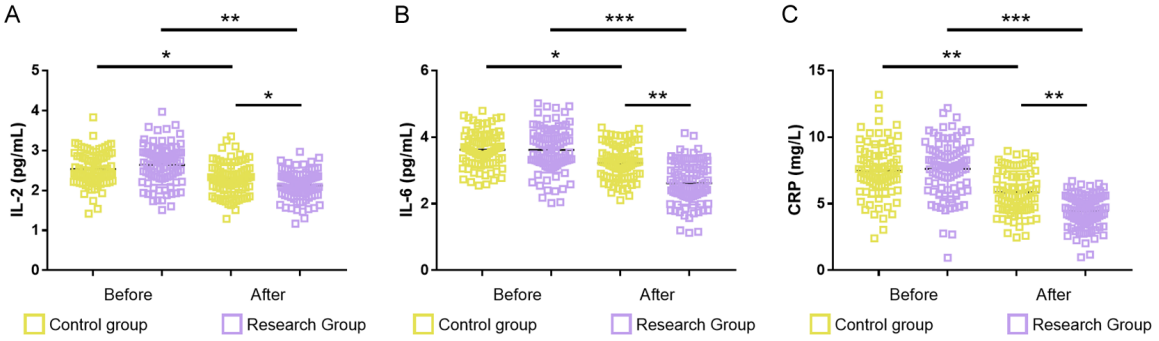

Figure 3. Comparison of serum inflammatory marker levels before and after treatment between the two groups. A. Interleukin-2 (IL-2). B. Interleukin-6 (IL-6). C. C-reactive protein (CRP). Note: *P<0.05, **P<0.01, ***P<0.001.

ment. VASI and Modified Duo's Pruritus Scale scores further confirmed that the combined intervention significantly reduced itching severity. The main components of Zicao Ointment include *Arnebiae Radix, Saposhnikoviae Radix, Rhizoma Bletillae, Atractylodis Macrocephalae, Poria, Chrysanthemum morifolium,* and *Radix Paeoniae Alba*. Of these, *Arnebiae Radix* is the core antipruritic component, which can promote the migration of human keratinocytes and dermal fibroblasts by increasing lipid synthesis, thus playing an effective antipruritic therapeutic role [19]. It also has anti-inflammatory, antibacterial, antioxidant, and antiviral activities, enabling it to reduce the production of pruritus mediators by inhibiting inflammatory factor release, while preventing the aggravation of itching caused by

Table 6. Comparison of safety profiles between the control and research groups

Indicator	Control group (n=85)	Research group (n=90)	χ^2	P
Contact dermatitis	2 (2.35)	3 (3.33)		
Liver injury	1 (1.18)	2 (2.22)		
Skin irritation/burning sensation	3 (3.53)	5 (5.55)		
Calcium-phosphorus metabolism fluctuation abnormalities	10 (11.76)	8 (8.89)		
Total	16 (18.82)	18 (20.00)	0.039	0.844

secondary infections [20]. *Saposhnikoviae Radix* and *Radix Paeoniae Alba* serve as important adjunctive agents for itch relief. The former, by decreasing transient receptor potential vanilloid subtype 1 (TRPV1) expression in macrophages and inhibiting nuclear factor κB p65 subunit (NF-κB p65) phosphorylation, helps mitigate inflammation and itching [21]. The root extract of *Radix Paeoniae Alba* can reduce skin inflammation and scratching behavior by lowering the ratios of serum immunoglobulin (Ig) E, IgG1/IgG2a, and IL-4/interferon (IFN)-γ [22]. *Fructus Cnidii*, the main antipruritic component of Xiaoyan Topical Granules, can suppress the activity of the transient receptor potential cation channel subfamily V, member 1 (TRPV1) ion channel to block histamine-dependent itching signal transmission, thus playing an antipruritic role [23]. When used together, these two TCM external therapies act through distinct pathways to exert synergistic antipruritic effects.

PSQI assessment revealed that Zicao Ointment combined with Xiaoyan Topical Granules more effectively improved sleep quality in HD patients. This may be attributed to paeoniflorin, an active component of *Radix Paeoniae Alba*, which can promote non-rapid eye movement sleep through the adenosine A1 receptor to improve sleep quality [24]. Chrysanthemum morifolium, another component of Zicao Ointment, may up-regulate γ-aminobutyric acid type A receptor (GABAA) and 5-hydroxytryptamine receptor 1A (5-HT1A) expression through its active component luteolin-7-glucoside, thus enhancing δ-wave activity and prolonging non-rapid eye movement sleep to play a role in improving sleep [25]. Notably, these findings should be interpreted with caution, as they represent possible mechanisms rather than definitive conclusions. Then, it was found that Zicao Ointment + Xiaoyan Topical Granules had significant advantages in enhancing dialysis adequacy and RRF in HD patients, achieved by positively modulating associated indexes (BUN, Scr, β2-MG). This may be attributed to the fact that Arnebiae Radix restores immune cell activity and balances cytokines by modulating the MAPK axis (especially p38 and JNK), thus enhancing kidney function [26]. Honeysuckle peptide, the bioactive peptide of Flos Lonicerae (a component of Xiaoyan Topical Granules), can effectively reduce the levels of serum uric acid, BUN, and Scr by inhibiting the activity of xanthine oxidase while inhibiting the secretion of inflammatory cytokines, thereby reducing renal inflammation [27], which can partially explain the renoprotection mechanism of Xiaoyan Topical Granules. The combined intervention also exerted a certain positive effect on ameliorating Ca-P metabolism fluctuation abnormalities (evidenced by decreased serum P and iPTH) without interfering with the homeostatic regulation of Ca levels. We also found that the combined intervention reduced inflammation in patients and alleviated imbalances in the inflammatory cytokine network. Finally, the safety evaluation indicated that pruritus treatment with Zicao Ointment + Xiaoyan Topical Granules in HD patients did not significantly increase overall adverse events.

Several studies have investigated TCM treatments for skin pruritus in HD patients. Lu et al. [28] reported that the use of TCM in uremic pruritus patients undergoing dialysis did not significantly increase adverse events, and that the antipruritic effect showed a time-dependent trend, similar to our results. Zhang et al. [29] found that Bushen Qudu Formula effectively relieved itching and inhibited BUN and CRP levels in uremic patients on HD, without significantly influencing serum Ca and P levels, which is largely consistent with our observations. Similarly, Bai et al. [30] demonstrated

that Uremic Clearance Granules effectively inhibited BUN and Scr, whose combination with high-flux HD further enhanced the body's clearance effect of internal and external toxins and alleviated the itching symptoms of uremic patients.

Several limitations of this study require refinement. First, the single-center retrospective design is a limitation; future multicenter, prospective, randomized, double-blind, placebo-controlled trials are warranted to confirm our findings. Second, patient adherence to topical treatment was not evaluated, and prospective collection of adherence data is needed in future studies. Third, given the short follow-up period, longer-term (e.g., 5-year) follow-up studies are needed to assess the durability of efficacy and long-term prognosis. Fourth, immunological indicators were not evaluated, and future prospective studies should assess immune-related indices to clarify the immunomodulatory effects of the combined regimen. Finally, the absence of a monotherapy control group (Zicao Ointment or Xiaoyan Topical Granules alone) limits our ability to distinguish synergistic effects from the effect of either agent alone or non-specific factors such as additional application time or patient attention.

Conclusion

Zicao Ointment combined with Xiaoyan Topical Granules, as a TCM external therapy, effectively relieves pruritus, reduces itching intensity, improves sleep quality, enhances dialysis adequacy and residual renal function, partially corrects Ca-P metabolic disturbances, and reduces inflammation, without increasing the overall incidence of adverse events.

Disclosure of conflict of interest

None.

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