Treatment of Steroid Resistant Nephrotic Syndrome

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Abstract

Background: The therapy of nephrotic syndrome with steroid resistance is still a matter of controversy. Optimal therapy for glucocorticoid-resistance MCD is not well defined. A prospective study was done on children who attained Tikrit Teaching Hospital and Beji General Hospital during the period from 1st of July 2004 to the end of July 2006.

Objective: To find out the benefit of immunosuppressive therapy (IV methylprednisolone followed by oral prednisolone therapy for one year along with six doses of monthly pulses of cyclophosphamide) for children with steroid resistant nephrotic syndrome.

Patients & Methods: Thirty-four children with steroid resistant nephrotic syndrome were treated with above regime. The remission of the disease was determined at the end of first and second year.

Results: The above protocol could induce and maintain remission in 81.8% (9/11) of children with minimal change nephrotic syndrome, 66.7% (6/9) of children with diffuse mesangial proliferation and in only 16.7% (1/6) of children with focal segmental glomerulosclerosis at the end of two years of the study. The therapy of IV methylprednisolone followed by oral prednisolone for one year plus 6 month pulse cyclophosphamide intravenously is beneficial for children with steroid resistant minimal change disease and diffuse mesangial proliferative glomerulonephritis. The therapy is not effective in focal segmental glomerulosclerosis.

Key words: Cyclophosphamide, Methyl prednisolone, Steroid resistant nephrotic Syndrome.

Introduction

Idiopathic nephrotic syndrome (INS) is the most common glomerular disease in children. Most cases of INS in children have minimal change histology and more than 90% will respond to steroids. Clinical non-responders include a heterogenous group comprising of histologically minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and diffuse mesangial proliferation (DMP) [1]. Ten percent of children with INS develop steroid resistance (SRNS) and 50% of them will progress to end stage renal disease [2]. Among non- responders, 25% or more have FSGS and half will progress to end stage renal failure, which constitutes about 10% of cases of end stage renal disease in children[1]. Small group of nephrotic children who are treated with various modalities including steroids, other immunosuppressives, immuno-modulators and antiproteinuric drugs. Cyclophosphamide and cyclosporine are drugs

Frequently used in combination with prednisolone. This study utilized a treatment protocol that combined IV methyl prednisolone, IV cyclophosphamide and oral prednisolone for the treatment of SRNS.

Patients &Methods

This prospective study was undertaken at the Department of Pediatric,

Tikrit Teaching Hospital and Beji General Hospital during the period 1st July of 2004 to the end of July of 2006 to evaluate the efficacy of a treatment regime consisting of IV methylprednisolone, IV cyclophosphamide and oral prednisolone in children with SRNS and correlate the response in relation to histology.

Nephrotic syndrome was defined as the presence of generalized edema, serum albumin < 2.5g/dl, serum cholesterol > 220mg/dl, with proteinuria more than 3+ by dipstick, protein creatinine ratio > 3.0, urine specimen or urine protein> 50mg/kg/day. All these children receive prednisolone at dose of 60mg/m²/ SA daily in single or 2 divided doses for 6 weeks followed by 40mg/m²/SA on alternate days for 6 weeks. Steroid resistance was defined in this study as a failure to achieve resolution of clinical or laboratory features of nephrotic syndrome after 6 weeks of daily prednisolone therapy [3]. All children with SRNS were included in this study. Children with documented SRNS but with clinical and laboratory pointers for secondary glomerulonephritis were excluded.

These children had renal biopsy after obtaining parental consent. All the biopsies were interpreted by the same pathologist and were classified as MCD, FSGS and DMP. Forty-two children fulfilled the criteria and had renal biopsy and the following protocol of therapy. Of 42 children, 34 completed the course of treatment and are included in the study. Criteria for remission were urine protein one plus or less with urine protein creatinine ratio < 0.3.

Therapy & monitoring

These children were admitted and IV methylprednisolone 30mg/kg/day,diluted in 5% dextrose solution, given over 3 hours daily for 5 consecutive days followed by oral prednisolone 1mg/kg on alternate days for one year. IV cyclophosphamide was given on the 6th day at the

dose of 750mg/m²/SA, diluted in 5% dextrose, as an infusion over 3 hours. The dose of IV cyclophosphamide was repeated at monthly intervals for 5 more doses. Blood pressure and side effects of cyclophosphamide, including vomiting, leucopenia, alopecia and hemorrhagic cystitis (administered drug in the morning and encouraging fluids if no edema) were noted. These children were follow-up at frequent intervals with monitoring of their urine protein, blood pressure, blood counts, renal functions and infections. The time to onset of remission and maintenance of remission were noted in every child on follow-up. The end point of the study was at the end of one year of completion of oral steroids and subsequently at the end of second year without repetition of the protocol. Remission status was confirmed with the defined criteria. Serum creatinine level was considered as an indicator of renal function. Renal parameters like serum creatinine, serum albumin, serum cholesterol and calculated creatinine clearance were noted at the beginning and end of first year and second year. During the second year, patients in remission received no treatment. Those who relapse were treated with prednisolone at a dose of 60mg/m²/day for 2 weeks followed by 4 weeks of 40mg/m² on alternate days. One child with FSGS was maintained on low dose prednisolone at a dose of 0.5 mg /kg on alternate days for 8 months during second year as child was showing non nephrotic proteinuria at the end of one year. No other drugs like azathioprine, cyclosporine A or mycophenolate were used during two years.

Result:

Of 34 children, 13 (38.2%) were girls and 21 (61.8) were boys. Seventeen (50%) patients were in the age group of 2-5 years and 8 (23.5%) were above 5 years of age. Primary hypertension was present in 23.5% of the children and 20.6% had hematuria. Renal failure was noted in 11.8% of the children, with serum creatinine ranging from 1.3mg/dl to 1.6mg/dl. Twelve patients (35.5%) each had either MCD or DMP, 10 (29.4%) had FSGS. After methylprednisolone and first dose of IV cyclophosphamide, remission not occur after one month.

While remission occur in 86.7% by 4th dose of IV cyclophosphamide and occur in one patient by fifth and sixth doses of IV cyclophosphamide respectively. At the end of one year, 83.3% with MCD, 41.7% with DMP and none with FSGS were in remission. By the end of second year 81.8% of MCD and 50% of DMP remission occur. Of seven patients with FSGS followed up to 2 years, one showed remission with low dose alternate day oral prednisolone therapy during the second year. Remission status at the end of two years from the time of starting the therapy is given in **Table 1**. In FSGS out of 6 children followed up to 2 years, 5 (83.3%) continued to be proteinuric. Patients with MCD did not show a change in the remission status. In DMP one more child showed remission with oral steroids increasing the percentage of remission to 66.7%. Remission rates at two years were 16.7% in FSGS, 81.8% in MCD and 66.7% in DMP (**Fig. 1).** It should be noted that the number of children who were lost to follow-up skews findings particularly in FSGS. Side effects like leucopenia, hypertension, dysuria and hemorrhagic cystitis were not seen in any patients. Following IV

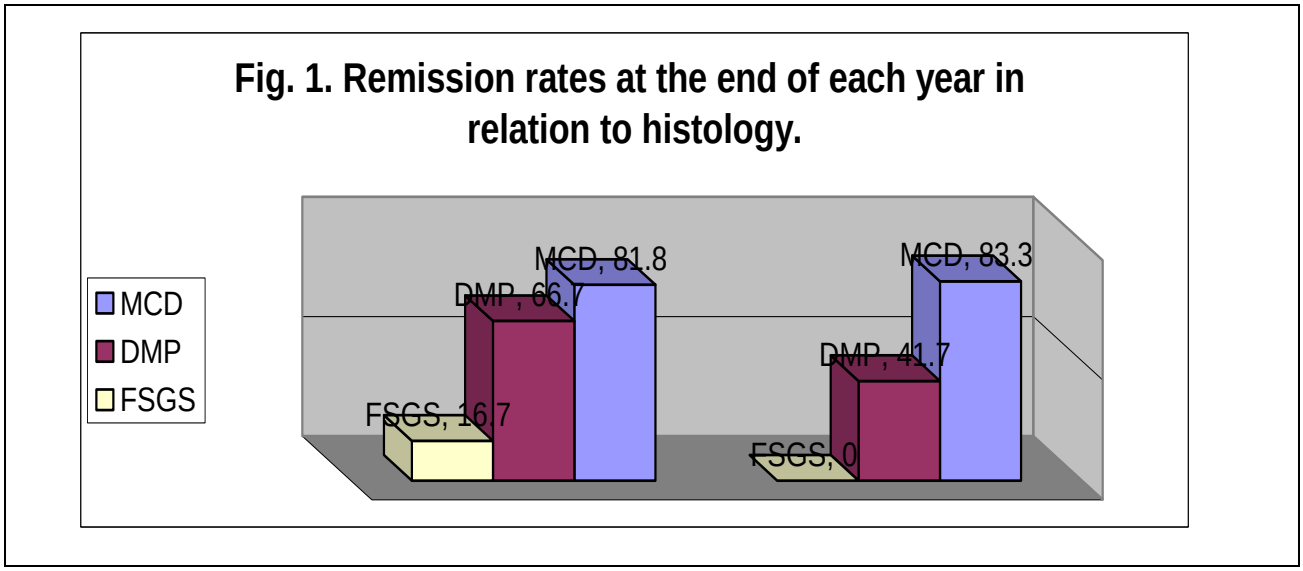
Cyclophosphamide, no deterioration of renal function occur. Infectious episodes during the study and follow-up, were 22 of them 5 had very serious infection.

Three had septicemia, two had pneumonia and cellulitis and one child had urinary tract infection. Other minor infections included upper respiratory tract infection and minor skin infection. Except two children, all of them had normal hair growth and even the two children who had episodes of hair falling improve with improvement of serum albumin levels. Those children with renal failure at the beginning of the study showed a reduction in the renal failure status at the end of one year with only one child showing persistent renal failure with serum creatinine ranging from 1.2 to 1.4 mg/dl on follow-up for 2 years. No significant difference were noted with serum creatinine and calculated creatinine clearance in other children. There was satisfactory decrease in mean serum levels of cholesterol from 362 ±122 mg/dl to 264±96 mg/dl. Similar response was noted with serum albumin following treatment with mean level increasing from 1.8 ± 0.6 g/dl to 2.8 ±0.7 g/dl.

Table 1: Remission Status at the End of Second Year Based on Histology.

Histology (N)	Remission	No remission Or relapse	Lost to follow-up or death
FSGS (10)	1 (16.7%)	5 (83.3%)	4
MCD (12)	9 (81.8%)	2 (18.2%)	1
DMP (12)	6 (66.7%)	3 (33.3%)	3

FSGS: Focal segmental glomerulosclerosis, MCD: Minimal change disease, DMP: Diffuse mesangial proliferation.



Discussion

The need for many therapeutic trials for SRNS indicates that final word has not been said [3-12]. Hence, we conducted this study with the regime mentioned.

Fifty percent were in the age group of 2-5 years and the peak age incidence of both MCNS and FSGS is in the preschool children. According to ISKDC, 80% are less than 6 years old at presentation with median age at diagnosis being 2.5 years for MCD and 6.8 years for FSGS [13]. However in our study majority of the children were less than 5 years (76.5%). No particular age predisposition in relation to histology could be made. There was preponderance of male children with male to female ratio 1.6: 1. This gender preponderance of male has been discussed in previous studies on SRNS. Hypertension (23.5%), hematuria (20.6%) and renal failure (11.8%) were more common than that described for primary nephrotic syndrome [14]. On histology, 35.3% each had MCD or DMP followed by FSGS in 29.4% of children. The remission rate at the end of two years was 16.7% in FSGS, 81.8% in MCD and 66.7% in DMP, with the number of children who were lost for follow-up skews findings particularly in FSGS. This is in contrast to the claims made in various studies particularly in FSGS where complete remission was documented in 70% by Rennet, et al, 40% by Adhikari, et al, and 65% by Gulati, et al, on varying periods of follow-up [7,15,16,17]. In our series it was 16.7% in FSGS, which may be due to various reasons; one child had died before first year of life due to septicemia and 3 more children were lost for follow-up by second year. Contrastingly, in MCD,

83.3% of the children were in remission at the end of one year and this status continued with 81.8% at the end of second year and is comparable to 100% complete remission reported earlier.

This is contrary to the study done by Bajpai, et al, where the remission rates were lower in the MCD and higher in the FSGS group following IV cyclophosphamide and oral steroids [18]. In this study, 16 out of 26 (61.5%) had sustained remission at the end of second year of follow-up compared to 7 out of 24 (29.2%) after a follow-up of 1.8 ± 0.4 years by Bajpai, et al. [18].

Conclusion:

* There was no isolated drug is effective 100% and the drugs used affected by their availability and compliance of patients.
*Pulse therapy with IV methylprednisolone followed by oral prednisolone, and IV cyclophosphamide has not been beneficial in FSGS but is promising in patients with MCD and DMP.

Recommendation:

* Immunosuppressive therapy plays a significant role in inducing long-term remission in SRNS and histopathology in SRNS is important to prognosticate.

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