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Steroid Response Pattern Among Childhood Idiopathic Nephrotic Syndrome, Systematic Review

[1]Talal Khalid O Alafif, [2]Naif Misfer J Alzhrany, [3]Atif Mohammed A Hakami, [4]Sahar Surour B Hussien

Abstract: **Background: Nephrotic syndrome (NS) is an important chronic disease in children. Approximately 90% of children with nephrotic syndrome have idiopathic nephrotic syndrome (INS), and the remaining 10% have secondary NS.**
Objective: aims to determine and evaluate the steroid responsiveness pattern and outcome of paediatric idiopathic nephrotic syndrome
Methodology: We conducted a systematic review study that identified most of based evidenced trials which were evaluating or determine corticosteroid agents in steroid responsive in children with nephrotic syndrome (SRNS) from Medline, Embase, and the Cochrane Controlled Trials Register to the time of july 2016.
Conclusion: our study showed higher incidents of steroid resistance in girls than boys. Although the frequency of progression to ESRD and mortality in girls was higher than boys, it was not statistically significant.

Keywords: **Nephrotic syndrome (NS), idiopathic nephrotic syndrome (INS), SRNS.**

1. INTRODUCTION

In nephrotic syndrome protein leaks from the blood to the urine through the glomeruli resulting in hypoproteinaemia and generalised oedema. Children with untreated nephrotic syndrome frequently die from infections. The majority of children with nephrotic syndrome respond to corticosteroids [1].

The pravelance of nephrotic syndrome (NS) is estimated to be cases per 100 000 children per year, and its cumulative prevalence rate is 16 per 100 000 children below age of 16. NS is 15 times more common in children than adults [3]. Approximately 90% of children with NS have idiopathic NS (INS), and the remaining 10% have secondary NS, related to infections, systemic diseases, malignancy, and other glomerular diseases[3,4,5,6,7,8]. Minimal change nephrotic syndrome (MCNS) accounts for 85% of INS, and more than 95% of these respond to steroid therapy and don't need renal biopsy [2,3]. Children with steroid-sensitive NS (SSNS), have a benign prognosis with good preservation of long-term kidney function. Steroid resistance is associated with a high risk of developing chronic kidney disease. Focal segmental glomerulosclerosis (FSGS) is the main cause of steroid resistant NS (SRNS) [6] and accounts for 10%–20% of end-stage renal disease (ESRD) in children [7]. Previous studies emphasize the considerable influence of racial and geographical factors on steroid response and histological pattern and outcome of INS[8]. Moreover, there are some reports indicating the changing face of childhood INS with time[9,10]. Recent studies show that the frequency of FSGS in children has dramatically increased over the past two decades in some parts of world[10,11,12].

Objectives:

This study therefore aims to determine and evaluate the steroid response pattern and long-term outcome of pediatric idiopathic nephrotic syndrome.

2. METHODOLOGY

Search Strategies and Design

We conducted a systematic review study that identified most of based evidenced trials which were evaluating or determine corticosteroid agents in steroid responsive in children with nephrotic syndrome (SRNS) from Medline, Embase, and the Cochrane Controlled Trials Register to the time of July 2016. The databases were searched using optimally sensitive strategies for the identification of randomized controlled trials developed for the Cochrane Collaboration, combined with text words and subject headings for (nephrotic syndrome, lipoid nephrosis, child, and steroid). Reference lists of review articles, relevant trials, nephrology textbooks, and proceedings of scientific meetings were also searched. Investigators known to be active in the field were also contacted to seek information about any unpublished trials.

Inclusion Criteria

Titles were screened by one reviewer (EH), who retained articles in which children with SRNS were treated with corticosteroid agents only. Abstracts were reviewed independently for study eligibility by two reviewers (EH, JK). Studies were selected if they were randomised , quasi-randomised trials, or systematic reviews if they involved children population group in their initial or subsequent episode of SRNS. Studies involving children with steroid resistant nephrotic syndrome, congenital nephrotic syndrome, or nephrotic syndrome associated with other glomerulonephritides were excluded. Studies reported in English language journals were included. Where more than one publication of one trial existed, only the publication with the most complete data was included.

3. RESULTS

We identified seven studies; one study[13] was available in abstract form only. Additional information on the results was not available from the investigators. Thus 7 trials involving 573 children were evaluated. **Table 1** shows the characteristics of the 6 trials[14-19] in children in their initial episode of SRNS. Five trials [15,16,17,18,19] compared standard therapy (60 mg/m^2/day prednisone for four weeks followed by 40 mg/m^2 on alternate days or on three consecutive days out of seven for two months), with regimes of at least three months of therapy comprising 1–2 months of daily and 1. 5–6 months of alternate day therapy. In one of these trials[17] standard therapy was compared with two experimental regimes. The outcomes from the experimental group treated for six months were included in the analyses. One of these trials[17] excluded those children who became steroid dependent. One trial[14] compared standard therapy with a shorter duration of treatment and one trial[13]compared five months with one year of therapy.

Table.1: Characteristics of trials of corticosteroid therapy in children in their first episode of steroid responsive nephrotic syndrome

Authors, year, country	*Patients (controls)*	*Patients (expt)1-150*	*Experiment intervention dose*	*Duration*	*Control intervention dose*	*Duration*
Kleinknecht *et al* 18, 1982, France	29	29	Prednisone 2 mg/kg/day for 4 weeks and taper alternate days	1 year	alternate days Prednisone 2 mg/kg/day for 4 weeks and taper	5 months
APN[14] 1-151, 1988, North Europe	29	32	Prednisone 60 mg/m^2/day till urine protein free for 3 days and 40 mg/m^2 alternate days till albumin >35 g/l	1 month (average)	Prednisone 60 mg/m^2/day for 4 weeks and 40 mg/m^2 alternate days for 4 weeks	2 months
Ueda *et al* [15], 1988, Japan	29	17	Prednisolone 60 mg/m^2/day for 4 weeks, 60 mg/m^{2}weeks and taper by 10 mg/m alternate	7 months	Prednisolone 60 mg/m^{2}mg/m /day for 4 weeks and 40	2 months

			days for 4 ^{2}/mth to zero		^{2} on 3 of 7 days for 4 weeks	
APN[16], 1993, North Europe	37	34	Prednisone—6 weeks each of 60 mg/m^{2}/day and 40 mg/m^{2}alternate days	3 months	Prednisone—4 weeks each of 60 mg/m^{2}mg/m /day and 40 ^{2}alternate days	2 months
Ksiazek and Wyszynska[17], 1995, Poland	44	681-152	and taper by 25% per week for 4 weeks Prednisone 1–2 mg/kg/day for 4 weeks, 1 mg/kg alternate days for 4 weeks	3 months	mg/kg on alternate days Prednisone 4 weeks each of 1–2 mg/kg/day and 1	2 months
		721-152	and taper by 25% each month Prednisone 1–2 mg/kg/day for 4 weeks, 1 mg/kg alternate days for 4 weeks	6 months		
Norero *et al*[18], 1996, Chile	27	29	Prednisolone—6 weeks each of 60 mg/m^{2}/day and 40 mg/m^{2}alternate days	3 months	Prednisolone—4 weeks each of 60 mg/m^{2}mg/m /day and 40 ^{2}alternate days	2 months
Bagga *et al*[19], 1999, India	23	22	alternate days, 1 mg/kg alternate days Prednisone—4 weeks each of 2 mg/kg/day, 1.5 mg/kg/day, 1.5 mg/kg	4 months	mg/kg alternate days Prednisone—4 weeks each of 2 mg/kg/day and 1.5	2 months

We also identified one important study [20] that reviewed the reports of children with the diagnosis of NS and found following:

Oral prednisolone therapy was given to all the patients with INS. After one month of treatment 16 out of 20 went into remission (SSNS), and four were SRNS. All except for one SSNS patient had at least a relapse after complete remission. Four children had FRNS, of which one became SDNS with short stature and cushingnoid facies. Oral cyclophosphamide was given to four FRNS; three relapsed after the first course and were given a second course of cyclophosphamide. Levamisole 2.5 mg/kg/alternate day was given to a patient with SDNS after two courses of cyclophosphamide. This was discontinued by parents after two months. Six of the SSNS have been in remission for >12 months, and one of those who received cyclophosphamide has remained in remission for >6 years[20].

We identified recent study[21] that involving total of 99 patients, 54 children received short term (ST) steroid therapy and the other 45 children received Long term (LT) steroid therapy. There were no significant differences of clinical characteristics including mean age, serum albumin, total cholesterol and days to remission between these two groups. Renal biopsy was performed in 36 of 54 children with ST and 27 of 45 with LT. Although some patients received additional immunosuppressive medications such as cyclosporine, chlorambucil and cyclophosphamide after renal biopsy, there was also no significant difference between these two groups. Total period of follow-up was 97.5±53.9 months in ST, 55.8±29.4 months in LT. As in other previous reports, the 45 children with LT showed significantly lower relapse rate during the first year after their first episode of NS, compared to children with ST (2.1±1.7 in ST vs. 1.3±1.4 in LT, P=0.014). In addition, the cumulative percentage of children with sustained remission in LT group was significantly higher than ST group (P=0.021) [21]**Fig.1.**

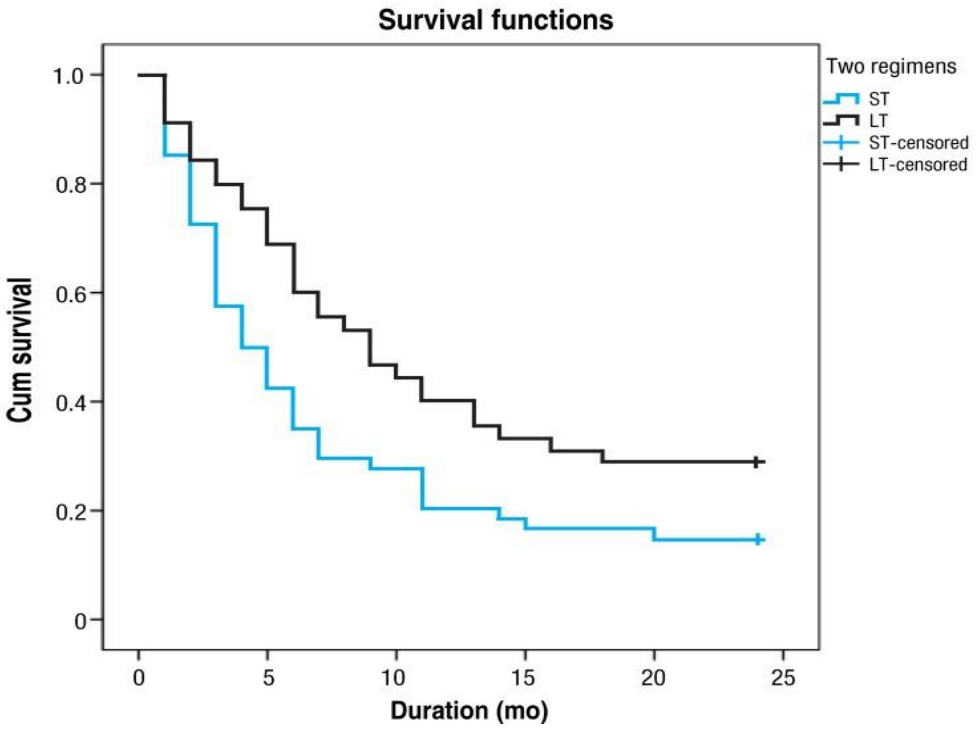

Fig.1: Cumulative percentages of children with sustained remission after 2 initial steroid regimens (ST vs. LT). ST, short-term therapy; LT, long-term therapy[21].

4. CONCLUSION

Children in their first episode of nephrotic syndrome should be treated for at least three months with an increase in benefit being demonstrated for up to seven months of treatment. In a population with a baseline risk for relapse following the first episode of 60% with two months of prednisone, daily prednisone for four weeks followed by alternate day therapy for six months would be expected to reduce the number of children experiencing a relapse by about 40%. our study showed a higher frequency of steroid resistance in girls than boys. Although the frequency of progression to ESRD and mortality in girls was higher than boys, it was not statistically significant.

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