Original Paper

Comparison of the Safety of Prednisone Plus Dipyridamole Versus Prednisone Plus Valsartan in the Treatment of Children with Primary Nephrotic Syndrome

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Introduction. In recent years, the incidence of pediatric nephrotic syndrome (NS) has been increasing, and timely and effective treatment is critical to protect the health of children with NS. This study is an attempt to compare the therapeutic effects of prednisone (Pred) plus dipyridamole (DIP) versus Pred plus valsartan (VAL) on pediatric NS.

Methods. Two hundred pediatric cases of NS were selected as the research participants, including 109 cases (group A) receiving Pred + DIP and 91 cases (group B) receiving Pred + VAL. The clinical efficacy, adverse reactions, and renal, coagulation functions and blood lipid levels, as well as the pre- and post-treatment levels of inflammatory factors (IFs) and immunoglobulins (Igs) were comparatively analyzed.

Results. No statistically significant differences were found between groups in terms of clinical efficacy, incidence of adverse reactions and renal function ($P > .05$). After receiving the corresponding treatment, group A showed better coagulation and immune functions than group B, but higher levels of IFs and poorer blood lipid function ($P < .05$).

Conclusion. Both Pred + DIP and Pred + VAL combination therapies can be used for the treatment of pediatric NS, with the former contributing to more obviously enhanced coagulation and immune functions, and the latter leading to more significantly inhibited inflammation and better regulated blood lipid function.

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INTRODUCTION

Pediatric nephrotic syndrome (NS) is a clinical syndrome in which a large amount of protein is lost from urine due to the increased permeability of glomerular basement membrane (GBM), which is very common in clinical practice.[1] Recent years have witnessed the rising prevalence of pediatric NS, with a global average incidence reaching 6 to 15 percent.[2] Some of the clinical manifestations of NS are oliguria, edema, hypercholesterolemia, hypoproteinemia, which can form thrombosis in severe cases, leading to acute kidney injury and other life-threatening critical illnesses.[3] The pathogenesis of NS has not been fully defined, but evidence links its occurrence to various factors such as heredity, immunity, and infection. As a result, treating NS in children can be challenging due to its recrudescent nature, which can significantly hinder their normal growth.[4]

Prednisone (Pred), as a glucocorticoid, is the

most commonly used medication in the treatment of NS. However, long-term use of Pred may cause metabolic disorders, peptic ulcers, cataracts and many other complications, so it is often used as an adjunct therapy in combination with other drugs.[5,6] Dipyridamole (DIP), as a coronary vasodilator and anti-platelet aggregation drug, has been documented to play a positive role in improving coagulation and renal functions in NS patients, which can effectively control disease progression, inhibit glomerular micro thrombosis, and improve patient's prognosis.[7,8] Valsartan (VAL) is an angiotensin receptor antagonist that can reduce proteinuria and protect renal function, and is a drug commonly used in the treatment of diabetic nephropathy. Recently, studies have also shown that its combination with Pred has a significant impact on the treatment of NS.[9,10] Although Pred combined with DIP or VAL has been confirmed to have a positive effect on the treatment of NS, the exact clinical efficacy of the two treatment regimens has not been reported, lacking reliable guidance on the choice of the two schemes for the treatment of pediatric NS.

Therefore, this study comparatively analyzed the clinical effects of *P*red + DI*P* versus *P*red + VAL in the treatment of NS, to provide more reliable and comprehensive reference and guidance for the future drug selection of pediatric NS.

MATERIALS AND METHODS

Study participants

This study prospectively included 200 children with NS admitted to Northwest Women's and Children's Hospital (Xi'an, Shaanxi,710000, China) between August 2017 and October 2022 for analysis. Among them, 109 children received Pred + DIP therapy and were included in group A; the rest 91 cases were given Pred + VAL and included in group B. The study was conducted with the informed consent of the guardians of all participants and in strict accordance with the *Declaration of Helsinki*.

The current study was approved by the Ethics Committee of Northwest Women's and Children's Hospital (YXY-2020-19). Comparing the age, sex, course of disease and other data between groups A and B, we found no statistical significance ($P > .05$, Table 1), indicating clinical comparability.

Inclusion and exclusion criteria

Inclusion criteria were: (1) All the study participants met the diagnostic criteria for primary NS[11] and were diagnosed by medical history, clinical manifestations (decreased urine volume, ascites, pleural effusion, and edema) and laboratory tests (positive urine protein [UP] test results within one week, and 24-hour UP quantitative examination > 3.5g), (2) First onset, (3) Complete medical records, (4) The guardian agreed to participate in and cooperate with this study. Exclusion criteria were: (1) Congenital NS, (2) Secondary NS caused by lupus nephritis or henoch-schonlein purpura nephritis, (3) Severe allergic constitution and hypertension, (4) Adrenocortical insufficiency, heart failure, liver dysfunction and other diseases, (5) Chronic malnutrition and long-term diarrhea, (6) Those needing heparin therapy.

Treatments

Children were given routine treatment according to the symptoms after admission: Those with severe edema and hypoproteinemia were allowed to rest in bed and gradually increase their activities after the resolution of edema. The diet was based on fish, eggs, beef, etc., reducing the intake of animal fat and ensuring the intake of sufficient calories (≥126-147 kJ/kg per day). Low-salt diet (< 3 g/d) was used when edema appeared. Those suffering from severe edema and oliguria were given diuretics (hydrochlorothiazide, etc.) according to the condition, with the water inflow and outflow, weight change and electrolyte disturbance closely observed. In addition, Pred Acetate Tablets (Xi'an Hanfeng Pharmaceutical Co., Ltd., H61023348)

Table 1. Comparison of clinical baseline information

Group	Age	Course of disease (months)	Sex male vs. female	Family history of illness yes vs. no
Control group (n = 109)	7.85 ± 2.10	22.12 ± 4.29	64 (58.72) vs. 45 (41.28)	12 (11.08) vs. 97 (88.99)
Research group (n = 91)	7.96 ± 3.15	21.80 ± 5.38	60 (65.93) vs. 31 (34.07)	8 (8.79) vs. 83 (91.21)
t (χ^2)	0.276	0.464	1.097	0.271
P	0.783	0.643	0.295	0.603

was administered orally at 1.5-2.0 mg/kg/d, twice a day; the dose was adjusted to 1.5 mg/(kg/d), once every 2 days, after the urine protein turned negative for 2 weeks; 4 weeks later, the dosage of Pred was gradually and regularly reduced by 2.5-5.0 mg every 2-4 weeks. On this ground, group A was further treated with DIP (Teyi Pharmaceutical Group Co., Ltd., H44021118) at 1.0 mg/(kg/d), three times a day. Group B was additionally treated with VAL (Huahai Pharmaceutical Co., Ltd., Zhejiang, China, H20183128), 40 mg/time for children under 7 years old and 80 mg/time for those ≥7 years old, once daily. Both groups were treated for 2 months.

Clinical efficacy evaluation

After the treatment, the efficacy was evaluated by referring to the NS clinical guidelines.[12] Cured: the symptoms such as high edema, massive proteinuria, hyperlipidemia and hypoproteinemia disappeared completely, the urine protein quantification turned negative, ALB > 35 g/L, and 24-hour UP quantification < 0.2 g, urinary protein excretion rate < 20 μg/min. Markedly effective: the symptoms basically disappeared, ALB was significantly improved after repeated detection, and the 24-hour urine protein quantification < 1 g. Effective: ALB was relieved after repeated detection, and the 24-hour UP was less than 3g. Ineffective: renal function did not change, clinical symptoms were still present, and ALB and UP did not change or even deteriorated. Total effective rate = (cured + markedly effective + effective) cases / total study population ×100%. In addition, the adverse reactions such as rash, nausea and vomiting during treatment in the two groups were counted to calculate the total incidence.

Sampling and testing

The fasting venous blood and urine of both groups of children was collected before and after treatment. Coagulation function indices such as activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) were detected with a coagulation function analyzer (Myriad ExC810); parameters of renal function and blood lipid levels, including proteinuria, blood urea nitrogen (BUN), serum creatinine (SCr), β2-microglobulin (β2-MG), uric acid (UA), triglyceride (TG), and total cholesterol (TC), were detected using an automatic biochemical analyzer (Myriad BS-350E); enzyme-linked immunosorbent assays (ELISAs) were performed to quantify inflammatory factors (IFs) such as interleukin-6/13 (IL-6/13), tumor necrosis factor-α (TNF-α), and hypersensitive-C reactive protein (hs-CRP), the kits were purchased from Pujian Biologicals (Wuhan) Technology Co.; immunoelectrophoresis was carried out to measure immune function indices immunoglobin A/M/G (IgA/M/G), the testing instrument was a Brocade BKI2200 chemiluminescence detector.

Statistical analysis

All the data were imported into SPSS software version 24.0 for statistical analysis, and differences with *P*-value < .05 were considered statistically significant. Counting data, represented by [n (%)], were compared between groups using chi-square tests While independent samples t tests were used for inter-group comparisons of measurement data described as (`c ± s) and paired t tests for intra- group comparisons.

RESULTS

Comparison of clinical efficacy

The statistical results of clinical efficacy of the two groups after treatment are shown in Table 2. The total effective rate was 85.32% in group A and 89.01% in group B, with no significant inter-group difference ($P > .05$).

Comparison of renal function before and after treatment

Figure 1 shows the renal function test results of the two groups before and after treatment. No difference was identified in renal function before

Table 2. Comparison of clinical efficacy

Group	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n = 109)	15 (13.76)	46 (42.20)	32 (29.36)	16 (14.68)	93 (85.32)
Research group (n = 91)	14 (15.38)	41 (45.05)	26 (28.57)	10 (10.99)	81 (89.01)
χ^2					0.597
P					0.440

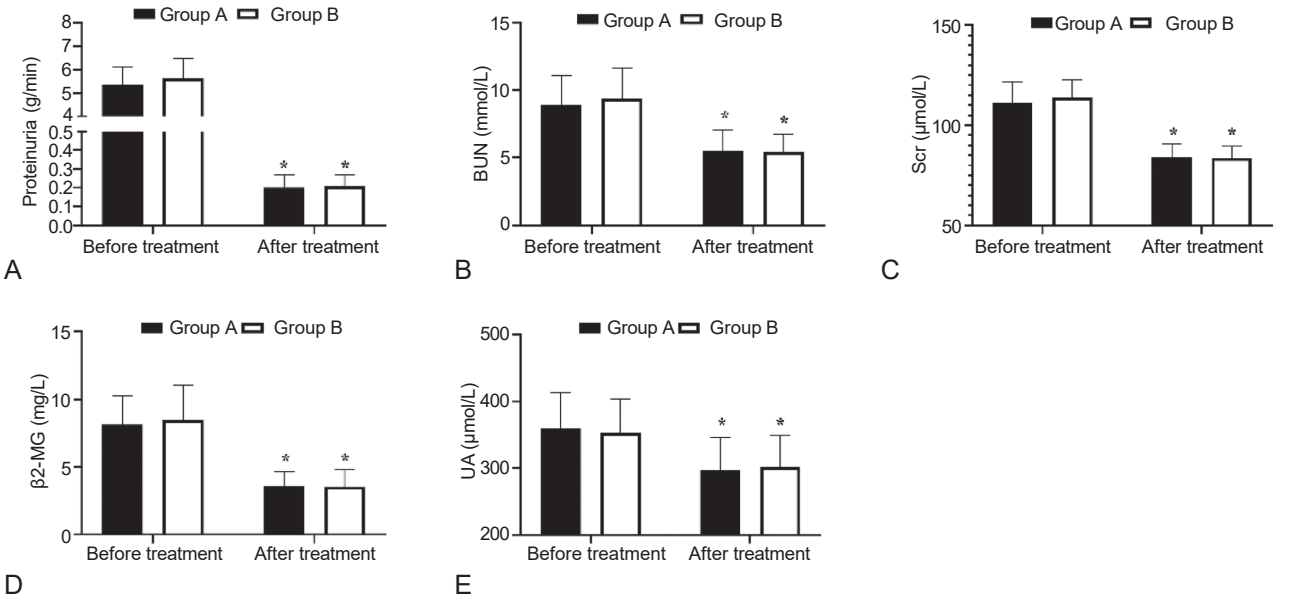

Figure 1. Comparison of renal function before and after treatment. (A) Comparison of proteinuria, (B) Comparison of BUN, (C) Comparison of SCr, (D) Comparison of β2-MG, E: Comparison of UA.
*indicates a statistically significant difference from before treatment ($P < .05$).

treatment between the groups ($P > .05$). The levels of proteinuria, BUN, SCr, β2-MG, and UA decreased in both groups after treatment ($P < .05$), but still showing no statistical significance inter-group differences ($P > .05$).

Comparison of coagulation function before and after treatment

As shown in Figure 2, the two groups were not significantly different in coagulation function before treatment ($P > .05$). An elevation in APTT, PT, and TT were determined in both groups after treatment, with even higher levels of all tests in group A compared with group B ($P < .05$).

Comparison of inflammatory reaction before and after treatment

The detection results of IFs (IL-6/13, TNF-α and hs-CRP), presented in Figure 3, revealed no notable difference between groups A and B before treatment ($P > .05$); while the levels of these IFs decreased in both groups after treatment, with even lower IL-6, IL-13, TNF-α and hs-CR*P* levels in group B ($P < .05$).

Comparison of immune function before and after treatment

As shown in Figure 4, pre-treatment levels of immunoglobulins (IgA/M/G) testing results are

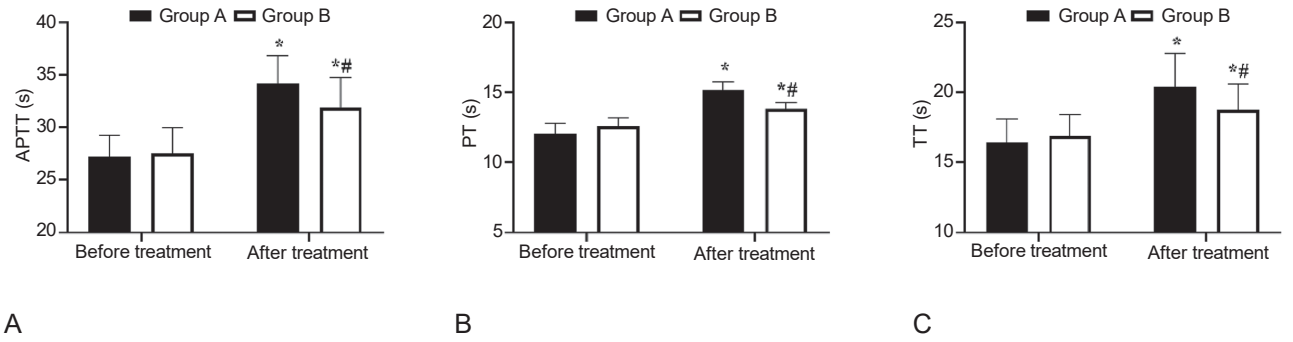

Figure 2. Comparison of coagulation function before and after treatment. (A) Comparison of APTT, (B) Comparison of PT, (C) Comparison of TT.
*indicates a statistically significant difference from before treatment ($P < .05$)
#indicates a statistically significant difference from group A (< 0.05).

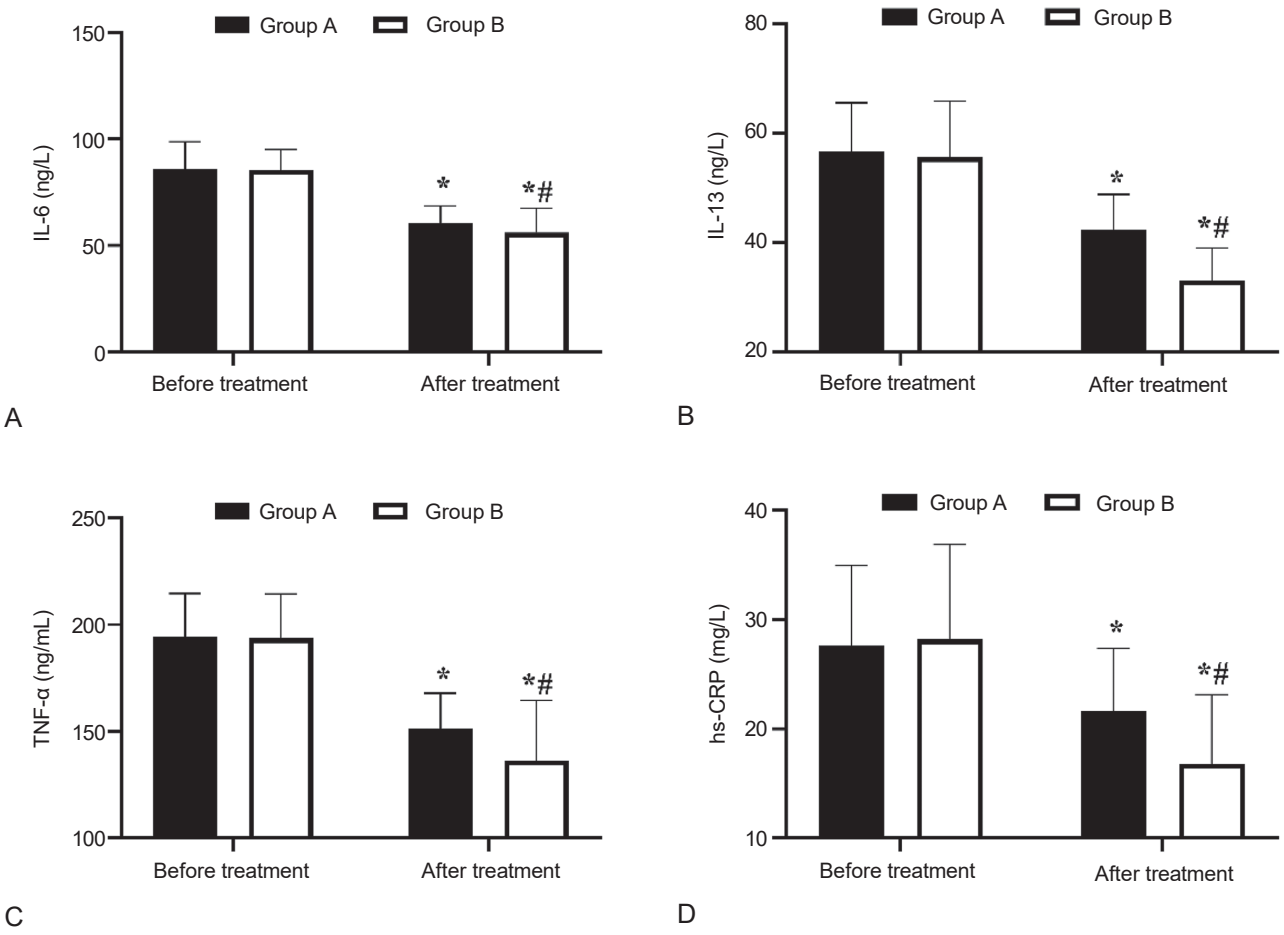

Figure 3. Comparison of inflammatory reaction before and after treatment. (A) Comparison of IL-6, (B) Comparison of IL-13, (C) Comparison of TNF-α, (D) Comparison of hs-CRP.
*indicates a statistically significant difference when comparing the pre-treatment results ($P < .05$)
#indicates a statistically significant difference from group A (< 0.05).

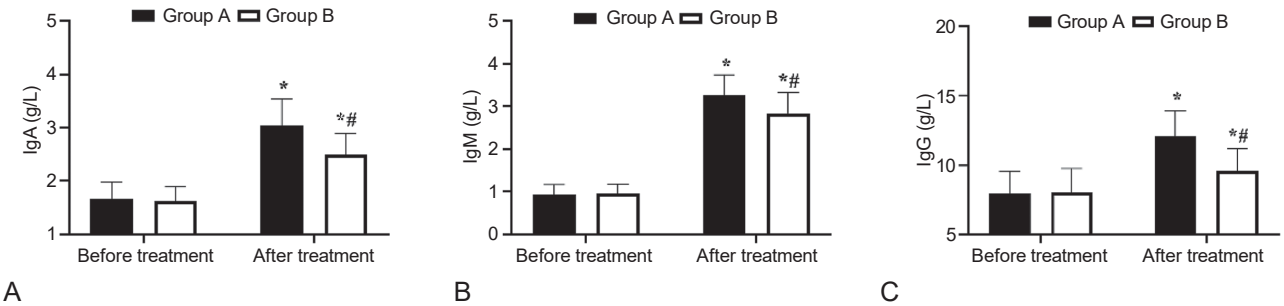

Figure 4. Comparison of immune function before and after treatment. (A) Comparison of IgA, (B) Comparison of IgM, (C) Comparison of IgG.
*indicates a statistically significant difference from before treatment ($P < .05$)
#indicates a statistically significant difference from group A (< 0.05).

similar ($P > .05$) while post-treatment IgA/M/G levels elevated in both groups, with higher IgA/M/G levels in group A versus group B after treatment ($P < .05$).

Comparison of blood lipid function before and after treatment

Blood lipid detection results before and after treatment of the two groups are shown in Figure 5. TG and TC of both groups reduced after treatment

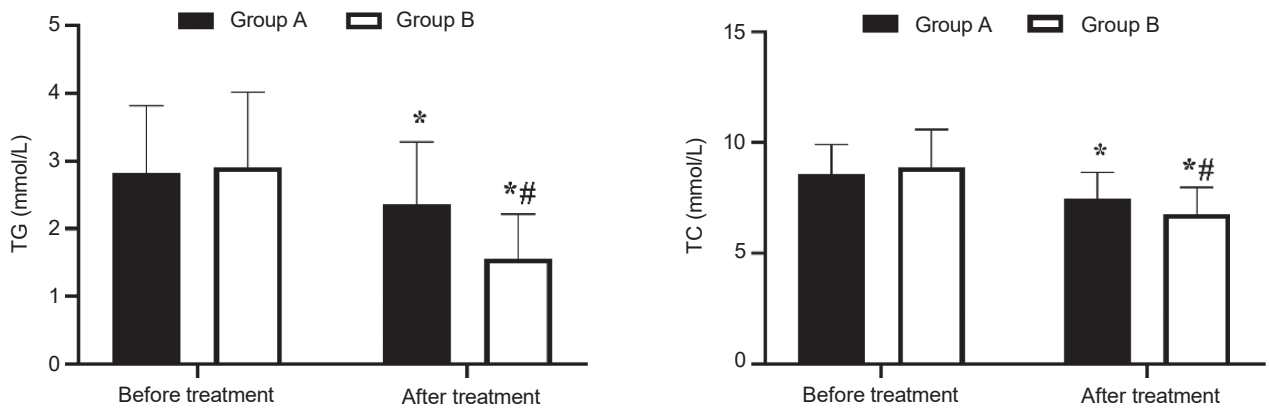

Figure 5. Comparison of blood lipid profile before and after treatment. (A) Comparison of TG, (B) Comparison of TC.
*indicates a statistically significant difference when comparing the pre-treatment results ($P < .05$)
#indicates a statistically significant difference from group A (< 0.05).

Table 3. Comparison of safety

Group	Vomiting	Headache	Rash	Loss of appetite	Diarrhea	Total incidence
Control group (n = 109)	1 (0.92)	2 (1.83)	2 (1.83)	3 (2.75)	2 (1.83)	10 (9.17)
Research group (n = 91)	2 (2.20)	1 (1.10)	2 (2.20)	4 (4.40)	3 (3.30)	12 (13.19)
χ^2						0.816
P						0.367

compared with the baseline and were even lower in group B compared with group A ($P > .05$).

Comparison of safety

The adverse reactions in both groups during treatment are presented in Table 3. The incidence rates of adverse reactions in groups A and B were 9.17% and 13.19%, respectively, showing no significant inter-group difference in the total incidence of adverse reactions ($P > .05$).

DISCUSSION

Currently, the pathogenesis of NS is not clear. Children will experience repeated episodes of NS, once the disease begins, and may face serious complications such as infection, acute kidney injury, thrombosis, and lipid metabolism disorders as the disease worsens, endangering their life and safety.[13] Parents and clinicians should therefore pay sufficient attention to NS to ensure that children receive timely and effective treatment. Although excellent application value of Pred + DIP and Pred + VAL have been reported,[14,15] the specific differences between the two treatment schemes remain unclear. This study was conducted to make a comparison of the therapeutic effects between two treatment approaches for pediatric NS, which carries significant relevance for clinical practice.

First of all, comparing clinical efficacy, renal function and safety, it can be seen that there were no statistically significant differences between the two groups, indicating that both Pred + DIP and Pred + VAL have an equal effect on NS, with high clinical application value, which is consistent with the results of previous studies.[14,15] Glucocorticoids are frequently prescribed medications for the treatment of NS, with Pred being the most extensively used.[16] Pred, as an adrenocortical hormone, has obvious pharmacological effects such as immunosuppression and anti-inflammation, which can alleviate inflammation by blocking the aggregation of leukocytes and macrophages, so as to reduce the deposition of IFs and immune complexes in glomerulus, and promote the recovery of renal function. It can also reduce capillary permeability, decrease inflammatory exudation, and relieve symptoms such as proteinuria and edema.[17] However, excessive dosage of Pred can easily cause hypercoagulability in children and increase the risk of thrombosis, so it is necessary to strictly control its dosage and use other drugs in combination to alleviate NS progression on the

premise of ensuring safety.[18]

Dipyridamole (DIP) is a coronary artery dilator and antithrombotic drug, which can exert an ideal anti-platelet aggregation effect by acting on the coagulation cascade. It can also activate adenylate cyclase, increase the level of adenosine, a platelet reaction inhibitor, inhibit the synthesis of thromboxane A2, reduce platelet activity, and improve the body's microcirculation.[19] When comparing the coagulation function between the two groups of children, we found that group A exhibited better coagulation function than group B after treatment, presumably because DIP has a more significant regulating effect on coagulation function. In addition, the level of Igs were found to be higher in group A than in group B, suggesting that Pred + DIP has a better effect on enhancing the immunity of NS children. Our assumption is that by inhibiting the uptake of adenosine and phosphodiesterase by red blood cells in glomerular capillaries, DIP can inhibit platelet function, dilate blood vessels, increase renal blood flow, improve GBM permeability, and reduce proteinuria, thereby improving children's immune function and playing a role in protecting kidneys.[20] In previous studies, DIP has also been shown to exert an excellent regulatory effect on the immune function of patients with chronic kidney disease,[21] which can support the results of this study.

In the comparison of IFs and blood lipid function, better therapeutic results were determined in group B, which suggests that Pred + VAL has a better inhibitory effect on inflammatory responses and blood lipid regulation in NS children. We believe that the reason behind it is that VAL, as an angiotensin II receptor antagonist, can selectively bind to the angiotensin II type I receptor, and by inhibiting the contraction of glomerular artery and the release of aldosterone, it can reduce the pressure in glomerular capillaries, improve renal microcirculation and accelerate the metabolism of IFs such as IL-6 and IL-13.[22] Moreover, VAL can change the structure of GBM, selectively reduce glomerular permeability, inhibit the change of glomerular filtration membrane pores, maintain the normal lipid metabolism, and avoid the risk of abnormal increase of blood lipids.[23] Consistently, Pontremoli R *et al.* put forward the same view as us when exploring the influence of VAL on patients with heart failure.[22]

However, due to the limitation of research conditions, we were unable to conduct follow-up investigations in both groups, making it impossible to evaluate the long-term prognostic effect of the two treatment modalities on children with NS. In addition, more objective indexes need to be analyzed to compare the effect of Pred + DIP versus Pred + VAL in the treatment of NS. Finally, we will further compare the effects of Pred in combination with other drugs such as Tacrolimus on NS, so as to provide a more comprehensive clinical reference.

CONCLUSION

Both Pred + DIP and Pred + VAL combination therapies have excellent effects in treating pediatric NS, which can significantly improve children's renal function and alleviate the progression of NS. Among them, Pred combined with DIP is more effective in improving the coagulation function and immune function of children, while Pred combined with VAL shows better effects on inhibiting inflammation and regulating blood lipid function. In the future clinical treatment of pediatric NS, we can use this as a reference to select the best drug therapy according to the specific situation of the child.

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Not applicable.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declare no potential conflicts of interest concerning this article's research data, authorship, and publication.

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Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used during the present study are available from the corresponding author upon reasonable request.

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