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Original Article

Randomized Controlled Trial to Compare the Efficacy of Low-dose Daily vs Alternate-day Prednisolone in Children With Steroid Dependent and Frequently Relapsing Nephrotic Syndrome

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ABSTRACT

Background and Aim: Tapering alternate-day doses of corticosteroid forms the cornerstone of the management of steroid-dependent nephrotic syndrome (SDNS) and frequently relapsing nephrotic syndrome nephrotic syndrome (FRNS). This study compares the reduction of relapses over a one-year follow-up, using equivalent steroid doses given as either daily or alternate-day therapy.

Methods: This was an open-label, randomized controlled trial. The participants were children with SDNS or FRNS, aged 2-10 years. After remission, steroid doses were tapered until a threshold below 0.75 mg/kg/day. Then, subjects were randomized to one of two arms as follows: Daily prednisolone at 0.15-0.30 mg/kg/day (intervention arm) or alternate-day dose of 0.5-0.75 mg/kg (control arm). Both groups were compared after 12 months for a reduction in relapse frequency. Secondary outcome measures included time to first relapse, proportion of relapse-free patients, mean steroid dose used, infection episodes, need for alternative medications, and side effects of corticosteroids.

Results: Median (interquartile range [IQR]) changes in relapse frequency did not differ between the groups, 0 (IQR: -1.0, 0.25) vs 0 (IQR: 0.0, 1.0) in intervention and control groups, respectively (P=0.46). The mean percentage change in relapse frequency was -18.1±42.4% (negative denotes decreased) in the intervention group and 6.0±26.9% in the control group (P=0.05). The median relapse frequencies during the trial period were 3 (IQR: 2, 3) and 3 (IQR: 3, 4) in the intervention group and control groups, respectively (P=0.021). At study completion, prednisolone dose was lower in the intervention group, 0.33±0.12 vs 0.40±0.05 (P=0.02). Both groups did not differ by other secondary outcome variables.

Conclusion: In patients with SDNS and FRNS, daily low dose (0.15-0.30 mg/kg/day) administration of prednisolone is not superior to conventional alternate-day dosing.

Keywords: Glucocorticoids, Minimal change disease, Nephrotic syndrome, Stunting

Introduction

Following the Indian Society of Pediatric Nephrology (ISPN) guidelines, tapering doses of prednisolone are usually the first treatment option in children with steroid-dependent nephrotic syndrome (SDNS) and frequently relapsing nephrotic syndrome (FRNS). This is done using a minimum possible dose of alternate-day prednisolone, preferably below 0.5 mg/kg, to avoid adverse effects of corticosteroids while maintaining disease remission [1]. Leisti et al. [2] proposed that patients of nephrotic syndrome with frequent relapses receiving prolonged corticosteroid therapy have suppressed the hypothalamic-pituitary-adrenal (HPA) axis, which may cause reoccurrence of relapses. They also concluded that the administration of a daily low dose of cortisol reduces the frequency of relapses and minor adverse effects due to prolonged steroid therapy. A study by Yadav et al. [3] has shown that FRNS patients receiving daily low-dose prednisolone (0.2-0.3 mg/kg/day) have fewer relapses compared to conventional alternate-day therapy (0.5-0.7 mg/kg). This study examines the efficacy of a lower dose of daily prednisolone against the standard alternate-day therapy.

Materials and Methods

A single-center parallel group open-label randomized controlled trial was conducted in the Nephrology Clinic, Jawaharlal Nehru Medical College, AMU, Aligarh, from April 2020 to October 2022. Children in the age group of 2-10 years diagnosed with SDNS/FRNS, who had at least 6-month follow-up records at this center, were considered for enrolment in this trial.

SDNS was defined as two consecutive relapses when on alternate-day steroids or within 14 days of its discontinuation. FRNS was defined as two or more relapses in the initial 6 months or >3 relapses in any 12 months [1]. Children with age at onset of nephrotic syndrome <1 year or >10 years, previous use of alternative medications (steroid sparing), pathology other than minimal change, secondary nephrotic syndrome, late steroid resistance, or unwilling to follow-up were excluded.

Meanwhile, patients with FRNS/SDNS were treated following ISPN guidelines at this center [4]. Treatment of relapse was initiated once the infection was under control. Prednisolone was given in a dose of 2 mg/kg/day until remission. After that, the dose was reduced to a single morning dose of 1.5 mg/kg given on alternate days for 4 weeks. Alternate-day prednisolone doses were subsequently tapered by 0.25 mg/kg every 2-week until a steroid threshold of <0.75 mg/kg/alternate day was achieved to maintain remission. The patients were available for enrolment in the trial at this stage. A parent-patient information sheet was provided and informed parental consent and permission (where applicable) were obtained. A detailed history and physical examination were recorded on pre-designed proforma. In particular, a record was made of the age at onset of nephrotic syndrome, type of nephrotic syndrome (frequent relapse/steroid-dependent), the relapse rate in the previous 12 months, treatment administered and duration. Investigations were done as required for the workup of a patient with nephrotic syndrome and confirmation of a relapse (complete blood counts, urinalysis, serum albumin, serum cholesterol, blood urea and creatinine). A few cases who could not come to the hospital due to COVID-19 lockdowns were telephonically followed up and their investigations were done at the local laboratory in their area. These reports were then collected from the patients.

Randomization and intervention

Randomization was done using a computer program, and the allocation sequence was kept in sealed opaque envelopes (serially numbered) by a colleague not directly involved in this trial. Subjects were allocated to one of the two intervention groups: A single dose of 1) Daily low-dose prednisolone (0.15-0.25 mg/kg; intervention group) or 2) Alternate-day prednisolone (0.50-0.75 mg/kg; control group). Both groups were asked to purchase Tablet Wysolone® (Pfizer Ltd.) so that the bioavailability and other aspects of pharmacokinetics would be similar. Either therapy regimen was continued for 12 months. Compliance was checked with regular visits to the pediatric nephrology clinic and a diary was maintained. Relapses during this period were treated with prednisolone at a dose of 2 mg/kg/day until remission, followed by 1.5 mg/kg on alternate days for 4 weeks. Subsequently, the doses were tapered, and the patient was reassigned to the original allocation. The patients who continued to have frequent relapses developed significant steroid toxicity (hypertension, stunting, ocular complications, cushingoid), required the addition of steroid-sparing agents, or developed steroid resistance were labeled as treatment failure. Subsequent data of such patients was censored from the study analysis.

Proteinuria was evaluated using a urine dipstick, Albustix® (Bayer pharmaceutical). The parents were trained to maintain a record of daily proteinuria and relapses. The cumulative steroid dose was calculated for the one-year follow-up or the trial duration period. Daily steroid intake was expressed as mg/kg/day.

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Outcome measures

The primary outcome measure was a percentage reduction in relapse frequency in one year. Secondary outcome measures included time to first relapse, relapse frequency at study completion, the proportion of patients relapse-free, steroid dose, number of infection episodes (peritonitis, meningitis and cellulitis), need for steroid-sparing medications and significant steroid toxicity (cushingoid, hypertension and ocular).

Sample size and analysis

In a previous study, the relapse rate declined by 83.9% and 34%, respectively, in patients taking daily and alternate-day treatment with prednisolone [3]. Assuming a 50% decline in relapse frequency using small-dose daily prednisolone, a sample size of 16 per group was needed to reject the null hypothesis with a power of 90% and α of 0.05. To account for a 15% drop-out over 1 year, we enrolled 19 patients per group. Analysis was done on an intention-to-treat basis. The missing data was calculated using the linear trend estimation method. The categorical data were compared using the chi-square test. Continuous variables were compared using an independent sample t-test. Median relapse frequencies were compared using the Mann-Whitney U test. The significance level was considered at a $P<0.05$. All statistical analyses were done using the SPSS software, version 26 (IBM USA).

Results

Of the 49 eligible patients, 11 had to be excluded (Figure 1). The remaining 38 patients were enrolled and randomized to either group (19 per group). One patient expired in the control group, and one was lost to follow-up in the intervention group. Since these patients were lost within 2 months of enrolment, their data was excluded from the final analysis. Thus, the data of 36 patients was analyzed. The mean age of the study population at enrolment was 68±24 months. The male gender constituted 26 (72.2%) patients. Enrolled patients included 16(44.4%) SDNS cases; the remaining were FRNS. The mean duration of SDNS/FRNS at enrolment was 6 months. The baseline parameters did not differ between the study groups (Table 1).

Outcome variables

The percentage change in relapse frequency compared to baseline frequency was -18.19±42.4% in the intervention group and +6.0±26.9% in the control group (P=0.05) (Table 2).

The median relapse frequencies during the trial period were 3 (IQR: 2, 3) and 3 (IQR: 3, 4) in the intervention group and control groups, respectively (P=0.02). Median (IQR) change in relapse frequency did not differ between the study groups, with 0 (IQR: -1.0, 0.25) in the intervention group and 0 (IQR: 0.0, 1.0) in the control group (P=0.46).

Time taken for the first relapse was statistically similar, 107±40.1 vs 88.5±36.3 days in the intervention and control groups, respectively (P=0.16). No patient from either group remained relapse-free during the study period of one year. However, five patients from the daily dosing group and six patients from the alternate conventional dosing group had no relapse in the initial 6-month period.

The frequency of infection episodes was similar in intervention group 1 (IQR: 1, 1), while in the control group, it was 1 (IQR: 1, 2) (P=0.26). None of the patients suffered from any serious infections.

Ten patients failed treatment: 4 from the intervention group (including 3 SDNS) and 6 from the control group (including 2 SDNS). These patients fared well when given additional levamisole therapy.

Adverse effects due to steroid toxicity

At the end of the study completion, the cumulative mean prednisolone dose was 0.33±0.12 mg/kg/day and 0.40±0.05 mg/kg/day, respectively, in the intervention and control groups (P=0.02). Corticosteroids could not be discontinued in any patient in the study.

Among the patients from the intervention group, 7 patients developed cushingoid habitus, 5 developed hypertension, and 2 patients had ocular complications (raised intraocular pressure and posterior subcapsular cataract). Among the 8 patients who were cushingoid in the control group, 5 were hypertensive, and 1 developed an ocular complication (cataract) due to steroid toxicity.

Discussion

We observed a more favorable change in relapse frequency at one-year follow-up in the intervention group, although statistical significance was not achieved. While the results of the previous comparison of daily versus alternate-day prednisolone showed superiority in the reduction of relapses in the daily group (84% vs 34%) in FRNS patients [3], we have tested with lower daily doses and also included SDNS patients in the study. SDNS

Table 1. Clinical parameters at study enrolment (n=18)

Parameter		Mean±SD/No. (%)		P
		Intervention	Control	
Age (m)	Disease onset	53.9±22.9	45.2±24.0	0.27
	FRNS/SDNS	67.2±22.8	55.8 ±23.9	0.16
	Study enrolment	71.1±23.3	64.2±25.3	0.40
Male		11(61.1)	15(83.3)	0.26
Z-score	Height	-0.5±1.3	-0.8±1.4	0.55
	Weight	0.6±0.9	0.1±1.1	0.33
	BMI	1.1±0.8	0.8±1.3	0.51
SDNS		10(55.6)	6(33.3)	0.32
Relapse frequency, median (IQR)		3 (IQR 3-3)	3 (IQR 3-3)	0.99

Abbreviations: FRNS: Frequently relapsing nephrotic syndrome; SDNS: Steroid-dependent nephrotic syndrome; BMI: Body mass index; IQR: Interquartile range.

atients respond less favorably compared to FRNS [5-7]. The subjects enrolled in their research were older children, mean age in the daily dosing group (83 months), and only 29% of patients were SDNS in each group. It has been shown that the outcome among the nephrotic patients improves with age [6].

Srivastava et al. have also previously reported lower relapse rates using daily low-dose prednisolone in FRNS over an 18-month observation period [5]. Also, 20% of their cases had previously shown unsatisfactory response to second-line agents like cyclophosphamide and levamisole. Accordingly, daily low-dose steroid therapy

Table 2. Outcome measures at study completion (n=18)

Parameters			Mean±SD/No. (%)		P
			Intervention	Control	
Primary outcome	Change in relapse frequency (%)		18.1±42.4	-6.0±26.9	0.05
Secondary outcomes	Time to 1st relapse (days)		107±40.1	88.5±36.3	0.16
	Relapse frequency*		3 (IQR 2-3)	3(IQR3-4)	0.02
	Patients relapse free		0	0	-
	Mean steroid dose (mg/kg/d)		0.33±0.12	0.40±0.05	0.02
	Infection episodes*		1 (IQR 1-1)	1 (IQR 1-2)	0.26
	Treatment failure		4(22.2)	6(33.3)	0.46
	Significant steroid toxicity,		7(38.8)	8(44.4)	0.4
	Z-score	Height	-0.03±1.0	-0.8±0.9	0.02
		Weight	1.08±0.7	0.6±1.1	0.13
		BMI	1.4±0.6	1.1±1.5	0.33

BMI: Body mass index; IQR: Interquartile range.

*Median (IQR).

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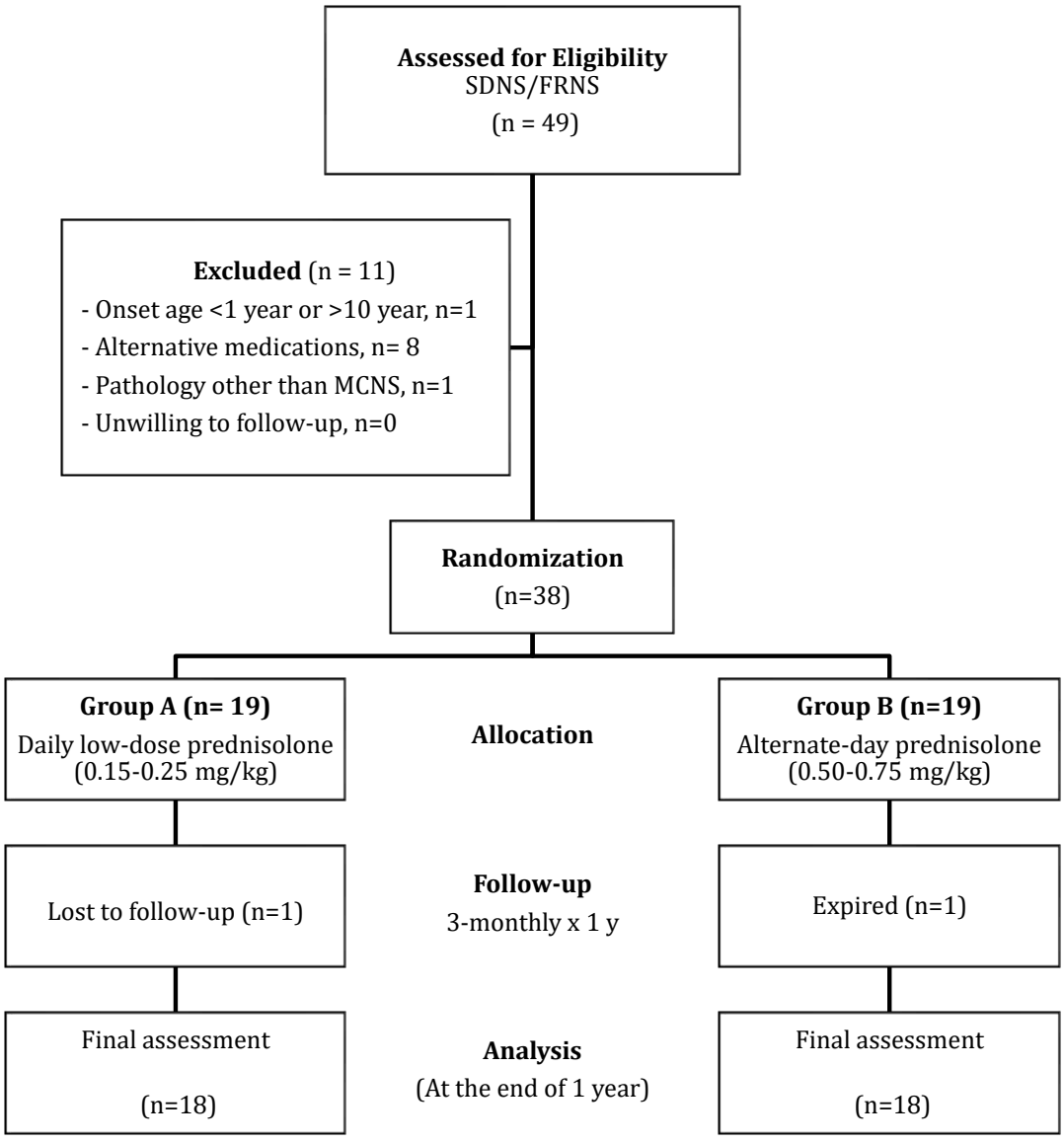

Figure 1. Plan of flow of patients in the study

Abbreviations: MCNS: Minimal change nephrotic syndrome; SDNS: Steroid dependent nephrotic syndrome; FRNS: Frequently relapsing nephrotic syndrome.

may have the edge over alternate-day treatment across patient groups, including SDNS patients and those who have not benefitted from the use of second-line agents.

While the time for the first relapse was longer in patients of the daily dosing group, it did not differ statistically. None of the patients in our cohort remained relapse-free during the entire study period. On a subgroup analysis, we noted that among FRNS but not among the SDNS patients, daily-low prednisolone use had lower chances of failure (1 out of 8 patients) than alternate-day treatment (4 out of 12 cases).

The threshold dose for achieving sustained remission using a small daily dose regimen has not been tested before. The dose used for daily therapy was slightly higher in the previous study by Yadav et al. (0.20–0.30 mg/kg/day) than that used in our study (0.15-0.25 mg/kg/day). Even though we enrolled younger patients and included those with SDNS, a dose over 0.20 mg/kg would likely be effective since we could not demonstrate a robust decline in relapse frequency using the lower doses.

Our study had limitations inherent in its unblinded design and short follow-up period. While the study duration was short, most randomized trials comparing the ef-

ficacy of treatment regimens in children with nephrotic syndrome have used similar observation periods. We did not stratify our patients for SDNS/FRNS, while it is known that SDNS patients fare less favorably concerning relapses. Also, none of the subjects enrolled in our study had biopsy-proven minimal change disease. While most steroid-sensitive patients are likely to have minimal change disease, at least some of these patients could likely have significant pathologies associated with unfavorable outcomes. Lastly, we did not measure for HPAxis suppression, while ideally, low daily doses should be correlated with HPA axis suppression [8, 9]. Despite the limitations, randomized patient allocation and prospective data collection lend credence to our results. Intention-to-treat analysis and low attrition rates ensured that all patients were accounted for throughout the study. Patients in both study groups were enrolled throughout the year to account for any bias on account of seasonal differences in relapses of nephrotic syndrome.

While ISPN [10] guidelines suggest the use of low-dose steroids for treatment in a select group of children with nephrotic syndrome, we suggest further studies on a larger patient cohort with a more extended observation period, using a blinded design stratified for SDNS/FRNS and for age at enrolment. Results from an ongoing trial (CTRI/2019/01/017091) will likely provide more clarity on the subject.

Conclusion

In patients with SDNS and FRNS, daily low dose (0.15-0.30 mg/kg/day) administration of prednisolone is not superior to conventional alternate-day dosing.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh.

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Authors' contributions

All authors equally contributed to the preparation of this article.

Conflict of interest

The authors declared no conflict of interest.

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