

Original Article

Efficacy of Shenkang injection and alprostadil for chronic nephritis and its influences on immunity, coagulation, renal function, VEGF and ACTH

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Received September 23, 2020; Accepted November 11, 2020; Epub February 15, 2021; Published February 28, 2021

Abstract: Objective: To investigate the efficacy of Shenkang injection combined with alprostadil for the treatment of chronic nephritis (CN) and the influences on immunity, coagulation, renal function, vascular endothelial growth factor (VEGF) and adrenocorticotrophic hormone (ACTH). Methods: The clinical data of 119 patients with CN who were admitted to our hospital were collected retrospectively. The patients were divided into Group A (n=59) and Group B (n=60) in accordance with the treatment options. Group A was treated with alprostadil, while Group B was treated with Shenkang injection and alprostadil. The clinical efficacies, the changes of the indices for renal functions, coagulation functions and immune functions, proteinuria and VEGF and ACTH were compared between the two groups before and after treatment. Results: The overall response rate (ORR) in Group B (93.33%) was higher than that in Group A (67.80%) ($P < 0.05$). Compared with those in Group A, the levels of blood urea nitrogen, serum creatinine, VEGF, Fibrinogen and 24-hour urine protein, and urinary albumin excretion rate were lower, thrombin time, activated partial thromboplastin time and prothrombin time were longer, and the levels of immunoglobulin IgM, IgG and IgA and the level of ACTH were higher in Group B after treatment ($P < 0.05$). Conclusion: Shenkang injection combined with alprostadil can improve immunity, coagulation, renal function, and the levels of VEGF and ACTH of patients with CN, exhibiting a remarkable efficacy.

Keywords: Chronic nephritis, shenkang injection, alprostadil, body's immunity, coagulation, renal function

Introduction

Clinically, chronic nephritis (CN), also known as chronic glomerulonephritis, is a glomerular disease characterized by glomerular lesions due to a variety of causes [1]. The main clinical manifestations of CN include edema, hypertension, hematoma and proteinuria. The onset of CN varies from person to person, and CN patients can develop a prolonged condition, have a slow progression, and experience a decline in their renal function to varying degrees. Without timely intervention, CN patients may eventually suffer from chronic renal failure [2, 3].

Currently, there is not a clinical option to treat CN. Hormone drugs, anti-platelet aggregation drugs and immunosuppressants are adopted to treat CN patients through delaying renal fail-

ure and reducing proteinuria. Although such medication has certain therapeutic effects, long-term medication can easily lead to multiple adverse drug reactions (ADRs), which is not conducive to the prognosis of CN patients [4, 5]. In recent years, in-depth studies on the treatment of CN with traditional Chinese medicine (TCM) have been widely applied. According to Traditional Chinese Medicine, CN has been classified into the categories of "Renal Wind", "Fatigue & Deficiency" and "Renal Water". CN is considered to be the syndrome of vacuity-repletion complex and root vacuity and tip repletion differentiation, and the root is renal deficiency and the tip is damp-heat and blood stasis [6, 7]. Due to the deficiency of kidney Qi, CN patients experience a decline of essential Qi, and then urinary turbidity. Therefore, the treatment should focus on activating blood circulation to dissipate blood stasis and supple-

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menting kidney Qi [8]. Shengkang injection is a TCM compound injection prepared using the modern pharmaceutical preparation techniques in strict accordance with the TCM theory [9]. This injection mainly contains Radix Salviae Miltiorrhizae, Flos Carthami, Radix Astragali seu Hedysari and rhubarbs, and has been widely used in the treatment of multiple renal diseases.

In view of this, it is scientific and feasible to adopt Shengkang injection combined with alprostadil to improve the renal function, coagulation function and immunity in CN patients.

Materials and methods

Clinical data

The clinical data of 119 CN patients admitted to our hospital from June 2017 to June 2020 were collected retrospectively. The patients were divided into Group A (n=59) and Group B (n=60) in accordance with the treatment options. Group A was treated with alprostadil, while Group B was treated with Shengkang injection and alprostadil. (1) Inclusion criteria: patients diagnosed with CN [10]; with no contraindications to the drugs in this study; strict compliance to medication regimen. All patients signed the informed consent. The study was conducted with the approval from the Medical Ethics Committee. (2) Exclusion criteria: lactation or pregnancy; allergic constitution; complicated with severe diseases of the hematopoietic system; complicated with severe diseases of immune system; complicated with severe organic diseases (e.g., cardiac and hepatic diseases); those who withdraw halfway; or were complicated with coagulation dysfunction.

Methods

Group A: After admission, the patients received the conventional treatment (e.g., reduction of blood pressure, diuresis, and diet control). The patients received 10 µg of alprostadil injection (approval number: SFDA approval number H20103100, Manufacturer: Xi'an Libang Pharmaceuticals Co., Ltd., standard dosage form: 2 ml: 10 µg) and 100 ml of 0.9% sodium chloride injection (approval number: SFDA approval number H34023837 (prescription drug), Manufacturer: Shanghai Huayuan Anhui Jinhui Pharmaceutical Co., Ltd., specification: 100 ml:

0.9 g) via an intravenous drip once a day for 12 d.

Group B: The administration of alprostadil in Group B was the same as that in Group A. Additionally, the patients received 250 ml of 5% glucose injection (approval number: SFDA approval number H52020414, Manufacturer: Guizhou Tiandi Pharmaceutical Co., Ltd., specification: 250 ml: 12.5 g) and 60 ml of Shengkang injection (Manufacturer: Xi'an Shiji Shengkang Pharmaceutical Industry Co. Ltd., approval number: SFDA approval number Z20040110, specification: 20 ml*5 pcs/box) via an intravenous drip once a day for 12 d.

Observational indices

Assessment criteria of efficacy [11]: After treatment, normal renal function and red blood cell number and negative urine protein were considered controlled, the basically normal renal function, a decrease by more than 3/H[P in the red blood cells, and a decrease by more than two "+" in the urine protein were considered marked response, the improved renal function, a decrease by less than 3/H[P in red blood cells, and a decrease by 1 "+" in the urine protein were considered moderate response, and no change of all indices was considered no response. Moderate response + marked response + controlled = overall response.

Renal function indices [12]: Before and after treatment, the levels of blood urea nitrogen (BUN) and serum creatinine (Scr) in the two groups were measured using a fully automated biochemistry analyzer.

Coagulation function indices [13]: Before and after treatment, a volume of 2 ml of venous blood from the elbow was drawn from the two groups of patients in a fasted state, followed by being centrifuged at 3000 r/min for 15 min. Fibrinogen (FIB), thrombin time (TT), activated partial thromboplastin time (APTT) and prothrombin time (PT) were measured using a fully automated coagulation analyzer.

Immune function indices [14]: Before and after treatment, a volume of 2 ml of venous blood was drawn from the two groups of patients in a fasted state, followed by being centrifuged at 3000 r/min for 15 min. The contents of plasma-derived immunoglobulins (IG), IgM, IgG and

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Table 1. Comparison of general data between the two groups [n (%)]/($\bar{x} \pm s$)

| Data | | Group A (n=59) | Group B (n=60) | t/ χ^2 | P |
|---------------------------|---|-------------------|-------------------|-------------|-------|
| Gender (Cases) | M | 38 (64.41) | 41 (68.33) | 0.206 | 0.650 |
| | F | 21 (35.59) | 19 (31.67) | | |
| Age (years) | | 39.96±1.28 | 40.02±1.19 | 0.265 | 0.792 |
| Course of disease (years) | | 4.06±0.16 | 4.09±0.15 | 1.055 | 0.293 |
| Weight (kg) | | 53.15±1.96 | 53.18±1.92 | 0.084 | 0.933 |

++) between the two groups ($P > 0.05$) (**Table 1**).

Comparison of treatment efficacies between the two groups

There were 18 cases that were controlled, 12 cases with marked response, 10 cases with a moderate response and 19 cases with

no response in Group A, and the corresponding data in Group B were 23 cases, 16 cases, 17 cases and 4 cases respectively. The overall response rate in Group B (93.33%) was higher than that in Group A (67.80%) ($P < 0.05$) (**Table 2**).

Comparison of renal function indices between the two groups

Before treatment, there was no significant difference in renal function indices between the two groups ($P > 0.05$). Compared with those before treatment, BUN and SCr levels in the two groups decreased after treatment ($P < 0.05$). BUN and SCr levels in Group B were lower than those in Group A after treatment ($P < 0.05$) (**Figure 1**).

Comparison of coagulation function indices between the two groups

Before treatment, there was no significant difference in coagulation function indices between the two groups ($P > 0.05$). Compared with those before treatment, TT, APTT, PT were prolonged and FIB levels were decreased in the two groups after treatment ($P < 0.05$).

Group B exhibited longer TT, APTT and PT and lower FIB levels than Group A after treatment ($P < 0.05$) (**Figure 2**).

Comparison of immune function indices between the two groups

Before treatment, there was no significant difference in immune function indices between the two groups ($P > 0.05$). Compared with those before treatment, the levels of IgM, IgG and IgA in the two groups decreased after treatment ($P < 0.05$). The levels of IgM, IgG and IgA in Group B were higher than those in Group A after treatment ($P < 0.05$) (**Figure 3**).

IgA, were determined by enzyme linked immunosorbent assay (ELISA).

Proteinuria indices [15]: Before and after treatment, a volume of 2 ml of venous blood was drawn from the two groups of patients in a fasted state in the morning, followed by being centrifuged at 3000 r/min for 15 min. Urinary albumin excretion rate (UAER) and 24-hour urine protein (24hUpro) were measured by turbidimetry and radioimmunoassay, and the operations were performed in strict accordance with the kit instructions.

Vascular endothelial growth factor (VEGF) and adrenocorticotrophic hormone (ACTH) [16]: Before and after treatment, a volume of 2 ml of venous blood was drawn from the two groups of patients in a fasted state in the morning, followed by being centrifuged for at 3000 r/min for 15 min. Serum ACTH levels were measured by turbidimetry and radioimmunoassay, and VEGF was measured by ELISA.

Statistical analysis

SPSS 22.0 was adopted for statistical analysis. The measurement data were expressed by mean \pm standard deviation. The data conforming to normal distribution were detected by t test, and the data not conforming to normal distribution were detected by Mann-Whitney U test. The enumeration data were expressed by [n (%)], and the enumeration data between groups were compared by chi-squared test. $P < 0.05$ indicated a statistically significant difference.

Results

Comparison of general data between the two groups

There was no statistical significance in terms of gender, age, weight and course of disease (9

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Table 2. Comparison of efficacies between the two groups [n (%)]

| Group | Number of cases | Controlled | Marked response | Moderate response | No response | Overall response |
|----------|-----------------|------------|-----------------|-------------------|-------------|------------------|
| Group A | 59 | 18 (30.51) | 12 (20.34) | 10 (16.95) | 19 (32.20) | 40 (67.80) |
| Group B | 60 | 23 (38.33) | 16 (26.67) | 17 (28.33) | 4 (6.67) | 56 (93.33)* |
| χ^2 | | | | | | 12.442 |
| <i>P</i> | | | | | | 0.000 |

Note: *indicates the comparison with Group A, $P < 0.05$.

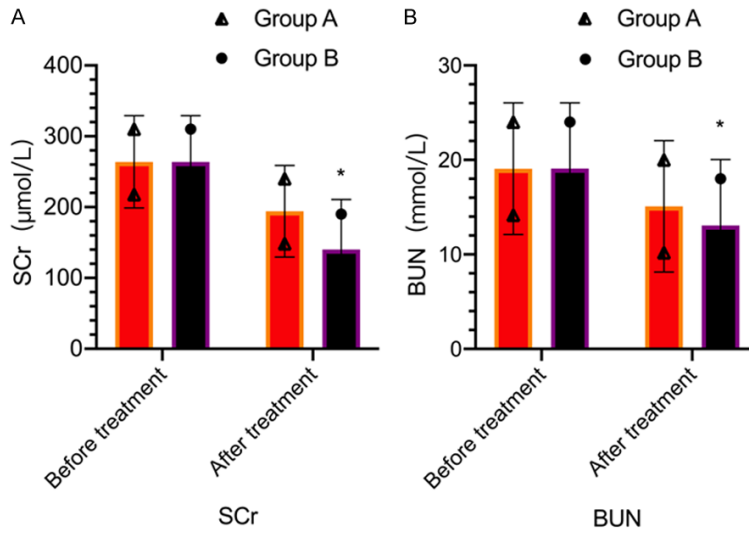


Figure 1. Comparison of renal function indices between the two groups. A. Shows the comparison of SCr between the two groups before treatment, $P > 0.05$; SCr level in Group B was lower than that in Group A after treatment ($P < 0.05$); B. Exhibits the comparison of BUN between the two groups before treatment, $P > 0.05$; BUN level in Group B was lower than that in Group A after treatment ($P < 0.05$). * indicates the comparison with Group A, $P < 0.05$.

Comparison of proteinuria indices between the two groups

Before treatment, there was no significant difference in UAER and 24hUpro levels between the two groups ($P > 0.05$). Compared with those before treatment, UAER and 24hUpro in the two groups decreased after treatment ($P < 0.05$). UAER and 24hUpro in Group B were lower than those in Group A after treatment ($P < 0.05$) (Table 3).

Comparison of VEGF and ACTH between the two groups

Before treatment, there was no significant difference in VEGF and ACTH between the two groups ($P > 0.05$). Compared with those before treatment, ACTH levels were elevated and VEGF levels decreased in the two groups after treat-

ment ($P < 0.05$). Group B showed higher ACTH levels and lower VEGF levels than Group A after treatment ($P < 0.05$) (Figure 4).

Discussion

Clinically, CN is an autoimmune disease characterized by proteinuria, hypertension and edema with a high incidence rate, and is believed to be induced by various protozoa, viruses or bacterial infections through immune or non-immune mechanisms and inflammatory mediators. In server cases, CN may develop into uremia, which seriously threatens the life of CN patients [17, 18]. Although western medicine therapy exhibits certain effects in the treatment of CN, the effects

of a single medication need to be further improved [19]. In this study, alprostadil, which is a natural prostaglandin substance with a high biological activity, can inhibit the formation of immune complexes and platelet aggregation, increase microcirculation, prevent thrombosis and protect vascular endothelium. However, the efficacy of alprostadil in the treatment of CN needs to be further improved [20]. In view of this, Shenkang injection combined with conventional western medicine therapy was adopted to treat CN in this study.

Based on the clinical features and manifestations of CN, CN has been classified into the categories of “Renal Wind”, “Fatigue & Deficiency” and “Renal Water” in TCM. It is considered that the common causes of CN include imbalance of seven emotions, namely postpartum, taxation damage, toxicity, heat,

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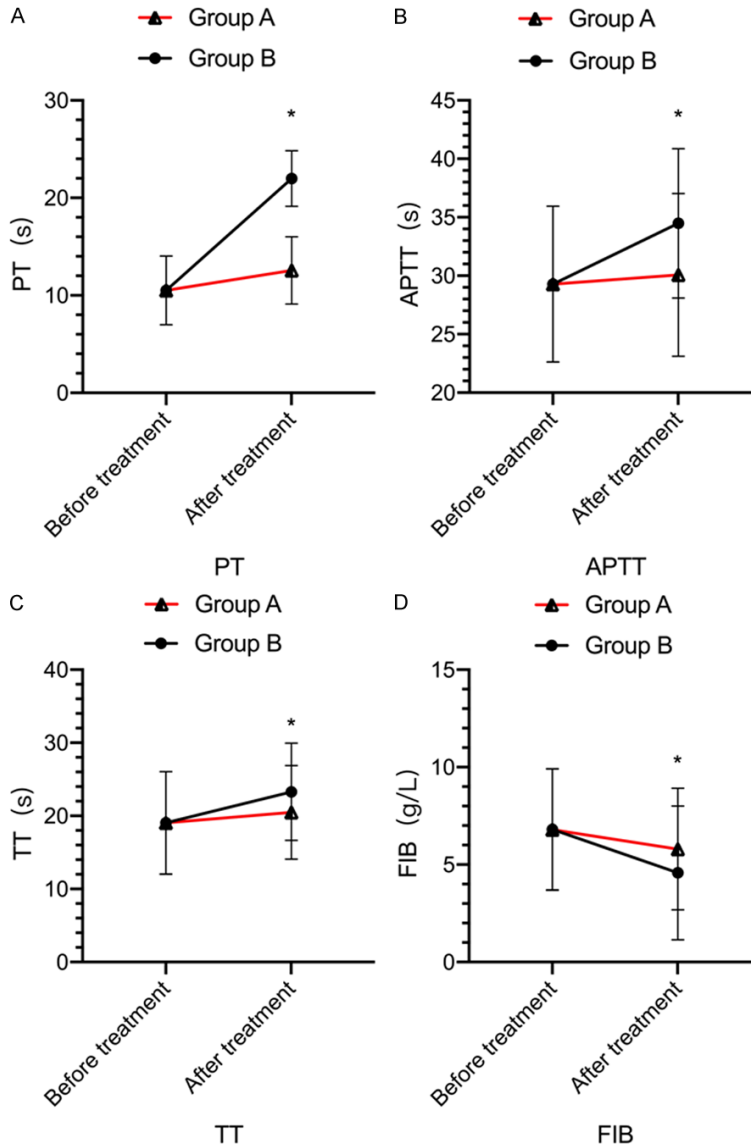


Figure 2. Comparison of coagulation function indices between the two groups. A. Shows the comparison of TT between the two groups before treatment, $P > 0.05$; TT in Group B was longer than that in Group A after treatment ($P < 0.05$). B. Suggests the comparison of APTT between the two groups before treatment, $P > 0.05$; APTT in Group B was longer than that in Group A after treatment ($P < 0.05$). C. Reveals the comparison of PT between the two groups before treatment, $P > 0.05$; PT in Group B was longer than that in Group A after treatment ($P < 0.05$). D. Shows the comparison of FIB between the two groups before treatment, $P > 0.05$; FIB in Group B was lower than that in Group A after treatment ($P < 0.05$). * indicates the comparison with Group A, $P < 0.05$.

dampness, cold and wind. Among them, dampness is the core of pathogenesis, and blood stasis is throughout the whole course of disease. Therefore, the attention should be paid to removing blood stasis and dispelling dampness during the treatment [21]. In this study,

remove stasis. Radix Salviae Miltiorrhizae is slightly cold and bitter, which can clear the heart and eliminate vexation, free channels and relieve pain, and quicken the blood and remove stasis. The combined medication of the above-mentioned herbs can quicken the blood

Group B was superior to Group A regarding the overall response rate, the renal function indices and proteinuria indices after treatment, suggesting that Shenkang injection combined with alprostadil can achieve satisfactory clinical efficacy and effectively improve the renal function of CN patients. Wang et al. [22] also found that the renal function indices and proteinuria indices of patients treated with Shenkang injection combined with alprostadil were better than those treated with alprostadil alone, which was highly consistent with the results of this study. To explore its mechanism of action, Shenkang injection, a TCM compound injection comprising Radix Salviae Miltiorrhizae, Flos Carthami, Radix Astragali seu Hedysari and rhubarb, fully embodies the TCM concept of “integrated treatment”, “overall conditioning”, “synergism” and “multi-component”, and can treat both tip and root of the issue’s cause. Rhubarb is cold and bitter in nature which can free the bowels and purge turbidity, and clear heat and resolve toxins. Radix Astragali seu Hedysari is warm in nature and sweet in taste, which can regenerate tissues to heal wounds, facilitate detoxification and expel pus, and supplement Qi and secure the exterior. Flos Carthami is warm in nature and acrid in taste, which can free channels and relieve pain, and quicken the blood and

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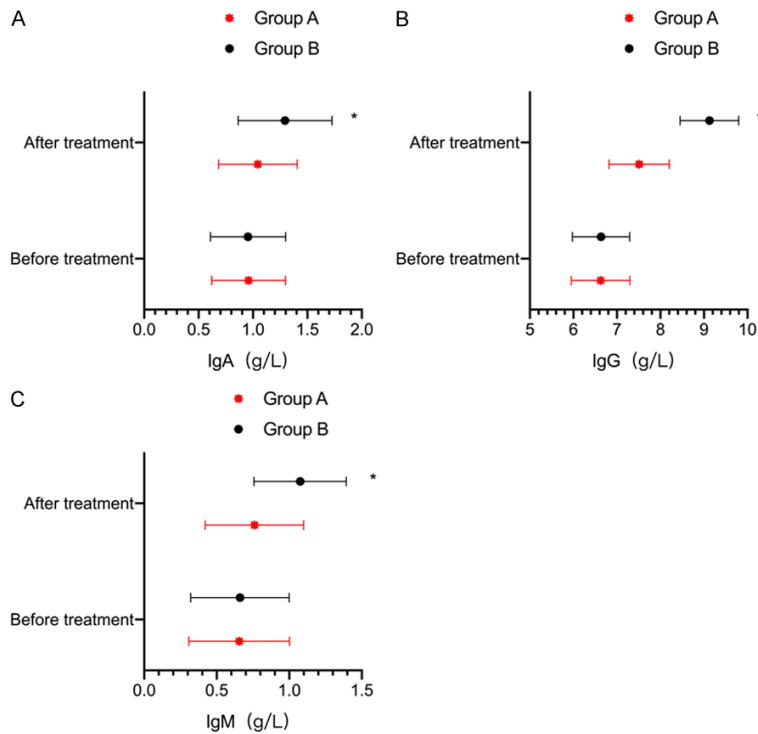


Figure 3. Comparison of immune function indices between the two groups. A. Shows the comparison of IgA between the two groups before treatment, $P > 0.05$; IgA in Group B was higher than that in Group A after treatment ($P < 0.05$). B. Shows the comparison of IgG between the two groups before treatment, $P > 0.05$; IgG in Group B was higher than that in Group A after treatment ($P < 0.05$). C. Reveals the comparison of IgM between the two groups before treatment, $P > 0.05$; IgM in Group B was higher than that in Group A after treatment ($P < 0.05$). * indicates the comparison with Group A, $P < 0.05$.

and remove stasis and free the channels and relieve pain [23, 24]. Shenkang injection combined with alprostadiil can exert drug effects from different mechanisms, and improve clinical symptoms and the renal function, thereby improving the clinical efficacy [25]. Additionally, clinical studies have shown that the incidence of CN is closely related to fibrinolysis, coagulation and collective immune system. Therefore, timely improvement of proteinuria can effectively protect the vascular endothelium and the renal function, improve immune function and coagulation function, and help delay or reverse the disease. In this study, Group B was superior to Group A regarding the indices for the renal function and immune function after treatment, exhibiting that alprostadiil combined with Shenkang injection can improve the immunity and coagulation function of CN patients. Based on the investigation of its mechanism of action, this may be due to the reason that Shenkang

injection can suppress the coagulation and platelet aggregation. Radix Radix Astragali seu Hedysari, containing proteins, amino acids and astragalus polysaccharides, can reduce the viscosity of fibrinogen and plasma. Astragalus polysaccharides can inhibit platelet aggregation, thus hindering thrombosis formation and improving renal blood flow [26]. Besides, Radix Astragali seu Hedysari has immunomodulatory effects, and can increase immunoglobulin content, promote the excretion of antibodies, and enhance immune systems. Flos Carthami, containing safflower pigment, can markedly improve blood viscosity, enhance fibrinolytic activity, and inhibit thrombosis formation. Radix Salviae Miltiorrhizae, containing tanshinone, can reduce blood viscosity, inhibit platelet aggregation and effectively increase the microcirculation of the body. Clinical studies have suggested that the HPA

(hypothalamus-pituitary-adrenal axis) plays a crucial role in the occurrence and progression of CN, and ACTH is an important factor of HPA. ACTH level in CN patients is lower than that in the healthy people [27]. VEGF is a powerful angiogenic factor expressed in mesangial cells and endothelial cells, and it can promote the proliferation of endothelial cells and improve vascular permeability. VEGF is a vasoactive factor and it plays a significant role in microangiopathy. The abnormal expression of VEGF may lead to an increase in the urine protein and microvascular leakage, causing the kidney to be in a state of high filtration. The obviously enlarged basement membrane and the hypertrophic glomerulus lead to the deterioration of the renal function [28]. In this study, Group B showed higher ACTH and lower VEGF levels than Group A after treatment ($P < 0.05$), exhibiting that Shenkang injection combined with alprostadiil could effectively protect the renal function and reduce renal dam-

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Table 3. Comparison of proteinuria indices between the two groups ($\bar{x} \pm s$)

| Group | UAER ($\mu\text{g}/\text{min}$) | | 24hUpro (mg) | |
|----------------|-----------------------------------|----------------------------------|---------------------|-----------------------------------|
| | Before treatment | After treatment | Before treatment | After treatment |
| Group A (n=59) | 1215.63 \pm 15.52 | 985.69 \pm 8.59 [#] | 2539.63 \pm 12.52 | 2118.63 \pm 9.52 [#] |
| Group B (n=60) | 1215.93 \pm 15.08 | 802.12 \pm 3.68 ^{#,*} | 2539.72 \pm 12.49 | 1801.26 \pm 5.16 ^{#,*} |
| t | 0.107 | 129.614 | 0.039 | 226.598 |
| P | 0.915 | 0.000 | 0.969 | 0.000 |

Note: [#]indicates the comparison with before treatment, $P < 0.05$, ^{*}indicates the comparison with Group A, $P < 0.05$.

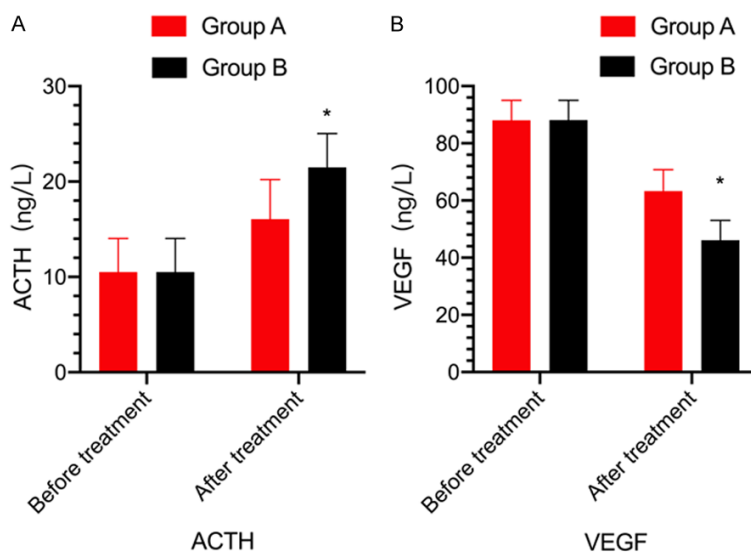


Figure 4. Comparison of VEGF and ACTH between the two groups. A. Shows the comparison of ACTH between the two groups before treatment, $P > 0.05$; ACTH in Group B was higher than that in Group A after treatment ($P < 0.05$). B. Exhibits the comparison of VEGF between the two groups before treatment, $P > 0.05$; VEGF in Group B was lower than that in Group A after treatment ($P < 0.05$). * indicates the comparison with Group A, $P < 0.05$.

age. Based on the investigation of its mechanism of action, this may be due to the reason that, the combined application of the four herbs in Shenkang injection can boost Qi and quicken the blood, and prevent counterflow and purge turbidity by targeting the pathological mechanism of root vacuity and tip repletion, thus improving the clinical symptoms and renal function of CN patients.

In summary, Shenkang injection combined with alprostadil can improve the immunity, coagulation, renal function, and the levels of VEGF and ACTH of CN patients, exhibiting a remarkable efficacy.

Although some results have been obtained in this study, there is a limitation of small sample size. Therefore, the future in-depth studies with a larger sample size should be conducted.

Disclosure of conflict of interest

None.

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