Original Article

Children with Steroid-resistant Nephrotic Syndrome: Long-term Outcomes of Sequential Steroid Therapy

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Abstract

Objective This study aimed to investigate the long-term outcomes in children with steroid-resistant nephrotic syndrome (SRNS), who received methylprednisolone pulse therapy (MPT)-based sequential steroid therapy. In particular, we aimed to observe whether these patients had a high risk of adverse events.

Methods We conducted a retrospective study over a 5-year period. The long-term outcomes for children with SRNS receiving sequential therapy were observed.

Results Sixty-three children were diagnosed with SRNS and underwent MPT-based sequential steroid therapy. Thirty-five (55.6%) achieved complete or partial remission, 19 (30.2%) of whom were in remission even after treatment cessation at last review. The mean time to initial remission after MPT was 24.3±13.1 days. Forty-nine children (77.8%) experienced relapses, of whom 31 (49.2%) demonstrated a frequent relapsing course. Adverse effects relevant to MPT were generally mild and infrequent. Five patients (7.9%) complained of vomiting or nausea during MPT infusion; 25 (39.7%) experienced excessive weight gain and developed an obvious Cushingoid appearance; and 26 (41.3%) had poor growth associated with long-term steroid use. Twenty-eight patients (44.4%) failed to respond to MPT, of whom 21 (33.3%) achieved complete or partial remission with immunosuppressive agents.

Conclusion MPT-based sequential steroid therapy appears to be a safe and effective method for inducing rapid remission in childhood SRNS. Further clinical studies are needed to comprehensively evaluate this therapy.

Key words: Methylprednisolone; Steroid resistance; Minimal change disease; Focal segmental glomerulosclerosis; Clinical outcome

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INTRODUCTION

Nephrotic syndrome (NS) is the commonest form of glomerular disease in children. It is characterized by the tetrad of heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema. Two major histological types of NS are found to affect children: minimal change disease (MCD, 85%) and focal segmental glomerulosclerosis (FSGS, 10%)[1]. The International Study of Kidney Disease in Children (ISKDC) suggested that more than 90% of children with MCD responded to corticosteroid therapy[2-3]. Although the prognosis in children with NS is favorable,

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relapses occur in 60% to 90% of the initial responders. This can lead to increased numbers of complications, morbidity, and decreased quality of life[4]. NS may also progress to a frequent relapsing course, which is often accompanied by steroid dependence or steroid resistance in 20%-60% of patients[5]. Resistance to steroid therapy represents 10% of idiopathic nephrotic syndrome (INS). Only 1%-3% of patients with initial steroid-sensitive disease subsequently develop steroid-resistance[6]. Most importantly, steroid-responsiveness can determine the prognosis of NS in children[3,7]. It has been reported that at least 50% of patients with steroid-resistant nephrotic syndrome (SRNS) progress to end stage renal disease (ESRD) within 10 years if they do not achieve complete or partial remission[8]. These challenges in management have led to the use of long-term steroids and various immunosuppressive agents in an attempt to induce remission and reduce the frequency of relapse. Despite the myriad of immunosuppressive agents that are currently available, some cases of SRNS remain refractory to treatment. At present, the optimal treatment for SRNS in children has not been established, and a better regimen with more benefits and fewer adverse effects is required. In recent decades, methylprednisolone pulse therapy (MPT) has become known as an effective treatment for a variety of glomerular diseases resistant to oral corticosteroids and even immunosuppressive agents[9-18]. Thus, this study aimed to investigate the clinical course and long-term outcomes in children treated with MPT-based sequential steroid therapy; in particular, to observe whether these patients had a high risk of adverse events.

PATIENTS AND METHODS

Patients

A total of 323 children diagnosed with NS were treated with the standard regime of oral prednisone for 8 weeks (60 mg/m^2 daily for 4 weeks followed by 40 mg/m^2 on alternate days for 4 weeks) between July 2008 and October 2013 at the West China Second University Hospital of Sichuan University. Of these, 63 patients were diagnosed with SRNS and were enrolled in the study: 28 had experienced primary steroid resistance after receiving standard oral prednisone therapy; another 35 became steroid-resistant during the course of treatment with oral prednisone, which was defined as secondary steroid resistance. None of them had any renal dysfunction, hypertension, gross hematuria and other systemic disease or concomitant infections. In addition, they had not been treated with methylprednisolone and other immunosuppressive agents before. The mean follow-up period was 3.0±1.8 years from treatment initiation. The baseline characteristics of the children with SRNS are summarized in Table 1. In general, the two groups were comparable in terms of duration of follow-up and biochemical parameters (P>0.05); however, the mean age at diagnosis was statistically different (P<0.05).

Complete remission was defined as the resolution of edema, and <1+ of urinary protein over three consecutive days. Partial remission was defined as a reduction of 50% or greater from the presenting value of urinary protein quantitation or absolute urine protein: creatinine ratio between 200 and 2000 mg/g or urinary protein (1+~2+). No response was defined as the failure to decrease urine protein by 50% or persistent urinary protein (3+~4+). Relapse was defined as positive urinary protein results for over 2 weeks or ≥3+ protein results for three consecutive days. Frequent relapse was defined as two or more relapses within 6 months of initial response or 4 or more relapses in any 12-month period[1,3].

Table 1. Baseline Characteristics of the Children with SRNS

Characteristics	Primary Steroid Resistance *n*=28	Secondary Steroid Resistance *n*=35
Male/female	17/11	26/9
Mean age at diagnosis (year)	10.8±7.2	8.2±7.1
Duration of follow-up (year)	3.2±1.7	2.9±1.8
Patients with relapse	23 (82.1%)	26 (74.3%)
Patients in response to MPT	15 (53.6%)	20 (57.1%)
Patients with renal biopsy	13 (46.4%)	15 (42.9%)
Clinical manifestations		
Edema	28 (100%)	35 (100%)
Gross hematuria	5 (17.9%)	7 (20.0%)
Hypertension	0	0
Biochemical parameters		
Albumin (g/L)	32.5±5.7	31.8±6.1
Cholesterol (mmol/L)	5.9±1.1	6.3±0.8
Total urinary protein (g/24 h)	2.2±0.7	2.6±0.8
GFR (mL/min/1.73 m^2)	137.7±29.2	141.5±31.5

Note. MPT, methylprednisolone pulse therapy.

Treatment Strategy

After the diagnosis of SRNS was made, each patient received sequential therapy comprising:

1) Administration of intravenous methylprednisolone at a dose of 15-30 mg/kg per day (maximum dose 1000 mg) for 3 consecutive days. The drug was diluted in 100-150 mL of 0.9% saline or in 5% glucose and was administered over one hour.

2) Full dose of oral prednisone only for 2-4 weeks (daily in divided 3 doses, maximum 60 mg/d).

3) Tapering dose of oral prednisone (a single dose of 60 mg/m^2 and 10 mg daily were administered orally every other day for the first 4-8 weeks, followed by a tapering regime of 2.5-5 mg every 4-8 weeks, then 0.5-1 mg/kg maintenance for 3 months until withdrawal of the prednisone).

If relapse occurred, two further courses of MPT were administered to induce another remission. Immunosuppressive agents were administered if complete or partial remission was not achieved, or if frequent relapses resulted.

Statistical Analysis

Descriptive data were expressed as mean±standard deviation and percentages. Statistical analyses were performed with SPSS software (version 18.0, SPSS). The χ^2-test was used to compare categorical data between the two groups, and variance analysis was used to compare continuous measurements. *P*-values of less than 0.05 were considered statistically significant.

RESULTS

Effect of MPT-based Sequential Therapy on Children with SRNS

Of the 63 patients, 35 (55.6%) achieved complete or partial remission and did not require a renal biopsy. Nineteen patients (30.2%) with complete remission achieved stable remission and were treatment-free at last review. There were no significant differences in the remission rates between the two groups of patients with primary and secondary steroid-resistance (*P*=0.956). The mean time needed to achieve initial remission after MPT was 24.3±13.1 days. The remaining 28 patients (44.4%) who failed to respond to MPT underwent renal biopsies. The outcomes as of the last follow-up visit are shown in Table 2.

In this study, a total of 49 patients (77.8%) experienced relapse, 31 (49.2%) of whom demonstrated a frequent relapsing course. Eighteen cases (28.6%) suffered from relapses induced by respiratory or urinary tract infections. It is noteworthy that some relapses still responded to multiple doses of MPT, of which 9 (14.3%) maintained remission on oral corticosteroids alone.

Adverse Effects Attributable to MPT-based Sequential Therapy

In our study, the adverse effects attributed to MPT were generally mild and infrequent. In addition to transient hypertension in 3 (4.8%) patients, gastrointestinal symptoms were also observed in 5 patients (7.9%) complaining of vomiting or nausea during MPT infusion. Adverse effects of long-term steroid therapy were also observed, including obesity, hypertension, poor growth, and diabetes mellitus. Twenty-five patients (39.7%) experienced excessive weight gain and developed obvious Cushingoid appearances. Twenty-six (41.3%) suffered from poor growth, which was defined as a growth rate below the fifth percentile for children of the same age and gender. Three patients manifested glycosuria and steroid-induced hyperglycemia. No severe adverse events such as severe renal dysfunction were noted.

The Clinical Characteristics of Patients who Underwent Renal Biopsy

The 28 patients who failed to respond to MPT-based sequential therapy underwent renal biopsies, and histological findings confirmed MCD or FSGS. Twenty-one subsequently achieved complete or partial remission with immunosuppressive agents, including cyclophosphamide (CPA), cyclosporine A (CsA), tacrolimus, and mycophenolate mofetil (MMF). The clinical characteristics of these 28 patients are shown in Table 3.

Table 2. The Outcomes of Follow-up at Last Review

Outcome	Primary Steroid Resistance *n*=28	Secondary Steroid Resistance *n*=35
Complete remission	8 (28.6%)	11 (31.4%)
Partial remission	7 (25.0%)	9 (25.7%)
No response	13 (46.4%)	15 (42.9%)
Biochemical parameters		
Total urinary protein (g/24 h)	1.9±0.8	2.2±0.6
GFR (mL/min/1.73 m^2)	114.6±22.7	98.7±10.4

DISCUSSION

A proper definition for SRNS is important in establishing diagnosis and determining treatment. However, no consensus definition of SRNS currently exists. Based on the ISKDC, more than 90% of children with steroid-sensitive nephrotic syndrome (SSNS) will respond to 4 weeks of oral corticosteroid, and 100% will respond after a further 3 weeks of alternate-day therapy[3]. Steroid resistance was described by Niaudet et al.[19] as the failure to respond to 4-6 weeks of oral corticosteroids and 3 courses of MPT. Other investigators have defined SRNS as not responding to 4-8 weeks of oral corticosteroids[20-21]. In this study, we used one of the common definitions for SRNS: failure to respond to 8 weeks of oral prednisone (60 mg/m^2 daily for 4 weeks and 40 mg/m^2 alternate-day for 4 weeks)[22].

When SRNS is suspected, to avoid misdiagnosis and over-treatment, it is important to first conduct a meticulous search for concurrent infection (e.g., skin infection), drug interactions (e.g., antiepileptic drugs), inappropriate corticosteroid doses, and compliance issues that could explain the apparent resistance.

Table 3. The Clinical Characteristics of 28 Patients Who Underwent Renal Biopsy

Characteristics	MCD *n*=10	FSGS *n*=18
Male	3 (30.0%)	6 (33.3%)
Female	7 (70.0%)	12 (66.7%)
Mean age at diagnosis (year)	4.5±1.3	7.4±3.4
Primary steroid resistance	2 (20.0%)	11 (61.1%)
Secondary steroid resistance	8 (80.0%)	7 (38.9%)
Mean duration of steroid prior to immunosuppressant agents (day)	148.1±27.4	89.3±37.5
Mean days to initial remission (day)	32.3±7.1	55.3±16.4
Outcome at last review		
Complete remission	3 (30.0%)	4 (22.2%)
Partial remission	6 (60.0%)	8 (44.5%)
No response	1 (10.0%)	6 (33.3%)
Immunosuppressive agents		
Cyclophosphamide	4 (40.0%)	6 (33.3%)
Cyclosporine A	0	1 (5.6%)
Tacrolimus	4 (40.0%)	7 (38.9%)
Mycophenolate mofetil	2 (20.0%)	4 (22.2%)

Note. MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis.

When the diagnosis of SRNS has been confirmed, inductive treatment should be started as soon as possible. In general, if patients do not achieve a complete or partial remission, they are at high risk of progressing to ESRD within 10 years[8]. As such, various methods have been explored to induce remission in these patients. Although the KDIGO group has published clear guidelines on treatment strategies for SRNS in children, currently, there is no evidence-based consensus on the optimal approach for achieving initial remission and maintaining it. The therapeutic protocol may also vary across different clinical situations, external environments, and healthcare systems. Moreover, two major problems result from long-term treatment with immunosuppressive agents: chronic nephrotoxicity and a heavy financial burden for the families concerned[3]. To this end, a better regimen with more benefits and fewer adverse effects is required for childhood SRNS. In recent decades, MPT, in combination with other drugs, has appeared to be an effective therapy for children with rapidly progressive glomerulonephritis[23-24], FSGS[9,11,16] and other common glomerular diseases[10,12,15,25]. In this study, we have observed the clinical course of 63 children with SRNS who had failed to respond to 8 weeks of standard oral prednisone and subsequently received MPT-based sequential steroid therapy. The mean time to remission with MPT treatment was much shorter (24.3 days) compared to the mean time for daily prednisone therapy (95 days) and cyclophosphamide therapy (38.4 days) reported by the ISKDC for the same population[3]. This was also shorter than the mean time to remission for cyclosporine therapy (approximately 2 months) reported by other studies[26]. Our findings showed that MPT-based sequential steroid therapy was relatively rapid in inducing remission in SRNS patients, which reduces the risk of complications and morbidity related to the disease. More than half of our patients experienced a marked decrease in urinary protein, and 35 patients (55.6%) achieved a partial or complete remission at follow-up. In addition, this treatment modality has other advantages, such as the reduced need for a renal biopsy, thus avoiding its attendant risks.

Beyond the efficacy of MPT-based sequential steroid therapy, its safety in children is a more important consideration. MPT has been linked to a variety of conditions, including hyperglycemia, hypertension, and behavioral problems[18,23-24]. In this study, MPT-induced adverse effects were

infrequent. In the short term, no patient suffered life-threatening infections, and only transient hypertension and gastrointestinal symptoms were noted. However, the long-term adverse events of MPT remain unknown. Further studies that evaluate bone density, growth, and steroid-induced cataracts in children treated with MPT need to be conducted.

One of the study's limitations was that proteinuria was assessed using dipstick urinalysis. This method is imprecise. However, it is a convenient and non-invasive method for assessing therapeutic effect in children, and can be repeatedly performed without affecting their compliance to follow-up. Even so, further studies that comprehensively evaluate this form of treatment in childhood SRNS are warranted.

In conclusion, MPT-based sequential steroid therapy is a safe and effective treatment for childhood SRNS. It may also restore steroid responsiveness in some patients. We suggest that all children diagnosed with SRNS should be treated with this sequential therapy first. However, those receiving the sequential therapy should be followed-up regularly and remain under intensive surveillance. Their families should also pay attention to the increased risk of adverse events and the potential need for immunosuppressive agents.

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CONFLICT OF INTEREST

All the authors declare that there are no conflicts of interests.

AUTHORS' CONTRIBUTIONS

Prof. WANG Zheng made a major contribution to the design and revised the article critically for important intellectual content; ZHANG Hui made a substantial contribution to the acquisition of data for analysis, the interpretation of data and drafted the paper; DONG Li Qun and Guo Yan Nan analyzed the data and revised the paper.

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