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ORIGINAL ARTICLE

Huai Qi Huang ameliorates proteinuria and hematuria in mild IgA nephropathy patients: A prospective randomized controlled study

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KEYWORDS
hematuria;
Huai Qi Huang granule;
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proteinuria

Background/Purpose: Huai Qi Huang (HQH) is a compound Chinese herbal medicine that contains *Trametes robiniophila* murr, wolfberry fruit, and *Polygonatum*. In the present study, we investigated the effects of HQH on patients with mild immunoglobulin A nephropathy (IgAN) through a prospective randomized controlled study.
Methods: Forty-five adults diagnosed with IgAN according to renal pathology, who had hematuria or/and proteinuria ($\leq$ 2 g/day), were randomly assigned to receive HQH or no treatment for 12 weeks. Twenty-four hour urinary protein excretion and hematuria were measured at Weeks 0, 4, 8, and 12. The rate of complete remission of proteinuria and hematuria was evaluated. Any adverse events induced by HQH were also observed during the treatment period.
Results: Twenty-four hour urinary protein excretion was significantly reduced by HQH treatment compared with that in the control group at Weeks 8 and 12. A much higher rate of complete remission of proteinuria was observed in the HQH group than in control group at Week 12. HQH administration also obviously reduced the extent of hematuria compared with that in the control group at Week 12. HQH treatment dramatically increased the rate of complete remission of hematuria compared with that in control group at Weeks 8 and 12. No obvious adverse events caused by HQH were observed.
Conclusion: HQH could be a new conservative therapy for IgAN patients who cannot tolerate steroids and immunosuppressive agents. The relapse rate after discontinuing treatment still needs further investigation.

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Introduction

Immunoglobulin A nephropathy (IgAN) is a common primary glomerulonephritis and also a leading cause of end-stage renal disease (ESRD) throughout the world.[1,2] The key clinical manifestation of IgAN is microscopic or episodic macroscopic hematuria and various degrees of proteinuria. It has been reported that 10—25% of patients with IgAN will proceed to ESRD within 10 years and 25—50% within 20 years.[3,4] Risk factors associated with a poorer outcome are impaired renal function at diagnosis, high blood pressure, and urinary protein excretion.[3] Proteinuria is the strongest independent predictive factor leading to renal fibrosis and renal failure in many kinds of glomerulonephritis and chronic kidney disease.[1,3,5—10] It has been recently recognized that young persons with persistent isolated microscopic hematuria have an increased risk for ESRD, mainly secondary to primary glomerular diseases.[11,12] Among these causes, the association with progression to chronic kidney disease is best established for IgA nephropathy and Alport syndrome.[11,12]

There is still no universally accepted optimal therapeutic strategy for IgAN, especially IgAN with non-nephrotic range proteinuria. Corticosteroid treatment is controversial,[13,14] and immunosuppressive agents such as mycophenolate mofetil may be effective.[15,16] Considering their toxicity, they are not recommended for use in patients with mild proteinuria ($<$ 1 g/day) and preserve renal function according to KDOQI and KIDGO guidelines. It is suggested that supportive therapy with inhibition of the renin angiotensin system including angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) should be used in these patients to control hypertension and reduce proteinuria. However, we have found that ACEI and ARB can only partly reduce proteinuria; they cannot work on ameliorating hematuria. So far, no ideal drugs have been found to reduce hematuria effectively. Therefore, it is highly desirable to seek better therapeutic strategies for IgAN patients that are not suitable for treatment with steroids and immunosuppressive agents.

Huai Qi Huang (HQH), a mixture of Chinese herbs, contains *Trametes robiniophila* murr (Huaier), wolfberry fruit, and *Polygonatum*. Aqueous extract of Huaier, the main component of HQH, has been commonly used in China for cancer complementary therapy in recent years.[17] Some evidence has shown that Huaier aqueous extract inhibits proliferation of breast cancer cells by inducing apoptosis.[18] Some studies have demonstrated that HQH can significantly reduce proteinuria, prevent podocyte injury, ameliorate tubulointerstitial damage and inhibit inflammatory cytokine expression and macrophage infiltration in Adriamycin nephrotic rats.[19] Recently, Sun et al demonstrated that Huaier exhibits antitumor potential and immunomodulatory effects.[20] HQH plays a key role in maintaining the balance of cell and humoral immunity by decreased IgE level and increasing cell numbers of CD3, CD4, and CD8 cells.[20] HQH is commonly used in children with repeated respiratory infection, primary nephrotic syndrome or IgAN in China, and has been shown to be effective in decreasing repeated infection and reducing proteinuria and hematuria,[21,22] but it is unclear whether it can work on adults with IgAN. In the present study, a randomized controlled open labeled trial was carried out to investigate the efficacy of HQH in the reduction of proteinuria and hematuria in adults with mild IgA nephropathy.

Patients and methods

Patients

Forty-five IgAN adult patients recruited from May 2012 to March 2013 from the Second Affiliated Hospital of Harbin Medical University in China were enrolled in this prospective open-label randomized controlled trial. The study protocol was approved by Ethics Committee of Harbin medical university. All participating patients signed the informed consent. To be included, eligible patients: (1) were all confirmed IgAN by renal biopsy; (2) were IgA stage I-II by pathology diagnosis according to Lee classification[2]; (3) had hematuria or/and proteinuria ($\leq$ 2 g/day); (4) exhibited 24-hour urinary protein excretion $<$ 2 g; and (5) had not previously taken any steroids or immunosuppressive drugs. Exclusion criteria were: (1) 24-hour urinary protein $>$ 2 g/day; (2) serum creatinine $>$ 133 μM; (3) active infection; (4) diabetes mellitus; (5) autoimmune disease; (6) tumors; (7) chronic liver disease and liver function test abnormalities; (8) blood pressure $>$ 160/100 mmHg; and (8) any other secondary glomerulonephritis.

Study protocol

Forty-five patients were randomly assigned to the HQH group or control group (without treatment). Patients in HQH groups were given oral HQH granules 20 g three times/day for 12 weeks. All patients with hypertension were prescribed oral antihypertensive drugs within the blood pressure tolerance range. The patients were asked to measure 24-hour urinary protein excretion, hematuria, and serum creatinine at Weeks 0, 4, 8, and 12. The blood pressure and adverse events during the treatment period were also recorded.

Efficacy and safety assessments

In the present study, hematuria and 24-hour urinary protein excretion was examined at different time points. The primary efficacy parameter was also evaluated by the rate of complete remission of proteinuria and hematuria during the treatment period. Complete remission of proteinuria was defined as a value of urinary protein $<$ 0.3 g/day and urine dipstick for protein was negative. Complete remission of hematuria was defined as $<$ 10 red blood cells (RBC) per high-power field (HPF) in urinary sediment. The extent of microscopic hematuria was graded as: Grade 1: $<$ 10 RBC/HPF; Grade 2: 10—29.9 RBC/HPF; Grade 3: 30—59.9 RBC/HPF; and Grade 4: $\geq$ 60 RBC/HPF according to previous study.[19]

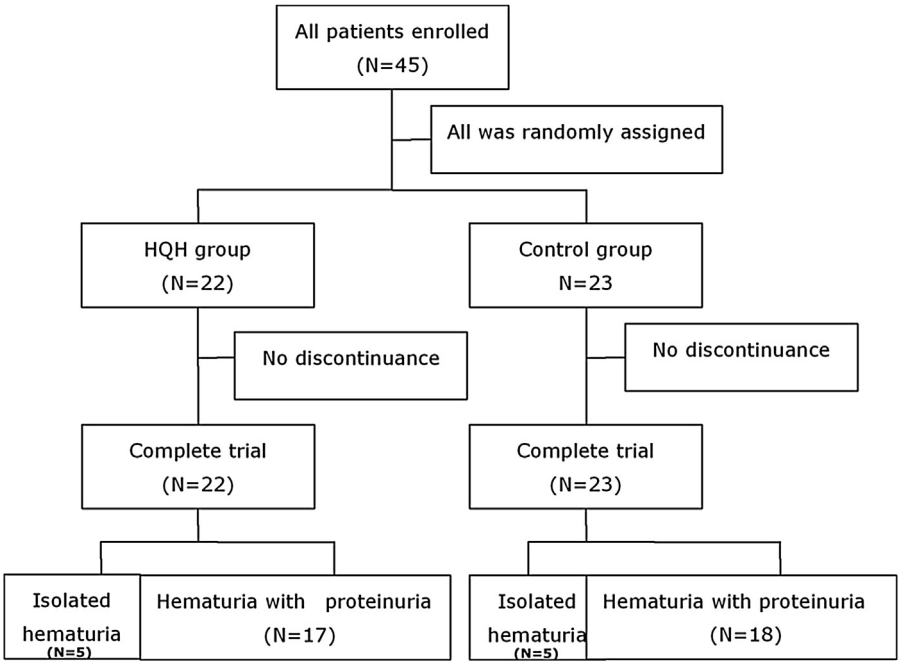

Figure 1 Patient profile. Forty-five patients with IgAN were randomly assigned to either the Huai Qi Huang (HQH) group ($n = 22$) or the control group ($n = 23$). Seventeen patients showed persistent proteinuria (0.3—2.0 g/day) in the HQH group, and 18 patients in the control group. Others presented isolated hematuria alone.

Statistical analysis

Continuous variables are described as mean ± standard deviation, and categorical variables are given as numbers and percentages. An independent two-sample *t* test was used in the comparison of means between groups, a paired *t* test was used in analyzing changes within each group during therapy, and the Mann—Whitney *U* test was used for nonparametric data. The incidence of remission was compared using the Chi-square or Fisher exact test. A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Forty-five IgAN patients were recruited in this study, 22 of them were assigned to the HQH group and the others were in the control group (Fig. 1). They all completed the treatment for 12 weeks and no patients dropped out of the study. The basic data about patients are recorded in Table 1. There was no difference between the two groups in

Table 1 Baseline characteristics of the study population.

	HQH group ($n = 22$)	Control group ($n = 23$)	p
Age (y)	30 ± 11	32 ± 9	0.589
Male/female	11/11	10/13	0.554
Urinary protein (g/d)	0.92 ± 0.53	0.92 ± 0.60	0.983
Urinary RBC numbers (/HPF)	66.5 ± 36.5	67.6 ± 28.8	0.905
Albumin (g/L)	43.3 ± 4.4	42.7 ± 4.7	0.657
Scr (μM)	78.1 ± 16.5	73.3 ± 16.6	0.335
Hypertension (*n*)	3	2	
Systolic blood pressure (mm Hg)	121 ± 15	120 ± 12	0.952
Diastolic blood pressure (mm Hg)	72 ± 9	71 ± 10	0.838
Extent of microscopic hematuria (*n*)			
Grade 1	0	0	
Grade 2	4	3	0.684
Grade 3	6	7	0.791
Grade 4	12	13	1.000

Values are expressed as mean ± standard deviation.
HPF = high-power field; HQH = Huai Qi Huang; RBC = red blood cells; Scr = serum creatinine.

clinical and pathologic characteristics. All patients who presented hypertension were given antihypertensive drugs at the beginning of treatment.

HQH significantly reduced proteinuria and increased rate of complete remission of proteinuria in mild IgAN patients

As is well known, proteinuria is an independent risk factor associated with progression of IgAN. Proteinuria was seen in 35 patients in this study: 17 patients in the HQH group and 18 in the control group ($p = 1.000$; Fig. 1). Twenty-four hour urinary protein excretion in the HQH group significantly lowered than that in the control group at 8 weeks and 12 weeks (Fig. 2A). Furthermore, the rate of complete remission of proteinuria in the HQH group (82.4%) was significantly higher than that in control group (33.3%, $p = 0.006$; Fig. 2B). The data demonstrate that treatment with HQH can significantly reduce proteinuria in mild IgAN.

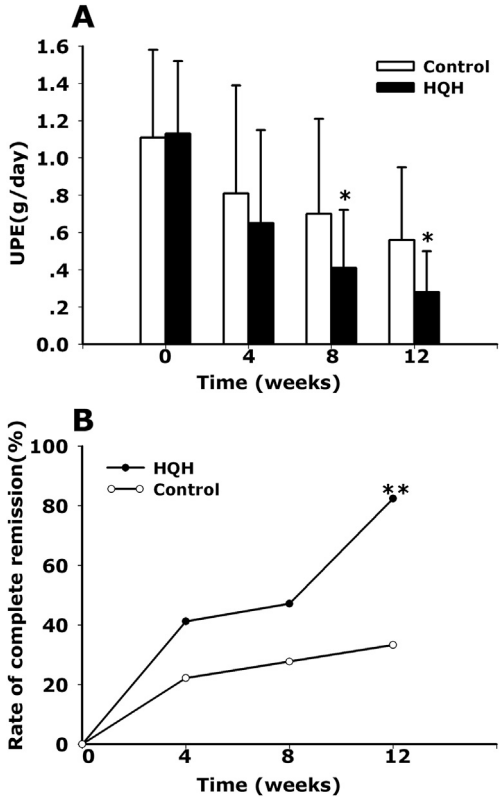

Figure 2 Twenty-four hour urinary protein excretion (UPE) and complete remission rate of proteinuria at Weeks 4, 8, and 12. The patients who presented only isolated hematuria were excluded in this statistic. (A) Twenty-four hour UPE was significantly lower than that in untreated group at 8 weeks ($p = 0.012$) and 12 weeks ($p = 0.014$). (B) The rate of complete remission of proteinuria was significantly increased at 12 weeks compared with that in control group ($p = 0.006$). HQH = Huai Qi Huang. * $p < 0.05$ versus control group. ** $p < 0.01$ versus control group.

HQH significantly ameliorated hematuria and increased the rate of complete remission of hematuria in mild IgAN patients

The grade of hematuria of two groups before and after treatment is shown in Fig. 3A. There was a striking reduction of hematuria after taking HQH, compared with control group (Fig. 3A). As shown in Fig. 3B, the average grade of hematuria was 3.27 before treatment and was down to 1.41 at 12 weeks in the HQH group. The grade of hematuria in the HQH group was greatly ameliorated compared with that in control group, which was 2.86 at 12 weeks ($p < 0.001$). Ten patients (45.5%) at 8 weeks and 14 patients (63.6%) at 12 weeks achieved complete remission of hematuria in the HQH group, which was significantly higher than that in control group ($n = 2$, 8.7%, at 8 weeks, $p = 0.007$; and ($n = 3$, 13.0%, at 12 weeks, $p = 0.001$), as shown in Fig. 3C. The data show that HQH administration can significantly ameliorate hematuria in mild IgAN.

A

	HQH group		Control group	
Grade of hematuria	baseline	12weeks	baseline	12weeks
G1 (<10)	0	14	0	3
G2 (10-29.9)	4	7	3	5
G3 (30-59.9)	6	1	7	7
G4 (≥60)	12	0	13	8

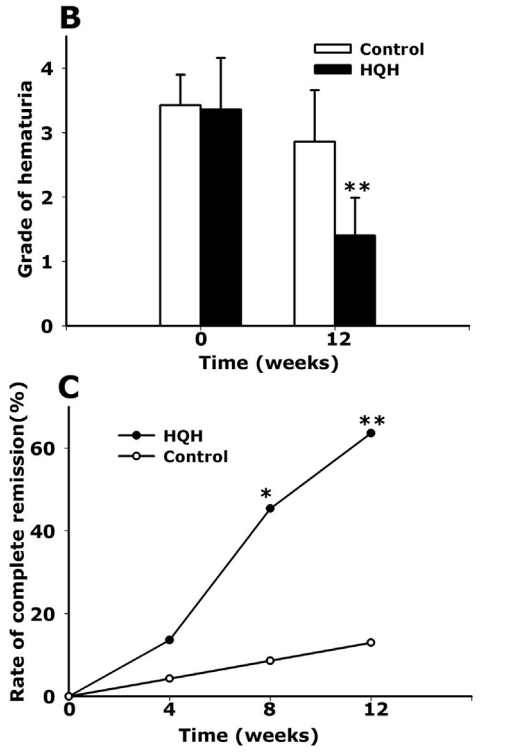

Figure 3 Hematuria grade and complete remission rate of hematuria. (A) The hematuria grade from the two groups before and after treatment for 12 weeks. (B) The extent of hematuria was significantly reduced at 12 weeks, compared with that in control group ($p < 0.001$). (C) The rate of complete remission of hematuria was significantly increased at 8 weeks ($p = 0.007$) and 12 weeks compared with that in control group ($p = 0.001$). HQH = Huai Qi Huang. * $p < 0.05$ versus control group. ** $p < 0.01$ versus control group.

Table 2 Comparison of serum creatinine (Scr) and blood pressure at baseline and 12 weeks between the two groups.

	HQH group (n = 22)		Control group (n = 23)		p
	Baseline	12 wk	Baseline	12 wk	
Scr (μM)	78.1 ± 16.5	70.3 ± 16.4	71.4 ± 16.7	70.9 ± 14.0	0.903
SBP (mmHg)	121 ± 15	118 ± 11.5	107 ± 13	111 ± 12	0.666
DBP (mmHg)	72 ± 9	66 ± 9	70 ± 8	67 ± 6	0.706

Values are expressed as mean ± standard deviation.
DBP = diastolic blood pressure; HQH = Huai Qi Huang; SBP = systolic blood pressure.

Adverse events and compliance

There were no adverse events associated with HQH apart from one patient with mild diarrhea in the treatment period. There were no differences in blood pressure or serum creatinine compared with the baseline in either group (Table 2 and Fig. 4). Patients treated with HQH showed a good compliance throughout our study.

Discussion

IgAN is characterized by mesangial deposition of pathogenic polymeric IgA1, proliferation of mesangial cells, increased synthesis of the extracellular matrix, and infiltration of macrophages, monocytes, and T cells.[23,24] IgAN is increasingly considered an immune complex deposition disease, with immune abnormalities. Multiple cytokines and chemokines are involved in glomerular and renal tubular injury in patients with IgAN.[25–27] Despite the available therapeutic options, 35–40% of patients with IgAN still develop ESRD and require dialysis and renal transplantation. Of the known of risk factors, one of the most important and potentially modifiable is proteinuria, which is associated with outcome improvement.[5] Registry data suggest a threshold of proteinuria of 1 g/day, below which there is significantly improved renal survival. A study showed that IgAN patients with proteinuria < 0.5 g/day have better prognosis than those with proteinuria of 0.5–1.0 g/day. An optimal goal of antiproteinuric therapy for patients with IgAN is < 0.5 g/day.[3] ACEI and ARB have been widely used in IgAN and have been demonstrated effective. However, a significant proportion of patients do not achieve complete remission of proteinuria despite maximal doses of ACEI or ARB.[28–30] There is increasing evidence that isolated hematuria, a forgotten chronic kidney

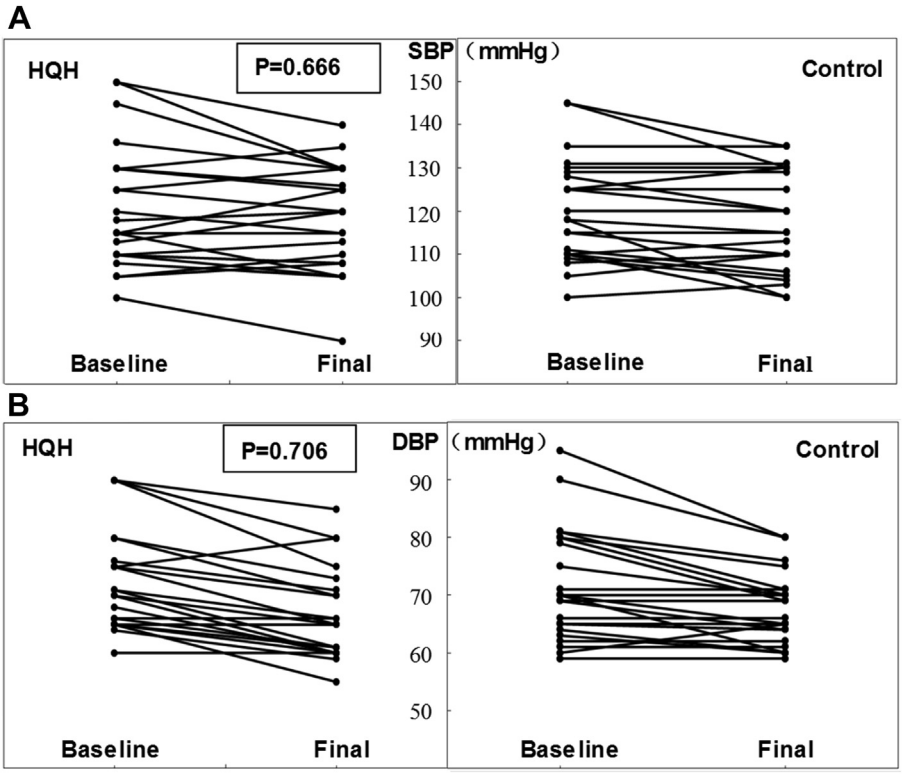

Figure 4 The blood pressure at baseline and 12 weeks. (A) Systolic blood pressure (SBP) changes before and after treatment for 12 weeks in both groups. (B) Diastolic blood pressure (DBP) changes before and after treatment for 12 weeks in both groups. HQH = Huai Qi Huang.

disease factor, associated with incidence of ESRD in IgAN.[11,12] So far, no drugs have obvious benefit on hematuria except steroids and immunosuppressive agents, which are not recommended to treat mild IgAN because of side effects and toxicity. Therefore, seeking a new therapy is highly desirable. With this purpose, we tested the hypothesis that in mild IgAN patients with hematuria and/or proteinuria not fully controlled with renin-angiotensin system inhibitor (RASI) and other antihypertensive drugs, the amelioration could be obtained by the antiproliferation and immunomodulating properties of HQH.

In our randomized controlled trial study, we observed that treatment with HQH for 12 weeks could significantly reduce hematuria and 24-hour urinary protein excretion, and increase the rate of complete remission of proteinuria and hematuria of patients with mild IgAN. In addition, no severe adverse events were observed.

HQH is primarily composed of Huaier, wolfberry fruit, and *Polygonatum*. Huaier, which contains six kinds of monosaccharide and 18 kinds of amino acid, is a biological response modifier that can stimulate many elements of the immune system to enhance immunity. The wolfberry fruit and *Polygonatum* provide synergetic effects. Aqueous extract of Huaier is used for cancer complementary therapy in China, and its immunomodulatory effects have been shown.[31,32] IgAN is also a kind of proliferative glomerulonephritis, which might explain why HQH is effective in treating IgAN. Recently, Zhu et al found evidence that HQH has protective effects on Adriamycin nephrosis in rats. They found that HQH can significantly reduce proteinuria, prevent podocyte injury, and ameliorate tubulointerstitial damage by inhibiting inflammatory cytokine expression and macrophage infiltration.[19] There is an imbalance between T helper 1 and T helper 2 cells in IgAN.[26] Some studies have considered that HQH can adjust this imbalance to achieve treatment of IgAN. The probable reasons for amelioration of proteinuria and hematuria achieved by HQH administration are the antiproliferation, prevention of podocyte injury, and anti-inflammatory effects, as suggested by the significant reduction in hematuria, a known marker of inflammation in IgAN patients.

In the present study, we found that urinary protein excretion had a downward tendency after using HQH, achieving a significant difference between two groups at 8 weeks and 12 weeks. This indicates that HQH was able quickly and effectively to reduce the proteinuria of patients with IgAN. There was also a higher rate of complete remission of proteinuria was calculated after HQH treatment. So far, drugs to reduce hematuria have rarely been reported. In this study, we found that HQH not only could reduce the proteinuria, but also obviously diminish the hematuria. The average grade and complete remission of hematuria significantly abated in HQH group compared with those in the control group. Therefore, HQH plays a distinctive role in ameliorating the hematuria of IgAN. No adverse event induced by oral HQH treatment was observed during the treatment period.

The present study is limited by the small sample size, without placebo and short follow-up. We need to observe the alterations of proteinuria and hematuria after discontinuing HQH. Follow-up time needs to be longer in future studies. We enrolled the patients with normal kidney function, and mild to moderate proteinuria, so there was no evidence of whether the HQH is effective on severe IgAN patients. This needs to be further investigated.

In this study, patients were offered HQH when proved to be IgAN by renal biopsy. Some evidence has demonstrated that a minority of adult IgAN patients may have a spontaneous remission of hematuria and proteinuria.[33,34] This might explain why about 33.3% complete remission of proteinuria and 13% complete remission of hematuria were observed in control group at the present study.

In conclusion, HQH is an effective and well-tolerated therapeutic strategy that could increase the rate of complete remission of proteinuria and hematuria in mild IgAN patients. It could be a new conservative therapy for IgAN patients who cannot tolerate steroids and immunosuppressive agents. The relapse rate after discontinuing treatment needs to be further investigated.

Acknowledgments

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