

Progress of Application of Shenfukang II Capsule in Iga Nephropathy

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Abstract: In this paper, Shenfukang II capsule was used to investigate the treatment of IgA nephropathy by literature review, mainly from three aspects: theoretical research, experimental research and clinical research, and obtained certain clinical efficacy, with fewer side effects and drug conjunctibles. Long-term application can reduce toxicity and increase efficacy of IgA nephropathy patients, and delay the deterioration of IgA nephropathy in the later stage. The efficacy of improving long-term prognosis was summarized and analyzed here.

1. Introduction

IgA nephropathy (IgAN ImmunoglobulinA nephropathy) is put forward by the French scholar Berger as early as 1968, pathological changes of glomerular mesangial area is given priority to with immunoglobulin A immune complex deposition, mesangial cell and mesangial matrix proliferation as the basic pathology of primary glomerular disease, Renal puncture pathological biopsy is an important method to confirm the diagnosis and the degree of lesion. Glomerulosclerosis, renal interstitial fibrosis and intrarenal artery lesions are important causes of poor prognosis. Its clinical manifestations are hematuria with or without varying degrees of proteinuria, hypertension and renal impairment. About 30-40% of patients will progress to end-stage kidney disease (ESRD) within 20 years [1,2]. IgA nephropathy has a complex and unclear pathogenesis and is currently considered to be an autoimmune disease limited to the kidney. The more widely recognized mechanism is the four-fold shock theory [3]. In addition, infection, lymphocyte dysregulation, genetic factors, intracellular signaling pathway activation, related immune factors, mucosal system (intestinal flora dysregulation mechanism), complement activation, etc. all participate in the occurrence and development of IgA nephropathy, making the mechanism of this disease complicated.

There is no record of the name of "IgA nephropathy" in ancient medical books, which can be summarized in the categories of "kidney wind", "kidney fatigue", "deficiency", "low back pain", "hematuria" and "edema" according to the description of relevant clinical symptoms. Its etiology is complicated and there are many uncontrollable factors. Modern doctors have more understanding of the etiology and pathogenesis of IgA nephropathy. They think that due to the common causes of

internal, external or internal and external causes, the pathogenesis is always due to deficiency and excess, deficiency of spleen and kidney, wind-heat, damp-heat, heat-toxin, blood stasis and so on. The disease is located in the kidney and is closely related to the lung, spleen and liver. Professor Chen Hongyu [4] believes that IgA nephropathy is located in the kidney, which is closely related to lung, spleen, liver and Sanjiao. Based on the deficiency of both qi and yin, and marked by pathological products such as qi stagnation, rheumatism and blood stasis, external pathogen is an indispensable inducement. Exogenous evil qi invades the kidney through the meridians and becomes poison, resulting in damage to the kidney collaterals, causing blood not to return to the meridian and bleeding out of the pulse, showing hematuria; chronic kidney qi deficiency is not solid, lost in sealing, and albuminuria can be seen. Professor Zhan Huakui [5] believes that the pathogenesis of hematuria in IgA nephropathy is complicated, but it is mainly divided into three categories: damp-heat, blood stasis and deficiency, and damp-heat and blood stasis are the key to treatment. Wang Liping et al. [6] found that blood stasis syndrome had a certain positive correlation with the pathological damage of kidney tissue in IgA nephropathy, which could reflect the severity of kidney disease in IgAN, suggesting that blood stasis is an important factor throughout IgA nephropathy. In general, IgA nephropathy mainly focuses on the deficiency of the lung, spleen, liver and kidney organs, and the evil gases such as congestion, dampness and heat, wind evil, turbidity and poison are the standard, and invade the human body, causing deficiency and insufficiency, and causing different pathological changes. Most patients with IgA nephropathy show a chronic and continuous development process, often characterized by positive deficiency, or mixed deficiency and deficiency, spleen and kidney deficiency combined with damp-heat, blood stasis is one of the most common syndrome types of IgA nephropathy.

2. Theoretical study on Shenfukang II capsule in treating IgA nephropathy.

2.1. Sification and clinical characteristics of IgA nephropathy

At present, Lee's grade, Hass's grade and Oxford classification are commonly used in the diagnosis and grading of IgA nephropathy. According to the degree of Mesangial cell proliferation and glomerular sclerosis and the severity of the disease, IgA nephropathy is divided into 5 grades [7]. The diagnostic criteria of each stage are as follows: Grade I: Most of the glomeruli are normal, without crescent formation or segmental lesions (such as sclerosis, adhesion, necrosis, etc.). Grade II: < 50% of glomeruli show mesangial cell proliferation and < 15% of glomeruli show visible or invisible crescent formation or segmental lesions. Grade III: Diffuse mesangial hyperplasia and widening, focal segmental exacerbation, occasional balloon adhesion and small cell fibrous crescent formation, rare tubular atrophy. Grade IV: < 45% of glomeruli are associated with crescent formation, segmental lesions, or whole glomerular sclerosis, tubular atrophy, interstitial inflammatory cell infiltration, and interstitial fibrosis. Grade V: > 45% of the glomeruli were accompanied by crescent formation, segmental lesions, or whole glomerular sclerosis. Tubular atrophy, interstitial inflammatory cell infiltration, and fibrosis were more severe than grade IV.

According to the Practice Guide for Western Medicine Diagnosis and TCM Syndrome Differentiation of IgA Nephropathy [8], TCM syndrome differentiation of IgA nephropathy can be divided into acute phase and chronic duration phase. In the acute phase, exogenous wind-heat syndrome and lower jiao damp-heat syndrome are included. Chronic duration is divided into lung qi deficiency syndrome, qi Yin deficiency syndrome, liver and kidney Yin deficiency syndrome, spleen and kidney Yang deficiency syndrome. Nie Lifang [9] Based on practical guidelines and the pathogenesis characteristics and clinical manifestations of IgA nephropathy, divided IGA nephropathy into acute onset period dominated by evil accumulation and chronic onset period dominated by positive deficiency. Acute onset period was divided into wind heat invading lung syndrome and lower jiao damp-heat syndrome according to different evil qi and invading sites.

According to the different functions of qi, blood and Yin and Yang of Zangfu organs, chronic extension can be divided into Qi and Yin deficiency, liver and kidney Yin deficiency, spleen and kidney qi deficiency and blood stasis blocking collaterals, and it is suggested that lung and kidney should be treated together during acute attack, while chronic extension should be treated with spleen and kidney.

Clinically, the development process of IgA nephropathy is insidious. When the disease is in a progressive state, only the changes in urinary protein cannot be completely reflected (some IgA nephropathy with more than minor lesions in urinary protein), the changes in renal function are not sensitive in the early stage, and the proportion of glomerulosclerosis and interstitial fibrosis is at least 30% when creatinine is elevated. In the early stage, the clinical symptoms of patients were not significant, proteinuria and hematuria were mostly found by physical examination, or the foam in urine increased for unknown reasons and did not dissipate for a long time when they came to the hospital, which may be consistent with the clinical symptoms of Lee's grade II renal pathology. In the middle stage, proteinuria and hematuria may be aggravated by recurring infection, which is consistent with the clinical characteristics of Lee's grade III renal pathology. Advanced patients present with large amounts of urinary protein, hematuria, and serious deterioration of kidney function with systemic symptoms, which may be consistent with the clinical features of Lee's grade IV to V renal pathology.

2.2. The creation of Shenfukang II capsule

Professor Cheng Xiaohong [10], a famous old TCM doctor in our hospital, combined the microscopic pathological changes of IgA nephropathy with the macroscopic four diagnoses of TCM by means of image comparison and other methods, and compared mesangial cell proliferation, endothelial cell proliferation, capillary necrosis, crescent body formation, etc., with the pathogenic characteristics of wind, phlegm, stasis, dampness and other pathogenic pathogens. Cellulose-like necrosis and microthrombus formation are consistent with the pathogenic characteristics of blood stasis, which is caused by blood stasis blocking kidney collaterals. Glomerular fibrous crescent, glomerular sclerosis, balloon adhesion and interstitial fibrosis, arteriole wall hyaline change, and renal tissue scar formation were compared with "blood stasis, phlegm, turbidosis" and other pathogenic characteristics. The former is divided into the acute stage (initial stage) of IgA nephropathy and the latter into the chronic stage of IgA nephropathy. It is concluded that the renal pathological changes of IgA nephropathy are the local micro "accumulation" of the kidney. Deficiency of kidney qi and blood stasis of kidney collaterals are the key to the pathogenesis of IgA nephropathy. The treatment takes tonifying the kidney and promoting blood circulation as the first principle, and organically combines "syndrome differentiation", "disease differentiation", "macro" and "micro" to treat the method of tonifying the kidney and promoting blood circulation. Then, our hospital has created Shenfukang II capsule ((patent number; ZL201110334097.6), is used to relieve the symptoms of IgA nephropathy and delay the deterioration of renal function, long-term use can improve the long-term prognosis.

2.3. Basis of the prescription of Shenfukang II capsule

Shenfukang II capsule is now also known as "Bushen Huoxue Sanjie Capsule", it is the hospital preparation of Shaanxi Provincial Hospital of Traditional Chinese Medicine (Shaanxi medicine system word Z20130011), It consists of 12 traditional Chinese medicines: Cornus officinalis, dodder, Radix Rehmanniae, Herba Epimedii, Rhizoma Rehmanniae, Radix Paeoniae Rubra, Radix Salviae Miltiorrhizae, Radix Astragali, Chinese yam, Wang Buliuxing, turmeric and vinegar turmeric. Looking at the whole prescription, Cornus officinalis, Radix Rehmanniae Preparata and Rhizoma Dioscoreae are derived from the "three supplements" in the prescription of Liuwei Dihuang Decoction

(Dihuang Pill) edited by the classic prescription Shenqi Pill in Zhang Zhongjing's synopsis of the Golden Chamber. Which takes the meaning of three yin and tonifying the liver, spleen and kidney, but also focuses on tonifying the kidney, which is good at tonifying blood and yin, nourishing essence and marrow. Radix Rehmanniae Preparata in the prescription is sweet, slightly warm and moist, and enters the kidney meridian, which is good at enriching blood, nourishing yin and replenishing essence, and is a good product for tonifying kidney; Cornus officinalis taste sour and astringent warm, entering the two meridians of the liver and kidney, tonifying the liver and kidney, astringent and astringent, the liver and kidney are homologous, tonifying the liver is tonifying the kidney; Yam is peaceful, mainly enters the middle jiao and spleen meridian, and has the effect of strengthening the spleen and solidifying essence, which is actually to replenish the spleen and stomach to nourish the innate. At the same time, the warm epimedium is added to supplement the three yin, and the yang in the kidney is encouraged, so that the yin and yang of the kidney can be supplemented. In the prescription, the Rhizoma Rehmanniae can tonifying kidney astringent essence, dodder seed tonifying liver and kidney, and the two drugs are combined as kidney-tonifying products. Radix Salviae Miltiorrhizae has the effect of promoting blood circulation and removing blood stasis, and Radix Paeoniae Rubra has the effect of cooling blood and removing blood stasis, which are matched with Radix Astragali for invigorating qi and promoting blood circulation. Turmeric for breaking blood qi, channels and collaterals. The soft-shelled turtle made with vinegar has the effect of being salty and cold, entering the liver and kidney meridian and softening and dispersing knots. Wang Buliuxing has mild medicinal properties and bitter smell, which has the effect of promoting blood circulation and dredging menstruation. Throughout the whole prescription, centering on the pathogenesis characteristics of "deficiency of kidney qi and combination of phlegm and blood stasis", legislation is made to tonify the kidney and disperse the knot, and the compatibility is appropriate, tonifying kidney yin and slightly tonifying kidney yang at the same time, making tonifying kidney achieve the effect of Yin and Yang secret, spirit is the treatment effect. The drugs complement each other, tonifying the liver, spleen and kidney, promoting blood circulation and promoting qi, dispersing knots and dredging collaterals, and finally achieve the goal of strengthening the upright and dispelling evil, so that this kind of clinical symptoms can be alleviated in varying degrees.

In summary, based on the different types and grades of IgA nephropathy combined with clinical characteristics, the integration of "micro" and "macro" dialectics, and the legislative creation of Shenfukang II capsule, from the theoretical level, Shenfukang II capsule treatment of IgA nephropathy is extremely important research value.

3. Experimental study of Shenfukang II capsule on IgA nephropathy

With the deepening of the research on traditional Chinese medicine, its advantages such as multi-components, multi-pathways, multi-targets and multi-pathways have been applied in various fields of diseases. Cornus officinalis, one of the components of Shenfukang II capsule formula, has been studied by two-dimensional electrophoresis (2DE) of mouse kidney tissue [11], and it is found that the differential protein expression profile of kidney tissue of mice with IgA nephropathy under the effect of FCE, a single traditional Chinese medicine, has significant changes, which indicates that Cornus officinalis alcohol extract exerts its effect on IgA nephropathy through multiple protein targets. It is also suggested that this co-action can be used as a fast detection method for pharmacological and toxicological studies and clinical evaluation of FCE in IgA nephropathy. In addition, Cornus officinalis [12] can significantly inhibit lymphocyte transformation, the production of broad-spectrum tumor-killing lymphokinin-activated killer cells (LNK) and interleukin-2 (IL-2), which is a kind of immunosuppressant. It is speculated that the active ingredient of Cornus officinalis has an immunosuppressant effect and can prevent the deposition of immune complex in the kidney

of IgA nephropathy. It is proved that Fructus Lonicerae and its extract can regulate thromboxane B₂ (TXB₂) 6-keto prostaglandin (6-ketone).Prostaglandin,6K-PGF₁ α) balance [13], regulation of transient receptor potential V5 (transient receptor potential).The expression of vanilloid-5 protein and calcium reabsorption [14] decreased the urine protein of IgA nephropathy rats, significantly decreased the elevated serum creatinine level and blood urea nitrogen of IgA nephropathy rats, slowed down glomerular Mesangial proliferation and protected renal function [15, 16]. In addition, Wei Yulan et al found that [17] water-alcohol extract of Rhizoma Euphorbiae can effectively inhibit the expression of TGF-β-MRN in renal tissue, reduce local inflammation and reduce renal damage. Epimedium warming and tonifying kidney yang, in which icariin [18] may inhibit the chemotactic infiltration of monocytes and regulate immunity by inhibiting the expression of NF-κB and MCP-1 in IgA nephropathy, thus reducing the damage to renal interstitium. In addition, Zhao Jin [19] et al.through the experiment of IgA nephropathy rat model,Icariin down-regulates the levels of transforming growth factor β₁ (TGF-β₁), collagen IV (Col-IV) and Fibronectin1, inhibits the secretion of IL-1β, IL-6 and IL-18, and decreases the levels of NF-κBP65, TNF-α and VCAM-1 proteins in the nucleus.Inhibition of the activation of NF-κB pathway can improve the fibrosis level and inhibit the inflammatory response in IgAN rats, while improving renal function and inhibiting the increase of urinary protein, serum creatinine and urea nitrogen levels. A study [20] found that the main active component of Radix Paeoniae Rubra, which has the effect of cooling blood and removing blood stasis, can inhibit the activation of immunomodulatory Toll-like receptor (TLR), reduce the infiltration of macrophages in renal tissue, reduce the amount of 24H urinary protein in nephrotic rats, and reduce renal injury. In addition, Pang Xinxin et al. [21] found that Radix Paeoniae Rubra can prevent and treat IgA nephropathy through multiple targets and pathways through network pharmacological analysis. The study [22] confirmed that Salvia miltiorrhiza can obviously improve renal vascular disease, renal interstitial fibrosis and glomerular sclerosis by reducing platelet aggregation, regulating blood coagulation system and antithrombotic mechanism, and can treat bleeding and low back pain caused by blood stasis in IgA nephropathy. Astragalus membranaceus and yam are indispensable in the treatment of IgA nephropathy based on spleen and kidney deficiency, which has been confirmed by studies [23]. The core target of astragalus and yam in interfering IgA nephropathy is through IL6, protein kinase B (AKT1), tumor suppressor gene p53 (TP53), interleukin-1 β (IL1B), caspase 3 (CASP3), proto-oncogene JUN (JUN), prostaglandin endoperoxide synthase 2 (PTGS2), epidermal growth factor receptor (EGFR) proto-oncogene MYC (MYC). Improve the degree of glomerulosclerosis, protect podocytes, inhibit the expression of inflammatory cytokines, improve renal inflammatory injury and delay interstitial fibrosis, improve renal ischemic injury, and delay the progression of IgA nephropathy through a variety of signal pathways. According to research reports [24], Wang Bulixing may alleviate tubulointerstitial damage, promote the transport and elimination of circulating immune complex (CIC), regulate cellular immune function, and reduce kidney injury or kidney inflammation mediated by circulating immune complex. The above studies on the interaction and superposition of various drug components in Shenfukang II capsule reflect its impact on the development of IgA nephropathy. Other studies have confirmed that [25] Shenfukang II capsule can inhibit the expression of vascular endothelial growth factor (VEGF), proliferating cell nuclear antigen (PCNA) and human matrix metalloproteinase-9 (MMP-9) by inhibiting aldosterone, further inhibit the proliferation and wall thickening of vascular endothelial cells in renal arterioles, and reduce the injury of renal arterioles in IgA nephropathy. It is speculated that this may be the role of Shenfukang II capsule in Lee's III~IV renal pathology of IgA nephropathy. In addition, through the study of Shenfukang II capsule on the animal model of renal interstitial fibrosis induced by unilateral ureteral ligation (UUO) [26], it was confirmed that Shenfukang II capsule could reduce the local renal interstitial fibrosis and the expression of transforming growth factor-β 1 (TGF-β 1) in UUO rats, so as to reduce renal interstitial fibrosis and renal tubule injury. It is also speculated that

Shenfukang II capsule can reduce the expression of TGF- β 1 in kidney, inhibit the expression of epithelial-mesenchymal transformation (EMT) from tubular epithelial cells to Mesangial cells, prevent the synthesis of extracellular matrix, delay the progression of IgA nephropathy to renal interstitial fibrosis and tubular injury to some extent, and protect the residual renal function to the maximum, thus affecting the further deterioration of IgA nephropathy. It is speculated that this effect may be caused by the stage of Lee's grade IV to V renal pathological changes in IgA nephropathy. Liu Lu et al. [27] established an experimental model of IgA nephropathy and tested the intima, media, tube wall/vessel outer diameter values of arteriole in renal tissue of rats, confirming that Shenfukang No. II capsule could inhibit ERK/NF- κ B signaling pathway in IgA nephropathy rats. Reduce the levels of vascular endothelial growth factor (VEGF), human matrix metalloproteinase-9 (MMP-9), proliferating cell nuclear antigen (PCNA), extracellular regulatory protein kinase (ERK) 1/2, nuclear transcription factor- κ B (NF- κ B), inhibit the proliferation of endothelial cells in renal arterioles, and alleviate kidney injury.

Based on the above experimental studies, it has been confirmed that the TCM drug components of Shenfukang II capsule can be derived from many aspects of renal vessels, glomeruli, interstitials and renal tubules, from multiple pathways of immune regulation TOL1-like receptor (TLR), NF- κ B and MCP-1 expression, and from multiple targets such as interleukin factors (such as IL6) and some inflammatory cytokines. Protein, gene expression and other ways affect and interfere with the progress of IgA nephropathy, act on all stages of renal pathological changes in IgA nephropathy, protect effective nephron, improve renal tissue microcirculation, and effectively improve the immunity of patients, so that clinical symptoms such as proteinuria and hematuria in IgA nephropathy can be alleviated to a certain extent. It can also reduce the levels of serum urea nitrogen and creatinine, and slow the further deterioration of kidney function.

4. Inical study of Shenfukang II capsule on IgA nephropathy

Shenfukang II capsule has been widely used in the clinical treatment of IgA nephropathy by doctors in our hospital for more than 20 years. In the study of Zhao Chunwei et al. [28] observing the clinical efficacy of Shenfukang II capsule, it was found that the combination of angiotensin-converting enzyme receptor inhibitor and Shenfukang II capsule was used to treat IgA nephropathy with renal tubulointerstitial fibrosis. Results The clinical indexes of Scr, BUN, Cys-c and 24h urinary protein decreased significantly compared with the control group, indicating that combined administration (plus Shenfukang II capsule) had better clinical efficacy in reducing proteinuria in IgA nephropathy and improving renal function than that of angiotensin-converting enzyme receptor inhibitor alone. This clinical study shows that the curative effect of Shenfukang II capsule on IgA nephropathy is closely related to its pathological damage. Qu Kai [29] observed the clinical efficacy of Shenfukang II capsule combined with western medicine in the treatment of chronic glomerulonephritis with spleen and kidney qi deficiency and blood stasis syndrome. It can not only reduce proteinuria and hematuria, protect renal function, but also relieve TCM clinical symptoms such as fatigue, lack of qi, easy to catch cold, hand and foot heart heat, dry mouth and pharynx, red pharynx, purple tongue and so on. In addition, the medication is safe and effective. In addition, Professor Yan Xiaoping of our hospital pointed out that while some patients were treated with immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil, tacrolimus, hormone and so on, after adding Shenfukang II capsule, the clinical indexes such as routine urine examination, quantification of urinary protein, blood lipid, liver and kidney function were relieved compared with immunosuppressants alone. And to varying degrees to relieve the clinical symptoms of low back pain, foam urine, hematuria, in addition, it can also reduce some of the side effects of immunosuppressants. Professor Shi Jian, chief physician of the nephrology Department of Shaanxi Provincial Hospital,

once reviewed a case of IgA nephropathy treated clinically and pointed out that the patient underwent kidney puncture in 2013: glomerular mesangial stroma hyperplasia under light microscope, renal tubular particle vacuolar degeneration, renal interstitial lymphocyte infiltration, intima thickening, Lee's Grade III IgA nephropathy, and the examination showed: Urinary protein 3+, occult blood 3+, urinary protein content 1674mg/24H, BUN 4.7mmol/L, creatinine 98umol/L; After about 3 years of treatment with cyclophosphamide combined hormone and Chinese medicine Shenfukang II capsule, the control of kidney function, urinary protein and hematuria was only about 4-9% higher than the normal range, and the condition tended to be stable. After withdrawal of the drug, Shenfukang II capsule was continued to be taken alone for adjuvant treatment so far, and the urinary protein quantity of the follow-up patients basically tended to the normal range. Urinary protein, hematuria and renal function were not abnormal, which proved that Shenfukang II capsule could increase the curative effect and stabilize the development of IgA nephropathy in the later stage. This shows that Shenfukang II capsule has obvious clinical effect in the treatment of IgA nephropathy and can regulate immunity. The tutor pointed out that Shenfukang II, a proprietary Chinese medicine, has obvious advantages in the treatment of IgA nephropathy, such as nourishing yin and clearing heat at the initial stage of the disease, avoiding the side effects of hormones or immunosuppressants prematurely, reducing clinical symptoms, tonifying the liver and kidney in the middle and later stages of the disease, restoring the balance of yin and yang, reducing recurrence, reducing toxicity and increasing efficiency, and greatly improving the effect of clinical treatment.

To sum up, the clinical application of Shenfukang II capsule has great potential and advantages in the prevention and treatment of IgA nephropathy, especially when combined with other immunosuppressants, it can obviously make up for the side effects of some drugs and have a synergistic effect, which naturally becomes the best choice for clinical doctors.

5. Summary and prospect

In this paper, through theoretical, experimental and clinical studies, it is concluded that Shenfukang II capsule has definite curative effect and certain applicable value in the treatment of IgA nephropathy. IgA nephropathy is a kind of disease with complex pathogenesis, various pathology, common and easy to occur. Western medicine mainly treats this disease with hormone or immunosuppressant, the purpose is to reduce hematuria, albuminuria and reduce renal function damage, but there are many side effects and adverse reactions. The pathogenesis of IgA nephropathy is not completely clear. With the deepening of medical research, some new pathogenesis and new treatment methods of the disease will be constantly discovered, and the mechanism of the action of traditional Chinese medicine compound prescription and the action target of drugs are also quite complex. This not only provides clinical experience, ideas and pharmacological basis for the treatment of IgA nephropathy with Shenfukang II capsule from the aspects of quadruple blow, infection pressure, lymphocyte imbalance, infection, activation of intracellular signal pathway, related immune factors, mucosal system (intestinal flora imbalance mechanism) and complement activation. And the breadth and depth of research in this area need to be studied and studied deeply by later scholars.

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