ORIGINAL ARTICLE

OUTCOME OF SHORT AND LONG DURATION STEROID THERAPY IN CHILDHOOD NEPHROTIC SYNDROME IN TERMS OF FREQUENCY OF RELAPSE RATE

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Background: Nephrotic syndrome is a clinical syndrome defined by massive proteinuria (greater than 40 mg/m2/hour) responsible for hypoalbuminemia (less than 30 g/L) resulting in oedema and hyperlipidaemia. Objective of the study was to compare the frequency of relapse rate with short and long duration steroid therapy in Nephrotic syndrome. It was a Quasi-experimental control group design, conducted at the Department of Paediatric Nephrology, The Children's Hospital and Institute of Child Health, Lahore. Duration of study: One year. **Method:** The data of 150 patients with steroid sensitive nephrotic syndrome was included with clinical presentation and diagnostic investigations. The children were randomly divided into long and short duration steroid treatment groups. Outcome was determined in terms of relapse rate after achieving remission with both treatment strategies. Independent sample t test was applied to compare the outcome in both groups with $p \leq 0.05$ considered as significant. Data was stratified for all the effect modifiers like age and gender and post-stratification chi square test was applied to see the effect on the outcome, taking $p \leq 0.05$ as significant. **Results:** The relapse rate of the disease was 0.8±0.72 per year in short-duration group and 1.28±0.61 per year in subjects receiving long-duration steroids, and difference between the two groups was found to be statistically significant ($p<0.001$). The relapse rate was less in the short duration therapy group as compared to the long duration therapy 62.7% (n=47) patients in group A had one or more relapses of the disease within one year of follow up in contrast to 94.7% (n=71) children in group B ($p<0.001$). **Conclusion:** Patients receiving short duration steroid therapy showed a lower relapse rate as compared to those who were administered long term steroids.

Keywords: Steroid sensitive; Nephrotic syndrome; Relapse; Steroids

Citation: Jamshaid AA, Akhtar N, Adnan A, Perveen S, Chaudhry A, Fatima T. Outcome of short and long duration steroid therapy in childhood nephrotic syndrome in terms of frequency of relapse rate. J Ayub Med Coll Abbottabad 2022;34(2):300–303.

INTRODUCTION

Nephrotic syndrome (NS) is a clinical syndrome defined by massive proteinuria (greater than 40 mg/m2/hour) responsible for hypoalbuminemia (less than 30 g/L) resulting in oedema and hyperlipidaemia. It is caused by increased permeability of the glomerular capillary wall to macromolecules like albumin. It may be primary with disease specific to the kidneys or it may occur secondary to congenital infections, diabetes, systemic lupus erythematosus, neoplasia or certain drugs.[1,2]

Nephrotic syndrome in childhood is usually idiopathic with absence of any systemic disease. Light microscopy of renal biopsy in Minimal change disease (77–85%) shows no change while effacement of the foot processes can be seen on electron microscopy and immunofluorescent staining for immune complexes is negative. Focal segmental glomerulosclerosis accounts for 10–15% of idiopathic Nephrotic syndrome with histological evidence of scarring or sclerosis of segments of glomeruli.[1,4]

The worldwide prevalence of Nephrotic syndrome is about 16 cases per 100,000 children. More than 90 percent patients with Minimal change disease respond to steroid therapy and have a favourable long-term renal outcome.[1,5]

The underlying pathology involving the glomerular filtration barrier in Nephrotic syndrome has been well studied in literature. Although steroids have long been used in the treatment of Nephrotic syndrome there still exists a worldwide controversy regarding the duration of treatment with steroids. This is of significance considering the side effect profile of steroids. Longer durations of steroid therapy are associated with greater side effects in children.[3,4] That being said multiple studies have shown a beneficial effect of long-term steroids when it comes to sustaining remission and

preventing relapses. A study by Thalgahagoda *et al*. has shown a relapse rate of 31.50% in Nephrotic syndrome with short term therapy as compared to 12.40% with steroids given for long duration.[6]

Although previous data reports low relapse rates with long-term steroid regimens, there is still no clear consensus about treatment duration.[7] Our study compared the frequency of relapse rate with short and long duration steroid therapy in children with Nephrotic syndrome. The rationale of the study is to reach a consensus regarding a standard regimen of steroid therapy for managing our Nephrotic population whilst limiting the side effects of this therapy.

MATERIAL AND METHODS

This Quasi-experimental study was conducted in the Department of Paediatric Nephrology at the Children's Hospital Lahore. Data was collected for one year from 1st November 2019 till 31st October 2020 after approval from the hospital ethical review committee. Children aged 2–12 years of either gender meeting the operational definition of Nephrotic syndrome, i.e., oedema; protein urea (greater than 40 mg/m2/hour) and hypoalbuminemia (less than 30 g/L) were included in the study. These children were allocated into short- and long-term therapy groups, randomly. Only patients presenting with 1st episode of Nephrotic Syndrome and without any other systemic illnesses were included in the study.

To obtain the calculated sample size, study data was collected for one year. One hundred and fifty children were selected and informed written consent was taken from parents. Demographic information of patients (age, gender, weight) was noted on the designed proforma. Clinical presentation and diagnostic investigations (CBC, serum chemistry for RFTs, Albumin, Cholesterol, and Urinalysis) were also documented.

Short Duration therapy (Group-A): 75 subjects received body weight regimen of steroids at 2 mg/kg/day for 4 weeks (maximum dose: 60mg) followed by 1.5 mg/kg/day on alternate days for 8 weeks (maximum dose: 40mg) and then discontinued without tapering. (12 weeks).

Long duration therapy (Group-B): 75 participants received body weight regimen of steroids at 2 mg/kg/day for 4 weeks (maximum dose: 60mg), 1.5 mg/kg/day on alternate days for the next 4 weeks followed by 5 mg decrements every 2 weeks and then discontinued gradually. (16–24 weeks).

Remission was defined as absence of oedema with urine protein ≤1+on dipstick, urinary protein/creatinine ratio ≤20 mg/mmol or ≤4 mg/m2/hour for three consecutive days. Relapse was described as presence of oedema with urine protein ≥3+ on dipstick for three consecutive days. Patients with poor compliance, Steroid-resistant nephrotic syndrome (failure to achieve remission following four weeks or more of prednisone at 2 mg/kg/day), Congenital Nephrotic Syndrome and Secondary Nephrotic Syndrome were excluded from the study.

Each patient was followed up for one year and duration of remission as well as number of relapses were noted as per operational definition. Adherence to medication and proteinurea record was ensured by diaries maintained by parents who were taught to carry out dipstick test on a freshly voided morning urine sample. Children were followed up initially after 2 weeks of starting steroids, then at 4 weekly intervals thereafter for a period of 6 months. Number of relapses occurring during follow up were recorded and grouped as nil, one or more.

Data was analyzed with statistical analysis program (SPSS 20). Frequency and percentage were computed for qualitative variables like gender and relapse rate. Mean±SD was presented for quantitative variables like age. Independent sample t test was applied to compare the outcome in both groups with $p \leq 0.05$ considered as significant. Data was stratified for all the effect modifiers like age and gender and post-stratification chi square or Fisher's exact test was applied to see the effect on the outcome, taking $p \leq 0.05$ as significant.

RESULTS

Out of 150, 75 patients were allocated to Group A for short duration therapy while the remaining subjects received long duration therapy with steroids (Group-B). Details of the demographic data are shown in Table-1 while Table-2 compares duration of remission and number of relapses in the two groups.

Our trial showed that the relapse rate of the disease was 0.8±0.72 per year in short-duration group (Group-A) and 1.28±0.61 per year in Group-B, showing statistical significance ($p<0.001$).

Furthermore, number of patients with no relapse of the disease during the follow-up period was much more in Group-A as compared to Group-B with longer duration of remission achieved in the former group.

Data was stratified for age and gender, to see the effect of these on the outcome variables. Out of the 28 patients in short duration group with no relapse of disease in a year, the ratio of males and females was equal (1:1); which was also seen in Group-B, showing that gender had no effect on the outcome variable.

Table-1: Baseline characteristics.

Characteristics		Short duration therapy (A) n=75	Long duration therapy (B) n=75	*p*-value
Age (years)		4.45±1.68	4.2±1.68	
2 to ≤5 years		60 (80%)	60 (80%)	>0.999
>5 to 10 years		15 (20%)	15 (20%)	
Gender	Male	35 (46.7%)	23 (30.7%)	0.044
	Female	40 (53.3%)	52 (69.3%)	

Table-2: Comparison of duration of remission and number of relapses.

Variables		Short duration therapy (A) No. (%)	Long duration therapy (B) No. (%)	*p*-value
Duration of Remission:		3.88±2.15 months	2.69±1.26 months	<0.001
Relapse rate	No relapse	28 (37.3%)	4 (5.3%)	<0.001
	One in a year	34 (45.3%)	48 (64%)	
	Two in a year	13 (17.3%)	21 (28%)	
	Three in a year	0 (0%)	2 (2.7%)	
Relapse of the Disease: (per year)		0.80±0.72	1.28±0.61	<0.001
Yes (1 or more)		47 (62.7%)	71 (94.7%)	<0.001

Table-3: Stratification of main Outcome Variable with age.

Age group	Relapse rate per year	Treatment group		
		Short duration (12 WKS) - A	long duration (16–24 WKS) - B	*p*-value
2-5 years	No relapse	23	4	< 0.001
	1 or more	37	56	
>5-10 years	No relapse	5	0	0.042
	1 or more	10	15	

DISCUSSION

Long-term use of oral steroids given beyond 3 months as treatment in Nephrotic syndrome has been described in various previous studies. Although prolonged initial therapy with prednisolone has been seen to reduce the frequency of relapses, 50% children follow a frequently relapsing course.[8]

Our study compared the short and long treatment regimens given for 12 weeks and 16–24 weeks respectively. 37.3% children treated with short duration of steroids had no relapse till the end of the study in contrast to 5.3% patients who received long term treatment (p<0.001). A meta-analysis of more than 30 studies concluded that by prolongation of steroid therapy beyond 12 weeks in children with Steroid sensitive nephrotic syndrome, there was no significant reduction in the risk of relapse irrespective to the dose of prednisolone.[10]

A Korean study by Baek *et al*. included 100 children - half received 8 weeks of steroid therapy while remaining patient were administered steroids for 12 weeks. It was reported that patients on prolonged treatment regimen had significantly lower relapse rates within first year of follow-up as compared to the short therapy group. The patients with early response showed significantly lower relapse rates in one and two years follow up comparatively although it was not statistically significant.[9]

Emad Momtaz H, *et al*. conducted a similar study comparing 8 and 12 weeks of steroid therapy in children with nephrotic syndrome. Remission rates observed were 47.1% and 73.5% in 8- and 12-weeks treatment groups respectively (p=0.026).[11] Sinha and co-workers also recommended 12 weeks regimen to be sufficient to manage steroid sensitive nephrotic syndrome. They concluded that extending the treatment to >12 weeks was not effective in modifying the course of disease - relapse rate in the 12 weeks treatment group was 51.7% vs. the longer treatment group (20–24 weeks), (46.9%).[12] Both these studies supported those 12 weeks treatment of steroid sensitive nephrotic syndrome is sufficient in children who achieve early remission.

Some studies comparing short- and long-term steroid therapy concluded that time to first relapse and frequent relapses had no significant difference between both the therapy groups.[13,14]

Yoshikawa and colleagues also showed that extension of initial prednisolone treatment from 2–6 months did not improve the clinical outcome in paediatric nephrotic syndrome.[15]

CONCLUSION

We conclude that receiving 12 weeks therapy showed a lower relapse rate after an initial episode of steroid sensitive nephrotic syndrome as compared to those who were administered prednisolone for 16–24 weeks.

AUTHORS' CONTRIBUTION

AAJ: Principal investigator and a major contributor in data collection, analysis and interpretation,

manuscript writing and literature search. NA: Helped in drafting the work, revising it critically as a supervisor, and final approval of the version to be published. AA, SP, AC, TF: Assisted in data collection, analysis and literature search.

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Submitted: March 16, 2021	*Revised: May 18, 2021*	*Accepted: October 22, 2021*

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