ORIGINAL RESEARCH

Efficacy and Safety of Methylprednisolone Pulse Therapy and Conventional Oral Prednisone for Pediatric Patients With Nephrotic Syndrome

Mingfang Liu, BS; Yingjian Cai, BS

ABSTRACT

Context • High-dose methylprednisolone pulse therapy and oral high-dose prednisone are two common treatments for pediatric nephrotic syndrome (NS). While both treatments have shown effectiveness for patients with pediatric NS to some extent, a clear comparison of their efficacy and safety remains elusive, posing a challenge for clinicians when devising treatment plans.

Objective • The study intended to compare the efficacy and safety of high-dose methylprednisolone pulse therapy and conventional oral high-dose prednisone for pediatric patients with NS, to provide more accurate treatment recommendations for clinicians to optimize their treatment plans, improve their QoL, and prevent complications.

Design • The research team conducted a randomized controlled trial.

Setting • The study took place at the Second Affiliated Hospital of Fujian Medical University in Quanzhou, China.

Participants • Participants were 60 patients with pediatric NS who received treatment at the hospital between November 2020 and March 2022.

Interventions • The research team randomly divided participants into two groups, each comprising 30 patients: (1) the intervention group, which received high-dose methylprednisolone pulse therapy, and (2) the conventional group, which received oral high-dose prednisone.

Outcome Measures • The research team measured: (1) clinical efficacy rates, the primary outcome measure; (2) time to symptom relief; (3) laboratory indicators, including blood urea nitrogen (BUN), serum creatinine (SCr), serum globulin (GLB), and 24-hour urine protein quantification; and (4) incidence of adverse events.

Results • Compared to the conventional group, the intervention group's: (1) clinical efficacy rate was significantly higher ($P < .05$); (2) resolution times for edema ($P < .001$) and urine protein turning negative ($P < .001$) were significantly shorter; (3) levels of BUN ($P < .001$), SCr ($P < .001$), GLB ($P < .001$), and 24-hour urine protein quantification ($P < .001$) were significantly lower; and (4) incidence of adverse reactions was significantly higher ($P < .001$).

Conclusions • High-dose methylprednisolone pulse therapy demonstrated better efficacy in treating pediatric NS patients, showing a shorter time to symptom relief, but it may also entail a higher risk of adverse reactions compared to conventional oral high-dose prednisone. Clinicians should consider the specific circumstances and needs of pediatric patients when selecting a treatment. (*Altern Ther Health Med.* 2025;31(1):430-435).

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INTRODUCTION

Nephrotic Syndrome (NS) is a prevalent kidney disorder in children, characterized by significant proteinuria, hypoalbuminemia, edema, and hyperlipidemia.[1,2] The proteinuria makes restoration of normal levels of urine protein crucial for patients. NS predominantly affects children between the ages of 2 and 6, possibly due to the association between NS and the development and maturation of children's immune systems, rendering them more susceptible to immune abnormalities.

Children with NS face serious health issues, including an increased risk of infections, thrombosis, and a reduced quality of life (QoL).[3,4] The global epidemiology of NS demonstrates variations, with higher prevalence rates observed in certain regions of Asia, Africa, and Latin America.[2] Factors such as infectious diseases, malnutrition, and environmental conditions may influence these regional disparities, contributing to the increased incidence of NS.[3] Epidemiological trends can also differ between age groups,

and various factors influence them, including genetics, environment, nutritional status, and sanitary conditions.[3]

The treatment of NS is crucial to alleviate symptoms, improve QoL, and prevent complications. High-dose methylprednisolone pulse therapy and oral high-dose prednisone are two commonly adopted treatments for NS. High-dose methylprednisolone pulse therapy involves short-term administration of high doses of methylprednisolone through injections, while oral high-dose prednisone involves long-term corticosteroid therapy taken orally.[5,6]

High-dose Methylprednisolone Pulse Therapy

Methylprednisolone pulse therapy, also known as intravenous methylprednisolone pulse therapy, is a highly effective treatment widely employed in the management of various autoimmune and inflammatory diseases. This therapeutic approach involves the rapid intravenous administration, typically completed within a few days, of high doses of the glucocorticoid hormone methylprednisolone to patients, providing potent anti-inflammatory properties capable of suppressing immune-system activity and alleviating inflammation.[7-9]

Clinicians primarily use methylprednisolone pulse therapy for the treatment of inflammatory conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and systemic sclerosis. These diseases often involve the immune system's abnormal activation and inflammatory responses, both of which methylprednisolone pulse therapy can rapidly suppress.

Typically, clinicians administer this therapy for a short duration of a few days to a few weeks rather than using it as a long-term treatment. After symptoms are under control, physicians often gradually reduce the dosage of methylprednisolone and transition patients to oral steroids or other maintenance treatments.

Oral Prednisone Therapy

On the other hand, clinicians oral commonly employ prednisone therapy as a pharmacological treatment for various inflammatory and autoimmune diseases.[10,11] This therapy involves the oral administration of a glucocorticoid medication called prednisone, which exerts potent anti-inflammatory effects by inhibiting the production of inflammatory mediators and attenuating the progression of inflammation, thereby alleviating disease symptoms.

Prednisone can also suppress immune-system activity, which is particularly important in the treatment of autoimmune diseases that involve abnormal immune-system activation.[12,13] Currently, clinicians widely use oral prednisone to treat a range of diseases, including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, allergic disorders, NS, asthma, and inflammatory bowel disease. Physicians also commonly use it for immunosuppression following organ transplantation.

However, oral prednisone therapy requires close monitoring because long-term or high-dose usage can lead to a range of side effects, including decreased bone density, hypertension, diabetes, muscle atrophy, weight gain, and skin problems.[14,15] Therefore, physicians typically monitor patients regularly for changes in weight, blood pressure, and blood-glucose levels and may recommend calcium and vitamin D supplementation to protect bone density.

Choice of Treatment

Compared to conventional oral steroids, one significant advantage of methylprednisolone pulse therapy is its rapid effectiveness. Patients often experience significant improvement in symptoms within a short period, especially in symptoms such as joint pain, skin lesions, and fatigue. However, some studies suggest that methylprednisolone pulse therapy may not be suitable for all diseases and all patients.[16,17] Methylprednisolone pulse therapy, though efficacious in certain clinical scenarios, lacks universal applicability across diverse diseases and patient populations. The nuanced response to this therapy is influenced by disease-specific nuances, patient-specific characteristics, and the inherent risks of potential side effects. Factors such as individual patient variability, adherence to disease-specific protocols, and the availability of alternative therapeutic options contribute to the complexity of its suitability.

Physicians typically decide whether to use this treatment based on the patient's specific condition and needs. Additionally, due to the potential side effects associated with high-dose steroids, physicians need to balance the disease's severity with the potential risks of treatment.

To elucidate the underlying mechanisms, Meng et al. have postulated that long-term high-dose prednisone usage can potentially enhance the glomerular filtration rate while counteracting the effects of diuretics, thereby reducing renal tubular-water reabsorption.[18]

In contrast, Nagai et al. found that methylprednisolone pulse therapy can significantly increase glomerular filtration rate compared to oral administration, leading to a more effective reduction in kidney damage.[19]

Additionally, Kamei et al. suggested that methylprednisolone pulse therapy may exert concurrent immunosuppressive effects, potentially resulting in superior anti-inflammatory effects.[20]

Current Study

While both treatments have shown effectiveness for patients with pediatric NS to some extent, a clear comparison of their efficacy and safety remains elusive, posing a challenge for clinicians when devising treatment plans.

Consequently, in recent years, considerable interest has existed in conducting comparative studies to evaluate the efficacy and safety of high-dose methylprednisolone pulse therapy and oral high-dose prednisone.[21] More in-depth research is necessary to gain a comprehensive understanding of the impact of these two treatments on pediatric NS.

The current study intended to compare the efficacy and safety of high-dose methylprednisolone pulse therapy and

conventional oral high-dose prednisone for pediatric patients with NS, to provide more accurate treatment recommendations for clinicians to optimize their treatment plans, improve their QoL, and prevent complications.

METHODS

Participants

The research team conducted a randomized controlled trial, which took place at the Second Affiliated Hospital of Fujian Medical University in Quanzhou, China. Potential participants were pediatric patients with NS who received treatment at the hospital between November 2020 and March 2022. As the attending physicians for the pediatric patients at the Second Affiliated Hospital of Fujian Medical University, we recruited participants for the study through our regular clinical interactions with patients diagnosed with Nephrotic Syndrome (NS). The recruitment process involved identifying eligible patients during their hospital visits between November 2020 and March 2022. We approached them during their routine medical appointments, explained the study details, and invited them to participate. The decision to join the study was entirely voluntary, and informed consent was obtained from the parents or guardians of the pediatric patients before their inclusion in the trial.

The study included potential participants if they: (1) were between one and 14 years of age; (2) met the clinical diagnostic criteria for NS, including typical symptoms such as significant proteinuria, hypoalbuminemia, edema, and hyperlipidemia; and (3) were physically and mentally able to comply with the study's requirements and follow its protocols.

The study excluded potential participants if they: (1) concurrently had other kidney diseases, autoimmune diseases, or other serious illnesses; (2) had clear allergies or intolerant reactions to methylprednisolone or oral prednisone; or (3) had developed relevant severe complications before the study's start, such as renal failure, severe infections, or thrombosis.

The research team based the age criterion on the disease's prevalence in different age groups, the potential impact of age on treatment response or safety, and the availability of age-specific treatment guidelines. The exclusion of patients with certain coexisting conditions was necessary to isolate the effects of the treatment under investigation and avoid potential interactions or confounding factors that could influence the study' outcomes. The inclusion of patients who are able to comply with the study's requirements and follow the protocols can help ensure the study's integrity and the collected data's reliability. Some criteria for exclusion included comorbidities, concurrent medications, or other factors that might interfere with the study objectives. The final 60 participants included in the study met all the specified criteria and provided informed consent for participation.

All patients and their guardians were informed about the study and voluntarily signed informed consent forms. Our study protocols received approval from the ethics committee at the Second Affiliated Hospital of Fujian Medical University in Quanzhou, China, ensuring that the research adhered to ethical standards and guidelines. Additionally, we prospectively registered the trial with a Clinical Trial Registry, and the study fully complied with the principles outlined in the Helsinki Declaration.

Procedures

Interventions. The research team randomly divided participants into two groups: (1) the intervention group, which received high-dose methylprednisolone pulse therapy, and (2) the conventional group, which received oral high-dose prednisone.

Based on the principles of random allocation, the research team used a computer-generated randomization sequence, commonly generated using a random number generator. This sequence assigns each participant a random chance of being allocated to one of the two treatment groups. This method ensures the fairness and impartiality of the random allocation. Using a computer-generated randomization sequence helps reduce selection bias and enhances the reliability of the study results.

Blinding. The research team used a single-blind design, where the participants are aware of the treatment they are receiving, but the researchers or investigators conducting the study are blinded to the treatment assignments. Blinding the researchers or investigators helps minimize bias that could arise from their knowledge of the treatment groups and potential expectations that they may have about the outcomes.

Outcome measures. The research team measured: (1) clinical efficacy rates, the primary outcome measure; (2) time to symptom relief; (3) laboratory indicators, including blood urea nitrogen (BUN), serum creatinine (SCr), serum globulin (GLB), and 24-hour urine protein quantification, to assess kidney function and proteinuria and to evaluate treatment response; and (4) incidence of adverse events, to evaluate the treatments' safety profiles.

Interventions

Intervention group The intervention group received a 10-30-mg dose of methylprednisolone pulse therapy, with the maximum total dose not to exceed 500 mg. The team added the methylprednisolone to 100-150 mL of glucose solution and administered it as an intravenous infusion over 1.5-2 hours. Three infusions constituted one treatment cycle.

Conventional group. The conventional group received 1.5-2 mg/kg of oral prednisone daily, not to exceed 60 mg in total. The team divided the medication into multiple doses, administering two-thirds in the morning when patients woke up and one-third in the afternoon. This treatment regimen occurred for 4 weeks.

Outcome Measures

Clinical efficacy. The research team conducted an evaluation of clinical efficacy based on the efficacy assessment criteria that Nephrology Group of the Chinese Pediatric Society, a subsidiary of the Chinese Medical Association, has

established.[22] The assessment criteria encompasses three distinct grades: effective, partial remission, and ineffective. The effective = relief of clinical symptoms accompanied by a reduction in 24-hour urine protein quantification to lower than 150 mg; the partial remission = some improvement in symptoms with a reduction of more than 50% in the 24-hour urine protein quantification; and ineffective = no improvement in the aforementioned indicators.

Time to symptom relief. The research team meticulously recorded the duration required for symptom relief in both groups, including the time taken for edema resolution and the time to urine protein turning negative.

Laboratory indicators. Postintervention, the research team collected a volume of 3ml of fasting venous blood from each participant. The team measured the levels of BUN, SCr, and GLB using a fully automated biochemical analyzer (Beckman Coulter Inc). The team determined the quantification of 24-hour urine protein levels using a colorimetric method (Merck, Germany).

Incidence of adverse events. The research team carefully documented the occurrence of adverse events for 2 weeks postintervention. These adverse events encompassed infections, mood changes, worsening of edema, and gastrointestinal symptoms. Furthermore, the team calculated the total number and proportion of adverse events in each group.

Statistical Analysis

The research team employed GraphPad Prism 8 software (GraphPad, San Diego, CA, USA) for image processing and organized and analyzed the data using SPSS 26.0 software (IBM Corp., Chicago, IL) . The team: (1) expressed continuous data as means ± standard deviations (SDs) and compared the groups using *t* tests and (2) expressed categorical data as numbers (Ns) and percentages (%s) and compared the groups using the chi-squared (χ^2) test. $P < .05$ indicated statistically significant differences.

Results

Participants

The research team included and analyzed the data of 60 participants, 30 in each group (Table 1). The intervention group included 26 males (86.67%) and four females (13.33%), ranging in age from one to 13 y, with a mean age of 5.34 ± 4.11 y. The intervention group's: (1) duration of illness ranged from 5 to 40 d, with a mean of 13.08 ± 8.24 d; (2) heights ranged from 108 to 132 cm, with a mean height of 124.25 ± 3.74 cm; and (3) body weights ranged from 25 to 31 kg, with a mean weight of 28.13 ± 2.68 kg.

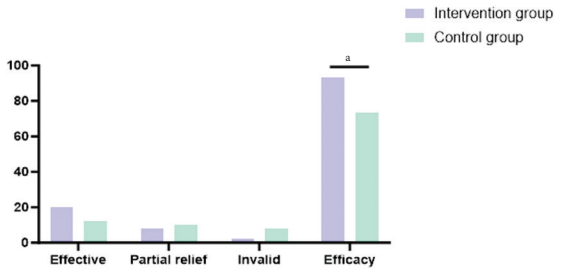
The conventional group included 28 males (93.33%) and 2 females (6.67%), ranging in age from one to 13 y, with a mean age of 5.66 ± 3.96 y. The conventional group's: (1) duration of illness ranged from 5 to 40 d, with a mean of 13.17 ± 8.16 d; (2) heights ranged from 108 to 132 cm, with a mean height of 124.84 ± 3.93 cm; and (3) body weights ranged from 25 to 31 kg, with a mean weight of 28.09 ± 2.87 kg.

No significant differences existed between the groups in any characteristic, indicating their comparability ($P > .05$).

Table 1. Participants Demographic and Clinical Characteristics at Baseline (N=60)

Characteristics		Intervention Group n=30 n (%) Mean ± SD	Conventional Group n=30 n (%) Mean ± SD	χ^2/*t* value	*P* value
Gender	Male	26 (86.67)	28 (93.33)	7.302	.562
	Female	4 (13.33)	2 (6.67)		
Age, y	Range	1-13	1-13		
	Mean	5.34 ± 4.11	5.66 ± 3.96	0.274	.831
Duration of Illness, d	Range	5-40	5-40	-	-
	Mean	13.08 ± 8.24	13.17 ± 8.16	0.218	.896
Height, cm	Range	108-132	108-132	-	-
	Mean	124.25 ± 3.74	124.84 ± 3.93	0.396	.711
Body Weight, kg	Range	25-31	25-31	-	-
	Mean	28.13 ± 2.68	28.09 ± 2.87	0.199	.904

Figure 1. Comparison of Clinical Efficacy Rate Between the Intervention and Control Groups (N=60)



[a]$P < .05$, indicating that the intervention group's clinical efficacy rate was significantly higher than that of the conventional group

Table 2. Comparison of Edema Regression Time and Time to Urine Protein Turning Negative Between the Intervention and Control Groups (N=60)

Time to Symptom Relief	Intervention Group n=30 Mean ± SD	Conventional Group n=30 Mean ± SD	*t* value	*P* value
Edema regression time, d	8.08 ± 1.12	13.31 ± 1.64	7.765	<.001
Urine protein turning negative, d	4.11 ± 0.37	8.29 ± 1.28	8.544	<.001

Note: $P < .001$, indicating that the intervention group's times for edema resolution and urine protein turning negative were significantly shorter than those of the conventional group

Clinical Efficacy Rate

Figure 1 shows that the intervention group's clinical efficacy was significantly higher than that of the conventional group ($P < .05$).

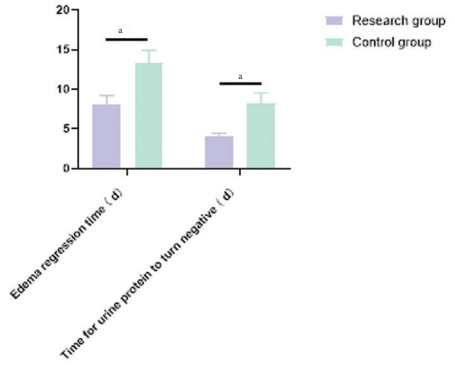
Time to Symptom Relief

The intervention group's time for edema resolution was 8.08 ± 1.12 d and time for urine protein turning negative was 4.11 ± 0.37 d (Table 2 and Figure 2). The conventional group's time for edema resolution was 13.31 ± 1.64 d and time for urine protein turning negative was 8.29 ± 1.28 d. The intervention group's times for edema resolution ($P < .001$) and urine protein turning negative ($P < .001$) were significantly shorter than those of the conventional group.

Laboratory Indicators

Postintervention, the intervention group's level (Table 3 and Figure 3): (1) of BUN was 5.23 ± 1.24 mmol/L, (2) of SCr was 70.96 ± 5.91 μmol/L, of GLB was 24.37 ± 2.24 g/L, and of 24-hour urine protein quantification was 1.37 ± 0.49 g/24h. Postintervention, the conventional group's level: (1) of BUN

Figure 2. Comparison of Edema Regression Time and Time to Urine Protein Turning Negative Between the Intervention and Control Groups (N=60)



[a]*P* < .05, indicating that the intervention group's edema regression time and time to urine protein turning negative were significantly shorter than those of the conventional group

was 8.29 ± 1.61 mmol/L, (2) of SCr was 115.62 ± 7.32 μmol/L, (3) of GLB was 36.18 ± 3.34 g/L, and (4) of 24-hour urine protein quantification was 3.74±1.03 g/24h.

The intervention group's levels of BUN (*P* < .001), SCr (*P* < .001), GLB (*P* < .001), and 24-hour urine protein quantification (*P* < .001) were all significantly lower than those of the conventional group.

Adverse Events

In the intervention group, six participants had infections (20.00%), three had mood changes (10.00%), two had increased swelling (6.67%), and two had digestive symptoms (6.67%), with a total incidence rate of 43.34% for 13 participants (Table 4). In the conventional group, two participants had infections (6.67%), one had mood changes (3.33%), one had increased swelling (3.33%), and one had digestive symptoms (3.33%), with a total incidence rate of 16.67% for five participants.

The intervention group's incidence of adverse reactions was significantly higher than that of the conventional group (*P* < .001).

DISCUSSION

In the current study, the research team conducted a comprehensive comparison of the efficacy of short-term high-dose methylprednisolone pulse therapy and conventional oral high-dose prednisone treatment in pediatric NS patients. Based on the analysis of multiple indicators of symptom improvement, the team drew some conclusions.

Pediatric patients in the intervention group demonstrated significantly faster symptom relief, indicating a clear advantage for methylprednisolone pulse therapy in alleviating NS symptoms. The reduction in edema may also be related to metabolic changes, indirectly suggesting that children in the intervention group exhibited a notable advantage in overall physiological improvement postintervention.

Furthermore, the current research team conducted a comprehensive analysis of various laboratory indicators related to renal function and demonstrated a significant improvement

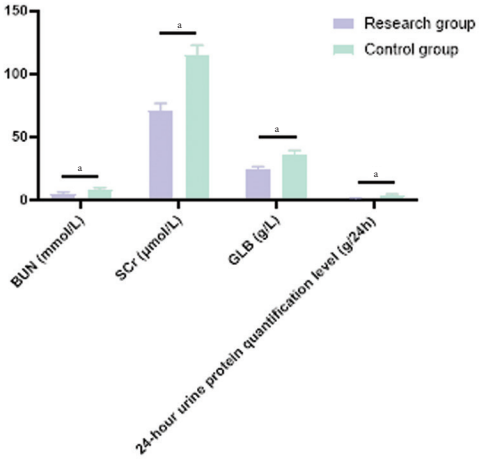
Table 3. Comparison of Levels of BUN, SCr, GLB, and 24-Hour Urine Protein Quantification Between the Intervention and Control Groups Postintervention (N=60)

Laboratory Indicators	Intervention Group n=30 Mean ± SD	Conventional Group n=30 Mean ± SD	*t* value	*P* value
BUN, mmol/L	5.23 ± 1.24	8.29 ± 1.61	8.774	<.001
SCr, μmol/L	70.96 ± 5.91	115.62 ± 7.32	37.981	<.001
GLB, g/L	24.37 ± 2.24	36.18 ± 3.34	10.764	<.001
24-hour urine protein quantification, g/24h	1.37 ± 0.49	3.74±1.03	4.773	<.001

Note: *P* < .001, indicating that the intervention group's BUN, SCr, GLB, and 24-Hour urine protein quantification were significantly lower than those of the conventional group

Abbreviations: BUN, blood urea nitrogen; GLB, serum globulin; SCr, serum creatinine

Figure 3. Comparison of Levels of BUN, SCr, GLB, and 24-Hour Urine Protein Quantification Between the Intervention and Control Groups Postintervention (N=60)



[a]*P* < .05, indicating that the intervention group's BUN, SCr, GLB, and 24-Hour urine protein quantification were significantly lower than those of the conventional group

Abbreviations: BUN, blood urea nitrogen; GLB, serum globulin; SCr, serum creatinine

Table 4. Comparison of Incidence of Adverse Events Between the Intervention and Control Groups (N=60)

Adverse Events	Intervention Group n=30 n (%)	Conventional Group n=30 n (%)	χ^2 value	*P* value
Infection	6 (20.00)	2 (6.67)		
Mood changes	3 (10.00)	1 (3.33)		
Increased swelling	2 (6.67)	1 (3.33)		
Digestive symptoms	2 (6.67)	1 (3.33)		
Overall incidence rate	13 (43.34)	5 (16.67)	11.765	<.001[a]

[a]*P* < .001, indicating that the intervention group's incidence rate was significantly lower than that of the conventional group

in renal-function parameters in the intervention group following treatment with methylprednisolone pulse therapy compared to the conventional group. Specifically, the intervention group exhibited significantly lower levels of blood urea nitrogen (BUN), serum creatinine (SCr), globulin (GLB), and 24-hour urine protein quantification, indicating a more favorable response to the methylprednisolone pulse therapy.

Although the current study indirectly suggests that prednisone usage could enhance the glomerular filtration rate while counteracting the effects of diuretics and that methylprednisolone pulse therapy could significantly increase glomerular filtration rate compared to oral administration, the research team didn't conduct a specific analysis of the body's inflammatory response, which warrants further investigation to comprehensively understand the therapeutic mechanisms at play.

In addition to evaluating the efficacy, the current research team also conducted a meticulous assessment of the safety profile of short-term high-dose methylprednisolone pulse therapy compared to oral high-dose prednisone treatment. The team recorded adverse events occurring within 2 weeks postintervention, with a particular focus on infections, gastrointestinal symptoms, mood changes, and other potential side effects. Interestingly, the team found that methylprednisolone pulse therapy may be associated with a higher incidence of adverse reactions, particularly infections, which occurred more frequently and could potentially lead to the discontinuation of treatment.

Therefore, the cautious use of methylprednisolone pulse therapy, along with close monitoring of patients, is imperative. Furthermore, clinicians should consider preventive measures to mitigate the potential occurrence of adverse reactions. For instance, infection is a common factor contributing to the premature termination of treatment, especially for pediatric patients. Hence, Deschenes et al and Hodson et al recommend administering prophylactic antibiotics during treatment and maintaining a clean patient environment as crucial steps in reducing the risk of infection by pathogenic bacteria.[23,24]

The current study highlights the potential superior efficacy of short-term high-dose methylprednisolone pulse therapy for pediatric NS patients but also underscores the differences in safety between the two treatments.

It's important to acknowledge the limitations of the current study. First, the sample size was relatively small, which may have limited the findings' generalizability. Additionally, the research team conducted the study at a single center, which may have introduced bias. The research team needs to conduct future studies with larger sample sizes and multicenter designs to further validate the results. Moreover, the current study evaluated only short-term outcomes and didn't assess the long-term effects of the two treatments. Long-term follow-up studies are necessary to determine the durability of the treatment effects and potential relapses.

Confounding factors, such as patients' underlying conditions, comorbidities, and individual response to treatment, may have influenced the results. Although the research team made efforts to randomize the patients into the intervention and conventional groups, unmeasured confounders may still have existed that could have affected the outcomes. It's important to consider these factors when interpreting the results.

Future research should also explore the optimal duration and dosing regimen for high-dose methylprednisolone pulse therapy. The current study used a specific treatment protocol, and variations in the timing and dosage may yield different outcomes. Furthermore, assessing the cost-effectiveness of the two treatments would provide valuable information for healthcare decision-making.

CONCLUSIONS

High-dose methylprednisolone pulse therapy demonstrated better efficacy in treating pediatric NS patients, showing a shorter time to symptom relief, but it may also entail a higher risk of adverse reactions compared to conventional oral high-dose prednisone. Clinicians should consider the specific circumstances and needs of pediatric patients when selecting a treatment. The current study provides clinicians with additional information regarding NS treatment, aiding in the optimization of treatment strategies, improvement of patients' QoL, and reduction of complications.

AUTHORS' DISCLOSURE STATEMENT

The authors declare that there are no relevant conflicts of interest to disclose.

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