

Original Article**A Comparative Study of Steroid and Steroid plus other Drugs in Relation to Growth and Renal Histopathology among Frequently Relapsing Nephrotic Syndrome Patients**

Ravi Modi*, Omprakash Shukla**

*Fourth year Resident, **Additional Professor

Department of Pediatrics, Medical College, Baroda, Gujarat, India

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ABSTRACT

Background: Corticosteroid is mainstay in the management of Nephrotic syndrome, but it has potential to impair linear growth and the repeated treatment regimens expose such children to the high risk of toxicity. Renal histopathology of FRNS patients is an important guide for management.

Aim: To study the linear growth, renal histopathology, spectrum of infections and complications of steroid therapy in FRNS patients.

Material and Methods: Combined retrospective and prospective study of 44 FRNS(Frequent Relapsing Nephrotic Syndrome) patients. Data were obtained from disease onset until follow-up of at least 3 years. Group I received steroid only and group II received Cyclophosphamide, Cyclosporine, Levamisole along with Steroids.

Result: The range for age of onset of 1st attack was 1-11 years with median of 5.5 years. Age distribution was 73% amongst 2-6 years and 20% in >6 years. Mean increase in height in group I was 4.89 cm/ year while in group II it was 6.43. After 3 years of treatment patients in group II had significantly higher improvement in linear growth as compared to those in group I ($p < 0.01$). Out of 17 biopsied patients, MCNS (Minimal Change Nephrotic Syndrome) was the commonest and seen in 88%, FSGS (Focal Segmental Glomerulo Sclerosis) in 6% and MPGN (Membrano Proliferative Glomerulo Nephritis) in 6%.

Conclusion: The addition of an immunosuppressive agent to steroid therapy decreases the risk of growth retardation. Renal biopsy is a safe and effective tool, which helps in further management and predicting prognosis.

Keywords: Renal Histopathology, Nephrotic Syndrome, Baroda

INTRODUCTION

Growth is an essential feature of childhood. It depends on genetic, nutritional, social and emotional factors. It is affected by chronic systemic disease. It follows a sigma shaped curve with a high velocity in the early postnatal period and during puberty, but a steady rate during mid-childhood. Nephrotic syndrome occurs most commonly in the age group of 2-8 years when the growth rate is in a steady state.

Patients having frequent relapses and requiring repeated courses of steroids often develop toxicity,

including growth retardation. Chronic steroid treatment

has long been recognized as a major risk factor for growth retardation in children. Therefore, immunosuppressive agents have been advocated for use in children with Nephrotic syndrome. Although prednisolone has been used as the first line of treatment of Nephrotic children, only a limited number of studies have investigated the effects of steroid treatment on linear growth. Early administration of an immunosuppressive agent could reduce the side effects of steroid on growth.

AIMS & OBJECTIVES

1. To study linear growth of frequent relapsing Nephrotic syndrome patients.
2. To know the renal histopathology of frequent relapsing Nephrotic syndrome patients.
3. To study the clinic-pathological correlation of all biopsied patients.
4. To study the complication of drug therapy in FRNS (Frequent Relapsing Nephrotic Syndrome) patients.

MATERIAL & METHODS

The data of 44 children with FRNS diagnosed and newly diagnosed, who were on regular follow-up for minimum period of 3 years at nephrology clinic of a tertiary level was analyzed retrospectively for linear growth assessment. 17 patients were biopsied using automated gun biopsy device under ultra sonography guidance with short general anaesthesia. These children were divided into two groups. Group I consisted of 24 children, who received prednisolone in the standard dose for the initial episode at 2 mg/kg/day till remission followed by 1.5 mg/kg/day for four weeks as per the guidelines of Indian Pediatric Nephrology Group [1]. Group II consisted of 20 children, who received the steroids along with steroid sparing agents like Cyclophosphamide, Cyclosporine and Levamisole.

Statistical Analysis: Initial height and weight were taken at the time of enrolment and subsequently for 3 years. By using WHO growth standards each group patient were categorized in to 3 categories as normal, stunted and severely stunted. Statistical analysis was done by SPSS software. Pearson's chi-square test was applied for comparison in between two groups from enrolment to 3 consecutive years. Spectrum of infections and other complication of steroid therapy were also noted in study.

RESULT AND DISCUSSION

44 children with FRNS were analyzed. The age of onset of 1st attack of Nephrotic syndrome patients ranged from 1 to 11 years. The youngest child was of 1 year of age. The median age of onset of 1st attack was 5.5 years, 73% of patients had onset between 2-6 years followed by 20% in >6 years and only 7% had onset before 2 years of age. There were 31 males (70%) and 13 females (30%). A male preponderance was seen with M: F ratio of 2.3:1. In a majority of cases the onset of MCNS (Minimal Change Nephrotic

Syndrome) is between the ages of 2 to 6 years. It is more common in boys (60-70%) [2]. In most of the studies the patients in the age group of 2-6 years with Nephrotic syndrome ranged from 60 to 72% which is comparable to our study with 73% in this age group. [3,4,5,6]. Out of 44, 52% patients were from rural area, 32% and 16% patients were from urban and tribal areas respectively. Study conducted by Sarker MN et al at Dhaka found 60% of the patients coming from rural area. [7] 86% patients were of Hindu religion and rest 14% were of Muslim religion.

Table1: Age and Sex wise distribution of study subjects

AGE	MALE (N=31)	FEMALE (N=13)	TOTAL (N=44)
1-2 years	3	0	3
2-6 years	23	9	32
>6 years	7	2	9
Total	31	13	44

Results were obtained using test analysis of variance with repeated measures.

In our study mean height at enrolment in group I and II was 96.68 cm and 90.82 cm respectively. Mean increase in height in group I was 4.89 cm per year while in group II it was 6.43 cm per year.

P value was obtained using Greenhouse-Geisser test for comparison of height during follow up between two groups. There was significant increase in height during follow up in both the groups. (P value <0.001). There was significant difference in average increase of height between two groups. Average increase in height was higher in group II as compared to group I (p value 0.010).

After 3 years of treatment patients in group II had significantly higher improvement in linear growth during follow up as compared to those in group I as p value is <0.01 compared to follow up after 1 and 2 years of treatment after applying Pearson chi square test. In our study in group I, 2 patients were lost to follow up in the 2nd & 3rd year and in group II, 3 patients were lost to follow up in the 3rd year.

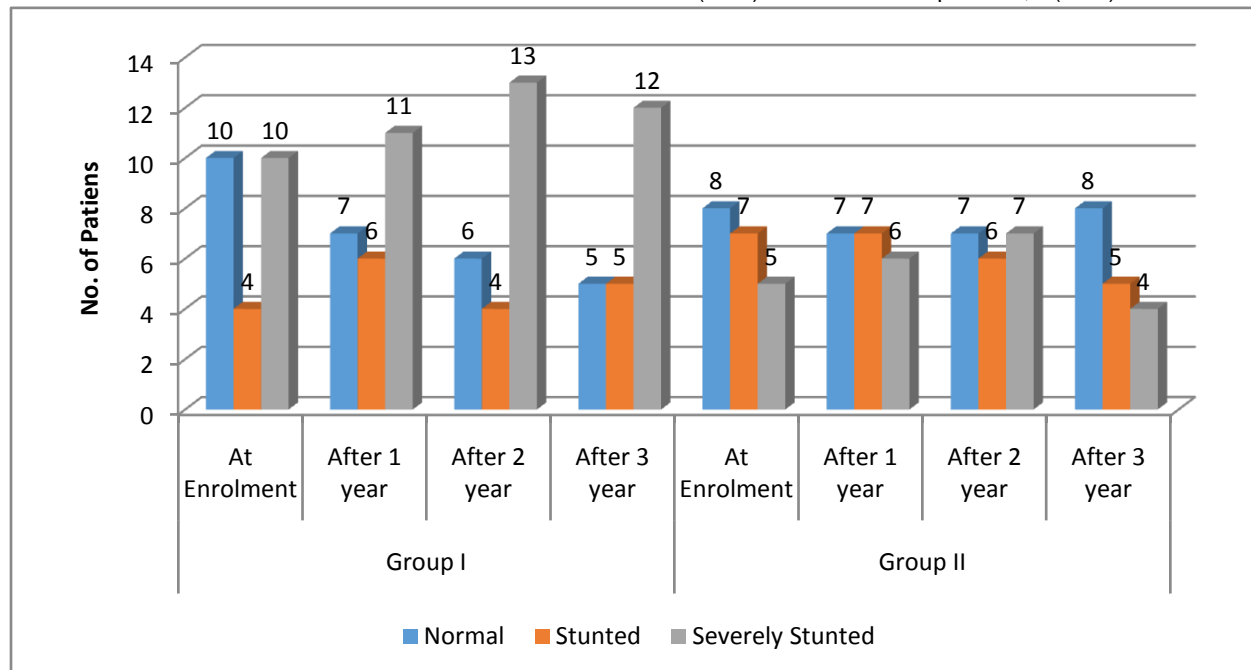
A study conducted by Yeh-ting H et al of 50 patients at Taiwan showed that prednisolone treatment was associated with progressive reduction in height standard deviation score, which became statistically significant (p<0.05) after 3 years. After 3 years,

patients receiving immunosuppressive agents in combination with steroids had significantly higher mean standard

Table 2: Comparison of height

Source		Type III Sum of Squares	df	Mean Square	F	p-value
Rise of Height(both group) during follow-up	Greenhouse-Geisser test	6236.864	1.483	4205.193	262.210	<0.001
Average Height(comparison between 2 groups)	Greenhouse-Geisser test	137.120	1.483	92.453	5.765	0.010

Fig. 1: Height comparison at enrollment and after 3 consecutive years in both the groups
8(53%) were steroid dependent, 4(27%) were steroid



responder and 3(20%) were steroid resistant. One case of FSGS was

deviation score values of height compared with prednisolone only patients. [8]

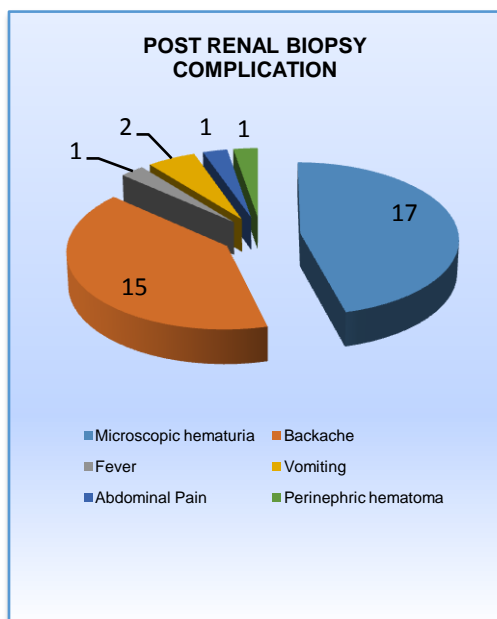
These findings were comparable to our study. Another studies by Donnati T et al, Emma F et al, Tsau Y et al showed similar findings, that steroid therapy was found to be the major determinant in the reduction of linear growth pattern of Nephrotic syndrome [9, 10, 11].

Renal biopsy was performed in 17 cases.MCNSwas the commonest and seen in 15 (88%) cases, FSGS(Focal Segmental GlomeruloSclerosis) was seen in 1(6%) patient and MPGN (MembranoProliferative GlomeruloNephritis) was seen in 1(6%) patient. Out of 15 patients of MCNS,

steroid resistant. One case of MPGN was steroid dependent. Studies by ISKDC, Reshmi et al at Srinagar from 1987 to 2000, and Srivastav et al at Mysore in 2008 showed MCNS in more than 75% of patients, which is comparable to our study (88% MCNS). FSGS was second common histopathological lesion in our study. While studies by Gulati S et al at SGPGI, Lucknow and Yap HK et al at Singapore in 1989 showed FSGS as commonest histopathology in their study which differsfrom our study possibly due to less number of patients and limited study period. [12, 13]

Study of 750 patients from 1983 to 2002 done by William L. et al at Chicago showed biopsy related complications in 98(13%) patients, with minor complications in 50(6.6%) patients, and major complications in 48(6.4%) patients. One (0.1%) patient died as a result of the biopsy. More than 90% of complications were evident by 24 hours [14].

Fig. 2: Percentage of post renal biopsy complications



Marwah DS et al, Meola M et al, and Hergessel O et al also showed most of the complications within 12-24 hrs and major complications were reported in very few patients[15,16,17].

Respiratory infection was the commonest infection seen in 39% patients out of whom 28% had upper respiratory tract infection and 11% had lower respiratory tract infection. Urinary tract infection was second most common in 33% patients followed by peritonitis in 17% and pulmonary tuberculosis in 3% patients. A study at SGPGI, Lucknow by Gulati S et al in 1995 showed one or more infectious complications were observed in 59 of the 154 children, with urinary tract infection being the commonest in 13.7%, followed by pulmonary tuberculosis in 10.4%, peritonitis in 9.1%, skin infections in 5.2%, upper respiratory infections in 5.2%, lower respiratory tract infections in 3.9% and pyogenic meningitis in 0.6%. [18] This differs from our study as we found UTI as

second common complication after respiratory tract infection. A study conducted by Sarker MN et al also showed UTI as common complication [7].

Hypertension was seen in 14% patients and Cataracts in 5(11%) patients in our study. Myopathy was seen in 1(2%) patients. Gangrene of tip of finger was seen in 1(2%) patient who required thrombolytic therapy, embolectomy and amputation for it. Hypocalcemic seizure was seen in 1(2%) patient. A study was conducted by Brocklebank J et al in 1982 at USA found 8(14%) children with cataracts which is comparable to our study [19].

CONCLUSION

The addition of an immunosuppressive agent to steroid therapy decreases the risk of growth retardation. Early identification of growth retardation is beneficial for early intervention in these patients. Renal biopsy is a safe and effective tool, which helps in further management and helps in predicting prognosis of FRNS patients. So, it should be routinely performed in FRNS patients. FRNS patients are more prone to respiratory infections so it is necessary to immunize against Pneumococcal, Hib, Influenza and Varicella vaccine along with the routine immunization and to screen FRNS patients for regular ophthalmologic examination for early changes of cataract.

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Corresponding Author:

Dr Ravi Modi
 Fourth Year Resident
 Department of Paediatrics
 Medical College
 Baroda, Gujarat
 Email:dravimodi575@gmail.com

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