HK J Paediatr (new series) 2009;**14**:103-107

Long Versus Standard Course Corticosteroid Therapy for Nephrotic Syndrome in Children

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Abstract Steroid sensitive nephrotic syndrome (SSNS) is a common disease in childhood. Although most children respond to corticosteroid, relapse is a common problem. We aim to compare the effect of 2-month steroid treatment (standard course) according to International Study of Kidney Disease of Children (ISKDC) versus 6-month treatment (long course) on the clinical course of SSNS in a 1.5-year follow up in our centre. Medical records of patients seen from 1997-2006 were reviewed. A total of 46 patients were included in the study (standard course group=22, long course group=24). Patients treated with long course steroid had significantly lower relapse rate (33% versus 75%, p= 0.026) and higher percentage of sustained remission (p=0.0046) than that of standard course. None of our patients had significant growth retardation or hypertension. Therefore, 6-month corticosteroid may be preferable to the standard course for the initial treatment of SSNS in children.

Key words Corticosteroids; Relapses; Steroid sensitive nephrotic syndrome

Introduction

Nephrotic syndrome (NS) is an important chronic renal disease in childhood.[1] Minimal change disease is the most commonly found histology in renal biopsy.[2] Although most patients respond to corticosteroids, a majority of patients relapse.[2-4] It has been suggested that children who present with a young age at onset or male sex were more likely to have relapses.[5,6] Some patients may require prolonged courses of steroids and later cytotoxic agents to maintain remission.[7] The optimal dose and duration of steroid therapy for the treatment of NS in children have been investigated.[1,8,9] Meta-analysis has concluded that children in their first episode of nephrotic syndrome should be treated for at least three months, with increased benefit up to seven months post treatment compared with 2-month therapy.[1] We aimed to compare the effect of 2-month steroid treatment (standard course) according to International Study of Kidney Disease of Children (ISKDC) versus 6-month treatment (long course) on the clinical course of steroid sensitive nephrotic syndrome (SSNS) in our centre.[10]

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Received January 12, 2009

Subjects and Methods

Patient Data

The data was collected retrospectively from medical records of children presented with first episode of SSNS seen in paediatric nephrology centre, Princess Margaret Hospital, Hong Kong from January 1997 till July 2006. All records were reviewed for 1.5 years from the completion of steroid treatment. All patients were treated with steroid alone. We have excluded patients who were previously treated, those who suffered from steroid resistant disease (defined as failure to achieve remission with 4-week course

of 60 mg/m^2/day prednisolone), those who were treated with cytotoxic agents and those who defaulted follow ups in the study period.

Outcome Measures

Percentage of patients with relapses, cumulative rate of sustained remission, total number of relapses, and the height standard deviation score (height SDS) before and after treatment were compared.

Protocol of Prednisolone Treatment for SSNS

Our department employed the ISKDC 2-month standard prednisolone regimen from year 1997 to 2001.[10] (Prednisolone 60 mg/m^2/day for 4 weeks then 40 mg/m^2/ alternate day for 4 weeks) We have subsequently changed our protocol to a 6-month regimen from 2002 till now. (Prednisolone 60 mg/m^2/day for 4 weeks, then 40 mg/m^2/ alternate day for 4 weeks and slowly tapering off by 10 mg/m^2/ alternate day in four months, total course of 6 months) (Figure 1). Our patients were therefore conveniently divided into standard course and long course group.

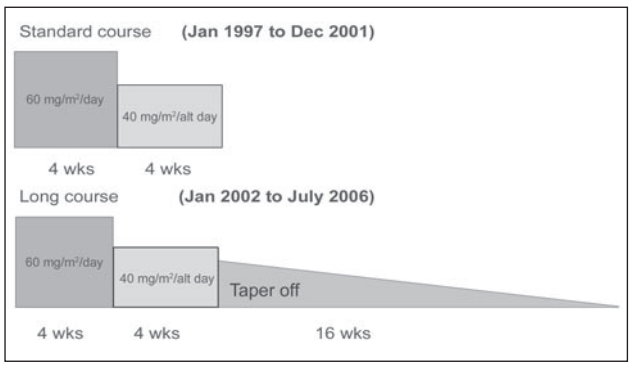

Figure 1 Standard and long course corticosteroid for treatment of SSNS in children.

Definitions of Remission, Relapse and Steroid Dependence

Remission was defined as the disappearance of proteinuria for at least three consecutive days[1] (urinary excretion of protein <4 mg/m^2/hr or negative to trace from urine dipstick test). Relapse was defined as a reappearance of proteinuria of 2+ of more continued for 3 consecutive days[1] (urinary excretion of protein >=40 mg/m^2/hr). Relapse was treated with the daily prednisolone does of 60 mg/m^2/ day until urine protein became negative for three consecutive days, followed by 40 mg/m^2/alternate day for 4 weeks.

Statistical Analysis

Results were expressed as mean ± standard deviation (SD). Comparisons between standard and long course groups were made using *unpaired t tests* for means of quantitative variables, and *Chi-squared* or *Fisher's exact test* for the frequencies of qualitative variables. The cumulative percentage of patients with sustained remission was demonstrated by *Kaplan-Meier* curve. The height SDS was compared at the beginning and end of treatment with local growth reference.[11] All statistical analyses were accomplished using the Statistical Package for the Social Sciences version 12.0 (SPSS 12.0). Statistical significance was considered at the value of $p<0.05$.

Results

A total of 46 patients were included in our study. Their age of presentation ranged from 2.1 to 15.1 years. There were 32 boys (68.1%) and 14 girls (29.8%). The standard course group consisted of 22 patients (mean age of 5.12, Male to female ratio=17:5). Long course group consisted of 24 patients (mean age of 6.29, male to female ratio=15:9). There was no significant difference between the two groups of patients in terms of number, age of disease onset, sex ratio, and serum parameters (Table 1).

Patients treated with standard course steroid had significantly higher relapse rate at the end of the study (75% vs 33%, p=0.026). Only six patients in the standard course group never relapsed while fifteen patients never relapsed in the long course group. The percentage of patients who remained in sustained remission is significantly higher in the long course group than the standard course group (log rank value=8.03, p=0.0046) (Figure 1). Although the number of relapses during the follow up period (per patient per year) did not differ significantly between the two groups, patients from the standard course group were more likely to relapse more than once in the study period (p=0.017). None of our patients was on anti-hypertensive agents. No significant difference was found in the mean height SDS before and after steroid treatment when comparison was made within the same treatment group, and between the two groups (Tables 2 & 3).

The results from the two groups were integrated in the last part of the study. We aimed to look at the impact on the course of disease by the absence of relapse within the first 6 months post-treatment (Table 3). In our study, 20 patients (43% of the total study population) had relapse

Table 1 Clinical and laboratory characteristics of patients

	Standard course	Long course	Significance
No of patients (n)	22	24	Not significant
M/F	17/5	15/9	Not significant
Age	5.12±3.18	6.92 ± 5.57	Not significant
Serum Albumin (g/dl)	15.5±2.41	15.6± 4.01	Not significant
Serum creatinine (umol/L)	42.5±12.5	47.1±18	Not significant

Table 2 Data comparison between the standard and long course groups

	Standard course (N=22)	Long course (N=24)	Significance
No. of patients without relapse	6	15	**P=0.026**
No. of patients with relapses	16 (75%)	9 (33%)	**P=0.026**
No. of patients with >1 relapses	15	5	**P=0.017**
Height SDS score			
Before steroid treatment	1.1±3.5	0.5±1.1	Not significant
After steroid treatment	0.8±1.54	0.27±1.04	

Table 3 Influence of the absence of relapses on further course of SSNS

	No. and % of patients who relapse in the following post treatment periods			
Course of disease	First 6m after treatment		Next 6 to 12m after treatment	
	No.	%	No.	%
Children with relapse(s)	20/46	**43%**	13/20	**65%**
Children without relapse	26/46	**56%**	7/26	**27%**

within the first 6 months after completing the initial therapy. Thirteen of these 20 children (65% of those who relapsed in the first 6 months) had further relapse in the next 6-12 months. On the other hand, for the remaining 26 patients who did not relapse (57% of the total study population), only seven relapsed in the next 6-12 months (27% of those who did not relapse in the first 6 months) (Odds ratio 5.04, 95% confidence interval 1.42-17.8). Therefore, patients with relapse within the first six months after initial therapy were more likely to relapse in the next 6-12 months.

Discussion

Corticosteroid has been the drug of choice for treatment of SSNS in children.[1,8,12] Although more than 90% of children are responsive to steroid therapy, over 70% of patients with SSNS subsequently relapse.[1,12] In our cohort, up to 75% of patients in the standard course group relapsed. This result could be related to the limitations of this study and will be discussed later. Nevertheless, we were able to demonstrate that nephrotic children who were treated with long course steroid therapy had fewer relapses, and were more likely to remain in remission (Figure 2). Our findings are consistent with the previous work showing an inverse relation between the risk of relapse and the duration of corticosteroids therapy.[1,3,13-17] Therefore, many centres now recommend steroid treatment of at least 12 weeks for better patient outcome.[3,16-17] The optimal protocol to treat SSNS, and more so relapsing SSNS, is yet to be defined and studies are underway.[5,9] Hopefully, more detailed approach will be available in the near future.

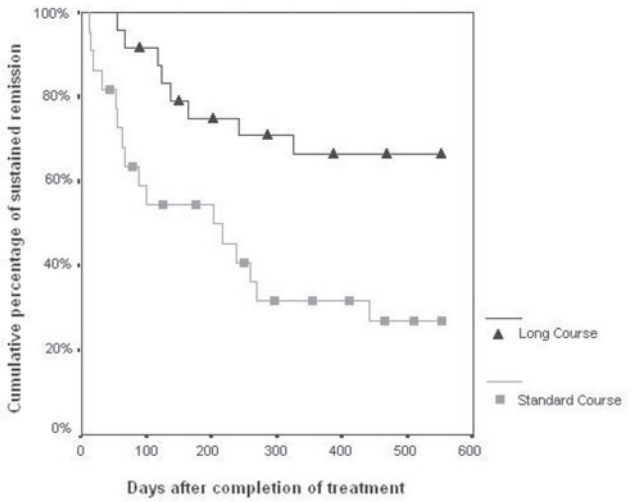

Figure 2 Cumulative rate of children with sustained remission of long course (black line with triangle) vs standard course (grey line with square) steroid therapy.

Steroid is not without side effects. Obesity, striae, hirsutism, osteoporosis, psychiatric disturbances, and cataract are some of the common side effects.[13] The occurrence of steroidal side-effects was only partly addressed by this study because of its retrospective nature and incomplete documentation of data. We were only able to conclude that none of our patients in this cohort was on anti-hypertensive agents, and there was no significant difference between the pre and post steroid height SDS in each study group. The degree of steroid toxicity was shown to be proportional to the dose and duration of treatment.[7,18] Hodson et al commented that six-month therapy results in less relapse without increase in adverse effects in comparison to three-month therapy.[1,18] This view was supported by various authors.[8,13] It was opined that the side effects of steroids were reversible or mild if further treatment courses were rarely required subsequently.[13] After all, physicians must judge clinically and take the balance between better relapse control and steroid toxicities.

According to APN (Arbeitsgemeinschaft fur Padiatrische Nephrologie) report in 1988, the percentage of patients with frequent relapses in the first 6 months after cessation of steroid was higher with the standard course regimen (61%) than the long course regimen (31%).[16] Similar results were shown by Ueda et al and Ehrich & Brodehl in 1988 and 1992 respectively.[7,13] Our results and theirs suggested that children with relapse early in their illness continue to have a stronger tendency to relapse throughout their illness than those who did not. It remains, however, unclear if the beneficial effect of long course is solely related to the extended duration of immunosuppression.[13] Apart from early relapse after disease onset, the duration of remission period immediately before the most recent relapse was also described to be a risk factor for prediction of relapse.[17] Patients having both risk factors may be more likely to have relapsing disease, and hence earlier treatment with immunosuppressants could be considered in selected cases.[17]

One interesting observation was the great difference between the survival curves of the two groups. This may be an over presentation and deserves explanation. In terms of patients' clinical characteristics, although their serum albumin and creatinine levels showed no significant difference between the two groups, there could still be difference in their disease severity to start with. Limited by the retrospective nature of the study, laboratory parameters such as initial cholesterol level, 24 hour urine protein level, and creatinine clearance were not well documented and therefore no valid statistical analysis could be carried out to compare the two groups of patients. In terms of management practice, despite the presence of a standard steroid protocol in the department, different physicians may have their own preference on dosage adjustments. This contributed to the difference in total cumulative dose of steroids given to patients and hence their outcomes. The failure to document patient's compliance to treatment was another limitation of the study. Therefore, despite the significant findings, we believe that the two groups of patients may represent patients with dissimilar severity of nephrotic syndrome which took cautions to compare.

There are certain limitations to our study. As mentioned, being a retrospective study, data collection was incomplete in some areas. Second, the sample size is relatively small and patient recruitment was not randomised. Moreover, all the data was obtained from a single centre and hence more prone to bias. Patients were recruited from different periods of time, and it was not known if there was change in the histopathological heterogeneity of children with nephrotic syndrome over the years which may contribute to the difference in response to steroid therapy. Last but not least, the follow up period was short and the duration of sustained remission after steroid treatment could not be accurately projected. All these factors may result in bias and should be taken into consideration.

In conclusion, with the limitations and constraints in mind, the 6-month corticosteroid therapy is more likely to provide better rate of sustained remission when compared

to the standard ISKDC regimen as the initial management of first episode SSNS. This pilot study sets the scene for future studies to further examine the implication of duration of corticosteroids on the clinical course of nephrotic syndrome in children.

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