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Contents

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OPINION REVIEW

- 10392** Regulating monocyte infiltration and differentiation: Providing new therapies for colorectal cancer patients with COVID-19

Bai L, Yang W, Qian L, Cui JW

REVIEW

- 10400** Role of circular RNAs in gastrointestinal tumors and drug resistance

Xi SJ, Cai WQ, Wang QQ, Peng XC

MINIREVIEWS

- 10418** Liver injury associated with acute pancreatitis: The current status of clinical evaluation and involved mechanisms

Liu W, Du JJ, Li ZH, Zhang XY, Zuo HD

- 10430** Association between celiac disease and vitiligo: A review of the literature

Zhang JZ, Abudoureyimu D, Wang M, Yu SR, Kang XJ

- 10438** Role of immune escape in different digestive tumours

Du XZ, Wen B, Liu L, Wei YT, Zhao K

ORIGINAL ARTICLE

Basic Study

- 10451** Magnolol protects against acute gastrointestinal injury in sepsis by down-regulating regulated on activation, normal T-cell expressed and secreted

Mao SH, Feng DD, Wang X, Zhi YH, Lei S, Xing X, Jiang RL, Wu JN

Case Control Study

- 10464** Effect of Nephritis Rehabilitation Tablets combined with tacrolimus in treatment of idiopathic membranous nephropathy

Ly W, Wang MR, Zhang CZ, Sun XX, Yan ZZ, Hu XM, Wang TT

Retrospective Cohort Study

- 10472** Lamb's tripe extract and vitamin B₁₂ capsule plus celecoxib reverses intestinal metaplasia and atrophy: A retrospective cohort study

Wu SR, Liu J, Zhang LF, Wang N, Zhang LY, Wu Q, Liu JY, Shi YQ

- 10484** Clinical features and survival of patients with multiple primary malignancies

Wang XK, Zhou MH

Retrospective Study

- 10494** Thoracoscopic segmentectomy and lobectomy assisted by three-dimensional computed-tomography bronchography and angiography for the treatment of primary lung cancer
Wu YJ, Shi QT, Zhang Y, Wang YL
- 10507** Endoscopic ultrasound fine needle aspiration *vs* fine needle biopsy in solid lesions: A multi-center analysis
Moura DTH, McCarty TR, Jirapinyo P, Ribeiro IB, Farias GFA, Madruga-Neto AC, Ryou M, Thompson CC
- 10518** Resection of bilateral occipital lobe lesions during a single operation as a treatment for bilateral occipital lobe epilepsy
Lyu YE, Xu XF, Dai S, Feng M, Shen SP, Zhang GZ, Ju HY, Wang Y, Dong XB, Xu B
- 10530** Improving rehabilitation and quality of life after percutaneous transhepatic cholangiography drainage with a rapid rehabilitation model
Xia LL, Su T, Li Y, Mao JF, Zhang QH, Liu YY
- 10540** Combined lumbar muscle block and perioperative comprehensive patient-controlled intravenous analgesia with butorphanol in gynecological endoscopic surgery
Zhu RY, Xiang SQ, Chen DR
- 10549** Teicoplanin combined with conventional vancomycin therapy for the treatment of pulmonary methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* infections
Wu W, Liu M, Geng JJ, Wang M
- 10557** Application of narrative nursing in the families of children with biliary atresia: A retrospective study
Zhang LH, Meng HY, Wang R, Zhang YC, Sun J

Observational Study

- 10566** Comparative study for predictability of type 1 gastric variceal rebleeding after endoscopic variceal ligation: High-frequency intraluminal ultrasound study
Kim JH, Choe WH, Lee SY, Kwon SY, Sung IK, Park HS
- 10576** Effects of WeChat platform-based health management on health and self-management effectiveness of patients with severe chronic heart failure
Wang ZR, Zhou JW, Liu XP, Cai GJ, Zhang QH, Mao JF
- 10585** Early cardiopulmonary resuscitation on serum levels of myeloperoxidase, soluble ST2, and hypersensitive C-reactive protein in acute myocardial infarction patients
Hou M, Ren YP, Wang R, Lu LX

Prospective Study

- 10595** Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia
Tang F, Yi JM, Gong HY, Lu ZY, Chen J, Fang B, Chen C, Liu ZY

Randomized Clinical Trial

- 10604** Effects of lower body positive pressure treadmill on functional improvement in knee osteoarthritis: A randomized clinical trial study
Chen HX, Zhan YX, Ou HN, You YY, Li WY, Jiang SS, Zheng MF, Zhang LZ, Chen K, Chen QX

SYSTEMATIC REVIEWS

- 10616** Effects of hypoxia on bone metabolism and anemia in patients with chronic kidney disease
Kan C, Lu X, Zhang R

META-ANALYSIS

- 10626** Intracuff alkalinized lidocaine to prevent postoperative airway complications: A meta-analysis
Chen ZX, Shi Z, Wang B, Zhang Y

CASE REPORT

- 10638** Rarely fast progressive memory loss diagnosed as Creutzfeldt-Jakob disease: A case report
Xu YW, Wang JQ, Zhang W, Xu SC, Li YX
- 10645** Diagnosis, fetal risk and treatment of pemphigoid gestationis in pregnancy: A case report
Jiao HN, Ruan YP, Liu Y, Pan M, Zhong HP
- 10652** Histology transformation-mediated pathological atypism in small-cell lung cancer within the presence of chemotherapy: A case report
Ju Q, Wu YT, Zhang Y, Yang WH, Zhao CL, Zhang J
- 10659** Reversible congestive heart failure associated with hypocalcemia: A case report
Wang C, Dou LW, Wang TB, Guo Y
- 10666** Excimer laser coronary atherectomy for a severe calcified coronary ostium lesion: A case report
Hou FJ, Ma XT, Zhou YJ, Guan J
- 10671** Comprehensive management of malocclusion in maxillary fibrous dysplasia: A case report
Kaur H, Mohanty S, Kochhar GK, Iqbal S, Verma A, Bhasin R, Kochhar AS
- 10681** Intravascular papillary endothelial hyperplasia as a rare cause of cervicothoracic spinal cord compression: A case report
Gu HL, Zheng XQ, Zhan SQ, Chang YB
- 10689** Proximal true lumen collapse in a chronic type B aortic dissection patient: A case report
Zhang L, Guan WK, Wu HP, Li X, Lv KP, Zeng CL, Song HH, Ye QL
- 10696** Tigecycline sclerotherapy for recurrent pseudotumor in aseptic lymphocyte-dominant vasculitis-associated lesion after metal-on-metal total hip arthroplasty: A case report
Lin IH, Tsai CH

- 10702** Acute myocardial infarction induced by eosinophilic granulomatosis with polyangiitis: A case report
Jiang XD, Guo S, Zhang WM
- 10708** Aggressive natural killer cell leukemia with skin manifestation associated with hemophagocytic lymphohistiocytosis: A case report
Peng XH, Zhang LS, Li LJ, Guo XJ, Liu Y
- 10715** Chronic lymphocytic leukemia/small lymphocytic lymphoma complicated with skin Langerhans cell sarcoma: A case report
Li SY, Wang Y, Wang LH
- 10723** Severe mediastinitis and pericarditis after endobronchial ultrasound-guided transbronchial needle aspiration: A case report
Koh JS, Kim YJ, Kang DH, Lee JE, Lee SI
- 10728** Obturator hernia - a rare etiology of lateral thigh pain: A case report
Kim JY, Chang MC
- 10733** Tracheal tube misplacement in the thoracic cavity: A case report
Li KX, Luo YT, Zhou L, Huang JP, Liang P
- 10738** Peri-implant keratinized gingiva augmentation using xenogeneic collagen matrix and platelet-rich fibrin: A case report
Han CY, Wang DZ, Bai JF, Zhao LL, Song WZ

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Case Control Study

Effect of Nephritis Rehabilitation Tablets combined with tacrolimus in treatment of idiopathic membranous nephropathy

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Abstract

BACKGROUND

Idiopathic membranous nephropathy (IMN) has a high incidence in the middle-aged and elderly population, and poses a great threat to the physical and mental health and quality of life of patients. Nephritis Rehabilitation Tablets have many potential effects, such as clearing residual toxins, tumefying the kidney and spleen, replenishing qi, and nourishing yin, and have played an important role in the treatment of a variety of kidney diseases.

AIM

To investigate the efficacy and safety of Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of IMN.

METHODS

Eighty-four patients with IMN recruited from January 2017 to September 2020 were randomly divided into a study group ($n = 42$) and a control group ($n = 42$). On the basis of routine symptomatic treatment, both groups were treated with tacrolimus, and the study group was additionally treated with Nephritis Rehabilitation Tablets. Both groups were treated for 12 wk. The therapeutic effect, the levels of renal function indexes [serum creatinine (Scr), serum albumin, and 24-h urinary protein], urinary immunoglobulin (IgG4), membrane attack complex (C5b-9), and the incidence of adverse reactions were measured before and after 12 wk of treatment.

RESULTS

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The total effective rate in the study group was significantly higher than that of the control group. Before treatment, there was no significant difference in Scr, serum albumin, or 24 h urinary protein between the two groups. After 12 wk of treatment, the levels of Scr and 24-h urinary protein in both groups were significantly lower and serum albumin was significantly higher than those before treatment ($P < 0.05$), and the levels of Scr and 24-h urinary protein were significantly lower ($P = 0.003$ and 0.000 , respectively), and the level of serum albumin was significantly higher ($P = 0.00$) in the study group than in the control group. Before treatment, there was no significant difference in urinary IgG4 and C5b-9 levels between the study group and the control group ($P = 0.336$ and 0.438 , respectively). After 12 wk of treatment, the levels of urinary IgG4 and C5b-9 in the two groups were lower than those before treatment, and the levels of urinary IgG4 and C5b-9 in the study group were significantly lower than those in the control group ($P = 0.000$). There was no significant difference in the incidence of adverse reactions between the two groups ($P = 0.710$).

CONCLUSION

Based on routine intervention, Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of IMN can effectively improve the renal function of patients and downregulate the expression of urinary IgG4 and C5b-9. In addition, they can improve the overall therapeutic effect while not increasing the risk of adverse reactions.

Key Words: Nephritis Rehabilitation Tablets; Tacrolimus; Idiopathic membranous nephropathy; Renal function; IgG4; C5b-9

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Core Tip: Generally, Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of idiopathic membranous nephropathy can effectively improve the renal function of patients and downregulate the expression of urinary IgG4 and C5b-9. In addition, they can help to improve the overall treatment effect while not increasing the risk of adverse reactions.

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INTRODUCTION

Idiopathic membranous nephropathy (IMN) is a common pathological type of primary nephrotic syndrome. It has a high incidence in the middle-aged and elderly population, and poses a great threat to the physical and mental health and quality of life of patients[1,2]. The incidence of IMN has continued to increase in recent years, and safe and effective treatments are of significant research interest.

Glucocorticoid therapy alone has difficulty achieving ideal effects in IMN, and comprehensive intervention combined with immunosuppressants is usually needed [3]. Cyclophosphamide is commonly used in IMN and can achieve certain therapeutic effects, but the incidence of adverse reactions is high. Tacrolimus is a new calcineurin inhibitor that can effectively improve renal function with low dose and high safety. However, the overall therapeutic effect is still different from that expected in the clinic [4-6].

Attention has been given to the adjuvant therapeutic effects of traditional Chinese medicine Nephritis Rehabilitation Tablets in recent years. Nephritis Rehabilitation Tablets have many potential effects, such as clearing residual toxins, tumefying the kidney and spleen, replenishing qi, and nourishing yin, and have played an important role in the treatment of a variety of kidney diseases. In the present study, 84 patients

with IMN at our hospital were selected and divided into groups to explore the therapeutic value of Nephritis Rehabilitation Tablets with tacrolimus.

MATERIALS AND METHODS

General data

Eighty-four patients with IMN were recruited from our hospital from January 2017 to September 2020 and were randomly divided into a study group ($n = 42$) and a control group ($n = 42$). In the study group, there were 27 males and 15 females, the age ranged from 46 to 77 years (mean, 61.56 ± 7.11 years), the course of disease ranged from 3.5 to 41.1 mo (mean, 22.29 ± 10.32 mo), and the disease stage was stage I ($n = 23$) or stage II ($n = 19$). In the control group, there were 29 males and 13 females, the age range was 45-79 years old with an average age of 62.01 ± 6.89 years, the course of disease range was 3.2-40.6 mo with an average of 21.91 ± 11.21 mo, and the disease stage was stage I ($n = 24$) or stage II ($n = 18$). The clinical data, including sex, age, course of disease, and stage of disease, were comparable between the two groups ($P > 0.05$).

Selection criteria

The inclusion criteria were: (1) The diagnosis of IMN was confirmed by renal puncture pathological examination, and the pathological stage was I or II; (2) age less than 80 years; (3) patients who were informed of the study and signed the consent form; (4) serum creatinine (Scr) $< 133 \mu\text{mol/L}$; and (5) urinary protein $\geq 4 \text{ g/24 h}$.

The exclusion criteria were: (1) Patients with acquired immunodeficiency syndrome, hepatitis C, hepatitis B, *etc.*, who are unable to take immunosuppressant or hormone therapy; (2) patients with malignant tumor; (3) patients with severe infection; (4) patients with coagulation dysfunction; and (5) patients with allergic constitution or history of allergy to research drugs.

Methods

Both groups of patients were given routine symptomatic treatment after admission, including lipid reduction, anticoagulation, blood pressure reduction, diuresis and detumescence, and oral prednisone acetate tablets 0.5 mg/kg once a day (8 wk after treatment, the dose was reduced by 10% at an interval of 2 wk to a maintenance therapy of $10\text{--}15 \text{ mg/d}$). On this basis, different treatment schemes were adopted: The control group was treated with tacrolimus orally at $0.05\text{--}0.1 \text{ mg/kg/d}$ twice a day, and blood trough concentration was maintained at $4\text{--}8 \text{ ng/L}$; the study group was treated with Nephritis Rehabilitation Tablets orally at 1.5 g three times a day in addition to the standard treatment of the control group. Both groups were treated for 12 wk.

Evaluation of therapeutic effects

After 12 wk of treatment, the therapeutic effects of the two groups were evaluate: Normalization of the levels of serum albumin and Scr and 24-h urinary protein $< 0.3 \text{ g}$ were considered as complete remission; 24-h urinary protein decreased by $\geq 50\%$ or total $< 1.0 \text{ g}$, normalization of serum albumin, and the increase or decrease of Scr $\leq 30\%$ were considered as partial remission. The total effective rate was calculated as (complete remission + partial remission)/total cases $\times 100\%$ [7]. The indexes of renal function (Scr, serum albumin, and 24-h urinary protein) were measured before treatment and after 12 wk of treatment. The levels of urinary immunoglobulin (IgG4) and membrane attack complex (C5b-9) in the two groups were measured before and after 12 wk of treatment. Mid-stream urine was taken and put into a clean container and stored at -20°C for detection. The level of urinary C5b-9 was determined by enzyme-linked immunosorbent assay (ELISA), and the level of IgG4 was determined by double antibody sandwich ELISA. The incidence of adverse reactions in the two groups was measured.

Statistical analysis

The data were analyzed with SPSS 22.0. Continuous data are described as the mean \pm SD and were compared by the *t*-test. Categorical data are described as frequency and constituent ratio (%) and were tested by the χ^2 test. A nonparametric test was used to compare the continuous data that do not meet a normal distribution. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Therapeutic effects

The total effective rate of the study group (90.48%) was significantly higher than that of the control group (71.43%, $P = 0.026$; [Table 1](#)).

Renal function indexes

Before treatment, there was no significant difference in Scr, serum albumin, or 24 h urinary protein between the study group and the control group ($121.97 \pm 40.36 \mu\text{mol/L}$ vs $124.55 \pm 38.68 \mu\text{mol/L}$, $24.21 \pm 2.35 \text{ g/L}$ vs $23.64 \pm 2.51 \text{ g/L}$, $7.41 \text{ g} \pm 2.19 \text{ g}$ vs $7.69 \pm 2.32 \text{ g}$; $P = 0.766$, 0.286 , and 0.571 , respectively). After 12 wk of treatment, the quantitative levels of Scr and 24-h urinary protein in the two groups were significantly lower than those before treatment, and the level of serum albumin was significantly higher than that before treatment ($P < 0.05$). The levels of Scr and 24-h urinary protein in the study group ($86.23 \pm 21.61 \mu\text{mol/L}$ and $1.63 \pm 0.59 \text{ g}$, respectively) were significantly lower than those in the control group ($101.55 \pm 23.67 \mu\text{mol/L}$ and $2.89 \pm 0.79 \text{ g}$; $P = 0.003$ and 0.000 , respectively), and the level of serum albumin in the study group ($36.69 \pm 3.69 \text{ g/L}$) was significantly higher than that in the control group ($31.26 \pm 3.35 \text{ g/L}$, $P = 0.00$; [Table 2](#)).

Urinary IgG4 and C5b-9 levels

Before treatment, there was no significant difference in urinary IgG4 or C5b-9 level between the study group ($14.67 \pm 2.39 \mu\text{g/mmol}$ and $83.79 \pm 10.66 \text{ ng/mg}$, respectively) and the control group ($15.13 \pm 2.53 \mu\text{g/mmol}$, and $85.65 \pm 11.20 \text{ ng/mg}$; $P = 0.336$ and 0.438 , respectively). After 12 wk of treatment, the levels of urinary IgG4 and C5b-9 in the two groups were lower than those before treatment, and the levels of urinary IgG4 and C5b-9 in the study group ($1.45 \pm 0.29 \mu\text{g/mmol}$ and $44.81 \pm 9.10 \text{ ng/mg}$, respectively) were significantly lower than those in the control group ($3.13 \pm 0.71 \mu\text{g/mmol}$ and $55.37 \pm 10.23 \text{ ng/mg}$; $P = 0.000$ and 0.000 , respectively; [Table 3](#)).

Incidence of adverse reactions

There was no significant difference in the incidence of adverse reactions between the study group (11.90%) and the control group (7.14%, $P = 0.710$; [Table 4](#)).

DISCUSSION

The incidence of IMN can account for more than 80% of nephrotic syndromes, and it can occur at any age. Most patients have different degrees of thrombosis and proteinuria, and 30% of patients' symptoms can be relieved by themselves. However, 50% of patients' conditions progress rapidly and can progress to end-stage kidney disease within 10 years, which is a great threat[8,9]. As a consequence, targeted treatment should be given quickly after the onset of IMN.

Glucocorticoids are an important therapeutic drug for IMN. However, hormone therapy alone has difficulty achieving ideal results. Relevant statistics show that the incidence of renal insufficiency in IMN patients without immunosuppressant can reach 40%. The combination of hormone and immunosuppressant therapy can effectively relieve clinical symptoms, improve renal survival, and inhibit the progression of renal insufficiency[10,11]. Cyclophosphamide is the most commonly used immunosuppressant in the clinic and can block the synthesis of DNA in cells to achieve immunosuppression. Combined with hormones, it can enhance hormone sensitivity and improve drug efficacy. However, the incidence of adverse events such as gonadal inhibition, liver function injury, and myelosuppression is high, resulting in significant limitations in its clinical application[12]. Tacrolimus is a new type of immunosuppressant that can interfere with calcium-dependent signal transduction, increase calcium influx, prevent dephosphorylation of activated T nuclear factors and transcription of inflammatory factors, and inhibit T cell proliferation. Lymphocyte aggregation is prevented in the early stage of the immune reaction and thus plays a therapeutic role[13,14]. In addition, the value of adjuvant therapy with traditional Chinese medicine in IMN has received widespread attention in recent years. There is no record of the name of IMN in traditional Chinese medicine, but according to its characteristics, it is classified into the categories of "edema" and "turbid urine". It is considered that the pathological mechanism of the disease lies in the deficiency of the spleen and kidney, blood stasis, damp-heat, wind evil, and water dampness. Spleen

Table 1 Comparison of therapeutic effects between the two groups, *n* (%)

Group	Number	Complete remission	Partial remission	Invalid	Total efficiency
Study	42	26 (61.90)	12 (28.57)	4 (9.52)	38 (90.48)
Control	42	16 (38.10)	14 (33.33)	12 (28.57)	30 (71.43)
χ^2					4.941
<i>P</i> value					0.026

Table 2 Comparison of renal function indexes between the two groups (mean \pm SD)

Time	Group	Number	Scr (umol/L)	Serum albumin (g/L)	24 h urinary protein quantification (g)
Before treatment	Study	42	121.97 \pm 40.36	24.21 \pm 2.35	7.41 \pm 2.19
	Control	42	124.55 \pm 38.68	23.64 \pm 2.51	7.69 \pm 2.32
	<i>t</i>		0.299	1.074	0.569
	<i>P</i> value		0.766	0.286	0.571
After 12 weeks of treatment	Study	42	86.23 \pm 21.61 ^a	36.69 \pm 3.71 ^a	1.63 \pm 0.59 ^a
	Control	42	101.55 \pm 23.67 ^a	31.26 \pm 3.35 ^a	2.89 \pm 0.79 ^a
	<i>t</i>		3.098	7.040	8.282
	<i>P</i> value		0.003	0.000	0.000

^a*P* < 0.05, before treatment *vs* after 12 wk of treatment.Table 3 Comparison of urinary IgG4 and C5b-9 levels between the two groups (mean \pm SD)

Time	Group	Number	IgG4 (ug/mmol)	C5b-9 (ng/mg)
Before treatment	Study	42	14.67 \pm 2.39	83.79 \pm 10.66
	Control	42	15.19 \pm 2.53	85.65 \pm 11.20
	<i>t</i>		0.968	0.780
	<i>P</i> value		0.336	0.438
After 12 weeks of treatment	Study	42	1.45 \pm 0.29 ^a	44.81 \pm 9.39 ^a
	Control	42	3.13 \pm 0.71 ^a	55.37 \pm 10.23 ^a
	<i>t</i>		14.196	4.928
	<i>P</i> value		0.000	0.000

^a*P* < 0.05, before treatment *vs* after 12 wk of treatment.

deficiency can lead to deficiency of qi and blood, and retention of damp turbidity leads to edema. Kidney deficiency can cause nontransformation of qi and water, such as edema and kidney loss and storage, to form proteinuria[15]. Combined with the above etiology and pathogenesis, on the basis of routine intervention such as tacrolimus, Nephritis Rehabilitation Tablets were used to treat patients with IMN at our hospital. The results showed that the total effective rate of the study group was higher than that of the control group, the quantitative levels of Scr and 24-h urinary protein of the study group were lower than those of the control group, and the level of serum albumin was higher than that of the control group. This showed that the combination of tacrolimus and Nephritis Rehabilitation Tablets has more significant advantages in improving the renal function of patients with IMN, which is helpful for improving the overall therapeutic effect on the disease. The main reason is that the main components of Nephritis Rehabilitation Tablets include *Salvia miltiorrhiza*, *Ginseng*, *Hedyotis diffuse*, *Motherwort*, and *Eucommia ulmoides*, which have many effects, such as dispelling dampness and removing blood stasis, diuresis, and detumescence; tonifying qi and

Table 4 Comparison of incidence of adverse reactions between the two groups, *n* (%)

Group	Number	Elevated transaminase	Gastrointestinal reaction	Vomiting and nausea	Dizzy	Total incidence rate
Study	42	1 (2.38)	1 (2.38)	2 (4.76)	1 (2.38)	5 (11.90)
Control	42	1 (2.38)	1 (2.38)	0 (0.00)	1 (2.38)	3 (7.14)
χ^2						0.138
<i>P</i> value						0.710

nourishing yin; and tonifying the kidney and detoxification. In addition, *Motherwort*, *Salvia miltiorrhiza*, and *Hedyotis diffusa* have many effects, such as anti-erythrocyte and anti-platelet aggregation, which can reduce blood viscosity, increase renal blood flow, and prevent thrombosis[16,17]. In addition, Nephritis Rehabilitation Tablets can reduce capillary permeability, regulate microcirculation and lipid metabolism, reduce swelling and diuresis, relieve urinary protein, enhance immunity, and improve renal function. In addition, some studies have demonstrated that Nephritis Rehabilitation Tablets can repair glomerular podocytes and reduce the expression of transforming growth factor beta 1 and α -smooth muscle actin in the renal interstitium. In addition, it can maintain the filtration barrier, improve the precipitation of extracellular matrix components such as laminin and fibronectin, and regulate immune function and renal function. Moreover, it can increase liver albumin synthesis, increase plasma protein levels, and antagonize glucocorticoid-induced adverse reactions[18].

In addition, urinary IgG4 can reflect renal IgG4 deposition and is closely related to IMN disease activity. Moreover, studies have shown that IMN autoantibodies play an intermediary role, while complement proteins play an important role in organ-specific autoimmune diseases. Podocyte antigens can bind to antibodies to form subepithelial *in situ* immune complexes, and complement activation can produce C5b-9. As a consequence, the condition, therapeutic effect, and prognosis of IMN can be evaluated by monitoring the levels of urinary IgG4 and C5b-9[19,20]. The levels of urinary IgG4 and C5b-9 in the study group were lower than those in the control group ($P < 0.05$), which further confirmed that Nephritis Rehabilitation Tablets combined with tacrolimus had high therapeutic value in IMN, which could reduce the contents of urinary IgG4 and C5b-9 and improve the therapeutic effect of the disease. In addition, from the results of this study, it can be concluded that there was no significant difference in the incidence of adverse reactions between the two groups, indicating that the combination of Nephritis Rehabilitation Tablets and tacrolimus can not only achieve a good therapeutic effect but also have a satisfactory safety profile.

CONCLUSION

Generally, Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of IMN can effectively improve the renal function of patients and downregulate the expression of urinary IgG4 and C5b-9 on the basis of routine intervention. In addition, they can help to improve the overall treatment effect while not increasing the risk of adverse reactions. However, since this study had fewer samples, further multi-center research is required to confirm our findings.

ARTICLE HIGHLIGHTS

Research background

Idiopathic membranous nephropathy (IMN) has a high incidence in the middle-aged and elderly population, and poses a great threat to the physical and mental health and quality of life of patients. The incidence of IMN has continued to increase in recent years, and safe and effective treatments are of significant research interest.

Research motivation

Glucocorticoid therapy alone has difficulty achieving ideal effects in IMN, and the incidence of adverse reactions is high. Tacrolimus is a new calcineurin inhibitor that can effectively improve renal function with low dose and high safety.

Research objectives

This study aimed to investigate the efficacy and safety of Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of IMN.

Research methods

On the basis of routine symptomatic treatment, the control group was treated with tacrolimus, and the study group was treated with nephritis rehabilitation tablets in addition to control group treatment. Both groups were treated for 12 wk. The therapeutic effect, the levels of renal function indexes, and the incidence of adverse reactions were measured before and after 12 wk of treatment.

Research results

The results showed that the total effective rate of the study group was higher than that of the control group, the quantitative levels of Scr and 24-h urinary protein of the study group were lower than those of the control group, and the level of serum albumin was higher than that of the control group. IMN autoantibodies play an intermediary role, while complement proteins play an important role in organ-specific autoimmune diseases. The levels of urinary IgG4 and C5b-9 in the study group were lower than those in the control group.

Research conclusions

Nephritis Rehabilitation Tablets combined with tacrolimus in the treatment of IMN can effectively improve the renal function of patients and downregulate the expression of urinary IgG4 and C5b-9. In addition, they can improve the overall therapeutic effect while not increasing the risk of adverse reactions.

Research perspectives

This study has fewer samples, and further multi-center research is required to confirm our findings.

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