

## Therapeutic Effects of Erzhi Pill on Liver and Kidney Yin Deficiency Type Immunoglobulin A Nephropathy

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### ABSTRACT

**Objectives:** To observe the clinical efficacy of Erzhi Pill in treating liver and kidney Yin deficiency type Immunoglobulin A Nephropathy (IgAN).

**Methods:** Biopsy diagnosed IgAN patients with liver and kidney Yin deficiency were included in our study. The demographics and clinical data, including Sex, Age, distolic blood pressure(DBP), systolic blood pressure(SBP), 24-hour urinary total protein (24hUP), white blood cells(WBC), serum hemoglobin(HGB), serum platelets(PLT), serum creatinine(Scr), blood uric nitrogen(BUN), estimated glomerular filtration(eGFR), serum albumin level(ALB), uric acid level (UA), total cholesterol (CHO), triglyceride (TG), immunoglobulin A(IgA), immunoglobulin G(IgG), immunoglobulin M(IgM), complement 3(C3) and complement 4(C4) were evaluated at baseline. Kidney biopsy was categorized using the Oxford classification, with a calculation of the MEST-C score. They were randomly divided into two groups. The experimental group received basic treatments, and the controlled group received Erzhi Pill and basic treatments for twelve weeks. Comparison of quantitative scores of syndromes before and after treatment between the two groups.

**Results:** Sixty-nine IgAN patients were enrolled in our study. After twelve weeks of treatment, the quantitative score of syndromes in the experimental group was lower than that in the controlled group. Patients in the treatment group were with lower quantitative score in lumbago, sore lumbar and knees, dry eyes or blurred vision, foam urine and haematuria ( $P<0.05$ ).

**Conclusions:** Intervention with Erzhi Pill in the treatment of IgA nephropathy patients can improve their TCM syndromes, and enhance their quality of life.

**Keywords:** Erzhi Pill; IgA Nephropathy; Traditional Chinese Medicine

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### 1. Introduction

Immunoglobulin A nephropathy (IgAN) is a disease with an immune complex mainly composed of IgA deposits in

the glomerular mesangium, leading to hematuria with or without proteinuria. It is the most common type of primary glomerulopathy in the world. At present, the pathological

mechanism is unclear and there is no specific treatment method. Therefore, it is necessary to conduct in-depth research on its pathogenesis to better guide clinical drug treatments. In term of traditional Chinese medicine(TCM), IgAN is classified into hemolysis, edema, and urine turbidity according to its diverse TCM syndrome differentiation<sup>1</sup>. In TCM, research has shown that the overall pathogenesis of IgAN is based on *Qi* deficiency and excess *Yin*. *Qi* and *Yin* deficiency is the main syndrome, and external sensations, damp heat, and blood stasis are the main accompanied symptoms<sup>2</sup>. Thus, clinical syndrome differentiation of IgAN is mainly characterized by liver and kidney deficiency, generally *Yin* deficiency, and excessive fire. The classic formula Erzhi Pill combined with Zhibai Dihuang Pill were commonly used to nourish *Yin* and reduce fire.

Er Zhi Pill originated from the “Fu Shou Jing Fang”<sup>3</sup>. It is composed of Ligustrum lucidum and Mohualian, with the effects of nourishing the liver and kidneys, nourishing *Yin* and blood. It is one of the most commonly used medicine pair in the treatment of kidney disease. The classic famous formula Erzhi Pill has a solid theoretical foundation in TCM. Clinical studies have shown that Erzhi Pill has good therapeutic effects on IgAN of liver and kidney *Yin* deficiency type and *Qi* *Yin* deficiency type. It can improve the symptoms, clinical indicators, and immune function in IgAN patients<sup>4</sup>. Our previous studies were based on network pharmacology. We found that Erzhi Pill can act on IgAN through multiple channels, targets and pathways. Erzhi Pill mainly acts on gene targets such as AKT1, IL6, TNF, CASP3, VEGFA. It plays a role through signaling pathways such as lipid and atherosclerosis, fluid shear stress and atherosclerosis, IL-17, TNF, and other signaling pathways through quercetin, luteolin, kaempferol,  $\beta$ -sitosterol, and locust. The results reflect the synergistic molecular mechanism of Er Zhi Pill's multiple pathways, targets, and pathways, providing research ideas and guidance for the clinical treatment of IgAN<sup>5</sup>. In this study, we further explore the effects of Erzhi Pill on the clinical syndromes of liver and kidney *Yin* deficiency type IgAN.

## 2. Materials and Methods

This study was a single-center, randomized, prospective, parallel controlled trial. The research subjects were all from the outpatient and inpatient departments of Nephrology in Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine. The demographics and clinical data, including Sex, Age, DSP, SBP, 24hUP, WBC, HGB, PLT, Scr, BUN, eGFR, ALB, UA, THO, TG, IgA, IgG, IgM, C3 and C4 were evaluated at baseline. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formulas<sup>6</sup>. All kidney biopsy specimens were reviewed and graded by an independent pathologist. The Oxford classification (including crescent scores) was used for the evaluation of pathologic lesions<sup>7</sup>. Diagnostic criteria for traditional Chinese medicine syndromes refers to the “Guiding Principles for Clinical Research of New Chinese Medicine Drugs (Trial)” (2002). The syndrome of liver and kidney *Yin* deficiency was formulated. The main symptoms were dry and astringent eyes, blurred vision, dizziness and tinnitus, burning sensation in the palms, soles and chest, feverish feeling in palms and soles, dry mouth and throat, and back pain. Secondary symptoms include nocturnal emission, slippery semen, menstrual disorders, red tongue with little coating, and thin pulse strings.

We used SAS9.3 software to generate random sequence

numbers. IgAN patients were randomly assigned to the Erzhi Pill treatment group (basic treatment plus Erzhi Pill granules treatment) and the basic treatment group in a 1:1 ratio according to the random sequence numbers. All the researchers assigned sequence numbers based on the order of the enrolled participants. The protocol and informed consent form of the subjects were approved by the Ethics Committee of Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine.

All eligible patients received optimized basic treatment, including lifestyle management (smoking cessation, alcohol restriction, weight control, low salt, low fat, and low protein diet), administered 150-300 mg irbesartan once a day under patient tolerance, orally for 12 consecutive weeks, achieving blood pressure control (systolic blood pressure < 140 mmHg, diastolic blood pressure < 90 mmHg); patients with diabetes use insulin or oral hypoglycemic drugs to make glycosylated hemoglobin  $\leq 7\%$ . Patients with eGFR  $\geq 30 \text{ ml/min/1.73 m}^2$  were randomly assigned to continue basic treatment, and different treatments were given according to the grouping. The treatment group was given Erzhi Pill granules (1 dose/day, 2 times/day) for 12 consecutive weeks. Erzhi Pill is composition of 15 g of Ligustrum lucidum and 15 g of Echinochloa grandiflorus. It was produced by Jiangyin Tianjiang Pharmaceutical Co.Ltd following the formula granules, with a shelf life of 3 years, and stored in a sealed and moisture-proof manner. Patients will be followed up at 4, 8, and 12 weeks after enrollment, and efficacy and safety indicators will be tested during the follow-up period.

### 2.1 Statistical methods

The content of statistical analysis mainly involves quantitative or qualitative indicators, the most important of which are baseline description and comparison, efficacy evaluation, and safety evaluation. The statistical description of the numerical variables provides the number of cases (N), missing cases (missing), mean (mean), standard deviation (SD), median (M), minimum value (Min), and maximum value (Max). The statistical description of categorical variables provided the number of examples (N) and percentages (%). Laboratory examination indicators and Chinese medicine syndrome scores were tested using t-tests.

## 3. Results

Sixty-nine biopsy diagnosed IgAN patients were enrolled in our study, with mean age of 37 years old. The demographics and clinical data, including Sex, Age, DSP, SBP, 24hUP, WBC, HGB, PLT, Scr, BUN, eGFR, ALB, UA, THO, TG, IgA, IgG, IgM, C3 and C4 were evaluated at baseline. MEST-C scores were also evaluated. Baseline demographic, clinical and pathological information were shown in **Table 1**.

Thirty-four IgAN patients were in controlled group and thirty-five IgAN patients were included into treatment group. There was no statistically significant difference ( $P > 0.05$ ) between the treatment group and the controlled group in terms of gender, age, and quantitative scores of TCM syndromes at baseline, as shown in **Table 2**.

Lumgago, lumbar and knee soreness and weakness, dry and blurred vision, foamy urine and hematuria were relieved in the treatment group after twelve weeks of treatment. Comparison of changes in various integral points of TCM syndromes between two groups after 12 weeks of treatment, as shown in **Table 3**.

**Table 1:** Baseline demographic, clinical and pathological information of the enrolled patients.

Characters	IgAN patients		
Male/Female	39/30	eGFR (mL/min/1.73 m <sup>2</sup> )	33.01±79.52
Age(years)	37.17±10.99	IgA (mg/dL)	1.064±3.047
SBP(mmHg)	21.61±133.8	IgG (mg/dL)	3.337±11.93
DBP(mmHg)	14.84±89.07	IgM (mg/dL)	0.6391±1.289
HGB (g/L)	20.13±131.4	C3 (mg/dL)	0.2197±1.104
WBC(×10 <sup>9</sup> g/L)	1.867±6.541	C4 (mg/dL)	0.07976±0.2897
PLT (10 <sup>9</sup> /L)	65.46±247.6	CHO(mmol/L)	1.157±5.305
ALB (g/L)	6.924±42.21	TG (mmol/L)	1.209±1.667
UA (μmol/L)	128.3±418.2	24hUP (mg/24h)	1541±1412
BUN(mmol/L)	3.031±6.364	eGFR (mL/min/1.73 m <sup>2</sup> )	33.01±79.52
Scr (μmol/L)	112.5±120.5	IgA (mg/dL)	1.064±3.047
Oxford classification, n(%)			
M(M0/M1)	0(0%) / 69(100%)		
E(E0/E1)	65(94.2%) / 4(5.8%)		
S(S0/S1)	39(56.5%) / 30(43.5%)		
T(T0/T1/T2)	53(76.8%) / 10(14.5%) / 6(8.7%)		
C(C0/C1/C2)	44(63.77%) / 23(33.33%) / 2(2.9%)		
Tubular Atrophy(%)	18.1919.44±(%)		
Hayline (Y/N)	62(89.9) / 7(10.1%)		

**Table 2:** Comparison of Patient TCM Baseline Information.

Syndromes	Controlled group	Treatment group	P value
Age	10.79±35.07	9.76±38.23	0.495
Male/Female	20/14	19/16	0.326
Edema	0.46±0.73	0.86±0.53	0.769
Heat sensation in palms, soles and chest	0.31±0.54	0.55±0.33	0.839
Night sweating	0.33±0.48	0.50±0.43	0.448
lumbago	1.60±0.72	0.59±1.83	0.214
Lumbar and knee soreness and weakness	1.33±0.16	1.00±1.40	0.774
Dry or blurred vision	1.17±0.79	0.84±1.10	0.774
Dizzy	0.47±0.57	0.50±0.47	0.999
Tinnitus	0.57±0.63	0.63±0.77	0.246
Dry mouth and throat	0.87±0.63	0.70±0.70	0.420
Foamy urine	1.43±0.90	0.84±1.67	0.269
Hematuria	1.77±0.86	0.83±1.93	0.455

**Table 3:** Comparison of changes in various integral points of TCM syndromes between two groups after 12 weeks of treatment.

Syndromes	Controlled group	Treatment group	P value
Edema	0.24±0.51	0.52±0.27	0.172
Heat sensation in palms, soles and chest	0.20±0.41	0.43±0.23	0.680
Night sweating	0.30±0.47	0.45±0.27	0.473
lumbago	1.33±0.55	0.64±0.93	0.032*
Lumbar and knee soreness and weakness	1.10±0.71	0.87±0.70	0.001*
Dry or blurred vision	0.90±0.55	0.50±0.57	0.002*
Dizzy	0.37±0.49	0.49±0.37	0.698

Tinnitus	0.50±0.57	0.56±0.63	0.260
Dry mouth and throat	0.73±0.45	0.51±0.50	0.115
Foamy urine	0.93±0.25	0.25±0.93	0.045*
Hematuria	1.17±0.53	0.18±0.97	0.017*

#### 4. Discussion

IgAN is the most common primary glomerulopathy in the world. The incidence rate of IgAN among adults worldwide is at least 2.5/100000 per year, and it is more common among Asian people. In China, IgAN accounts for 30-40% of primary glomerulopathy, and 20-40% of IgAN patients progress to end-stage renal disease (ESRD) within 10-20 years after diagnosis<sup>8</sup>. Numerous studies have indicated that IgAN is caused by multiple factors, such as genes, immunity, and the environment; however, the specific pathogenesis is still unclear. At present, the most basic treatment modes for IgAN in clinical practice are prevention and treatment of infection, control of blood pressure, administration of sufficient renin angiotensin aldosterone system blockers, control of protein and salt intake, avoidance of fatigue and use of nephrotoxic drugs, smoking cessation, control of metabolic syndrome, and regular follow-up, among other supportive treatments<sup>9</sup> lack specific treatment methods. TCM has good therapeutic effects against IgAN. In the field of kidney disease, Erzhi Pill can be used for chronic nephritis, hematuria, lupus nephritis, purpura nephritis, chronic kidney failure and other diseases<sup>10</sup>. It has pharmacological effects, such as anti-inflammatory, antioxidant, and immune-regulatory effects. Basic research indicated the protective effect of Erzhi Pill extract on podocyte injury in rats with diabetes nephropathy<sup>11</sup>. It also suggests that Erzhi Pill extract can regulate the expression of CD2AP and podpcin in podocytes of diabetic nephropathy rats, protect podocytes, and repair renal function.

Erzhi Pill is derived from the “Fu Shou Jing Fang” of the Ming Dynasty. It is composed of two medicinal herbs, Ligustrum lucidum and Mohualian, at a 1:1 ratio. Ligustrum lucidum seeds were harvested on the winter solstice day, whereas lotus flowers were harvested on the summer solstice day; hence, the name Erzhi Pill. Ligustrum lucidum is sweet and smooth, the essence of Shaoyin. It does not wither in deep winter, and its colors are green and black. It benefits the liver and tonifies the kidneys. The sweet and cold taste of Modrylian enters the kidney meridian, which is beneficial for nourishing the kidneys, dispersing blood and promoting blood circulation. When used in combination. Erzhi Pill has a calm and slightly cold nature. It can nourish Yin without generating dampness, nourishes without stagnation, moistens without greasiness. Thus, Erzhi Pill is a good tonic for calming and tonifying the liver and kidney. It also disperses blood. Erzhi Pill is known as the “first prescription for clearing the upper and tonifying the lower”. It is a representative formula for calming and tonifying the liver and kidney.

Our study showed that Erzhi Pill had significant therapeutic effects on improving clinical syndromes of IgAN patients with liver and kidney Yin deficiencies. After 12 weeks of treatment, main syndromes low back pain, sore waist and soft knees, dry eyes or blurred vision, foamy urine, and hematuria were relieved better in the control group. IgAN is equivalent to “urine turbidity” in TCM. However, modern medical treatment cannot fully intervene with the syndrome characteristics. In TCM, the liver and kidney are homologous, with liver and kidney Yin

fluids nourishing each other. If liver *Yin* is sufficient, it is hidden in the kidneys. If the kidney *Yin* is strong, the liver is nourished. The liver *Yin* could also benefit the kidneys. The essence of the liver and kidneys is abundant, and the fine substances disperse the muscles and bones, improving back pain, soreness, and weakness of the waist and knees, opening the orifices in the eyes, nourishing and clearing the orifices, and remitting dry or blurred vision. *Suwen* · Inverse Regulation Theory indicated that “The kidney is the water and viscera, and governs the body fluid”. Deficiency of kidney essence, *Yin* deficiency, and blood heat leads to hematuria. Deficiency of kidney essence or *Yin* deficiency and internal heat cause foamy urine. In this way, liver and kidney *Yin* nourishment can improve foam hematuria and other symptoms. In summary, *Erzhi* Pill intervention in IgAN could help to the supplement of *Yin* deficiency and relieve the TCM syndromes in liver and kidney *Yin* deficiency patients.

## 5. Conclusion

*Er Zhi* Pill has significant therapeutic effects in improving the clinical symptoms of IgA nephropathy with liver and kidney *Yin* deficiency. This method can be further applied in clinical practice. As this study only included patients with liver and kidney *Yin* deficiencies, the number of patients was limited. Further clinical observations will be conducted to provide a more comprehensive direction for the prevention and treatment of IgAN by TCM.

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## 7. Conflict of Interests

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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