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Single- versus divided-dose prednisolone therapy for relapses of nephrotic syndrome

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Abstract. Relapses of nephrotic syndrome are usually treated with prednisolone, initially in three to four daily divided doses. The divided-dose regimen may cause poor patient compliance and greater adrenal suppression. In a prospective randomized controlled trial, we compared the efficacy of prednisolone in inducing remission of nephrotic syndrome, when given either as a single dose or in divided doses. Patients with steroid-responsive nephrotic syndrome with relapse were randomized to receive prednisolone 2 mg/kg per day, either as a single morning dose or in three divided doses for 2 weeks, followed by 1.5 mg/kg on every alternate day for 4 weeks. Parents tested the urine for protein daily until remission (nil proteinuria for 3 consecutive days). The duration between initiation of treatment and achievement of remission was recorded. Of 106 patients, 94 (47 each in single-dose and divided-dose groups) completed the study. The patients in the two groups were similar in relation to age, sex, number of relapses in the preceding year, and blood levels of creatinine, albumin, and cholesterol. The mean time for achievement of remission in the single- and divided-dose groups was 8.6 and 8.5 days, respectively (P = 0.94, power 96%). After 9 months' follow-up, there were no differences in the frequency of relapses and cumulative dose of prednisolone received in the two groups. The observations suggest that prednisolone administered in a single daily dose or in divided doses is equally effective in inducing remission in patients with relapsing nephrotic syndrome.

Key words: Corticosteroids – Nephrotic syndrome – Relapse

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Introduction

The large majority of children with idiopathic nephrotic syndrome respond to corticosteroid therapy with remission of proteinuria. More than two-thirds, however, show subsequent relapses. These relapses are usually treated with prednisolone, administered daily in three to four divided doses, until remission, followed by intermittent [1] or alternate-day [2] therapy for 4 weeks.

The use of corticosteroid therapy in divided doses is associated with significant adrenocortical suppression [3, 4]. The compliance of patients in taking drugs three to four times a day also may be unsatisfactory [5]. Two previous reports, one a retrospective comparison [6] and the other published as an abstract [7], suggest that administration of prednisone or prednisolone in a single daily dose or in divided doses is equally effective in inducing remission in patients with nephrotic syndrome. Single-dose therapy was also associated with less adrenocortical suppression and fewer side effects [6, 7]. Prospective controlled trials comparing single-dose and divided-dose corticosteroid regimens are, however, lacking. We have compared in a randomized controlled trial the effect of single- or divided-dose prednisolone treatment in inducing remission of the nephrotic syndrome.

Patients and methods

Patients with steroid-responsive nephrotic syndrome who presented with a relapse (proteinuria 2+ or more for 3 consecutive days) to the pediatric nephrology clinic of the All India Institute of Medical Sciences, New Delhi, during December 1993–June 1995 were included in the study. A patient was considered steroid-responsive if he showed absence of proteinuria (nil urine protein) following previous treatment with prednisolone [8]. Patients who had received corticosteroids or other immunosuppressive drugs for treatment of the current relapse and those with steroid resistance or dependence were excluded [8]. Informed parental consent was obtained.

The patients were randomized to receive prednisolone, 2 mg/kg body weight per day, either in three divided doses or as a single dose for the initial 2 weeks. Patients in the single-dose group received the entire amount of prednisolone in the morning after breakfast. Parents were instructed to test urine for protein daily using dipsticks and record

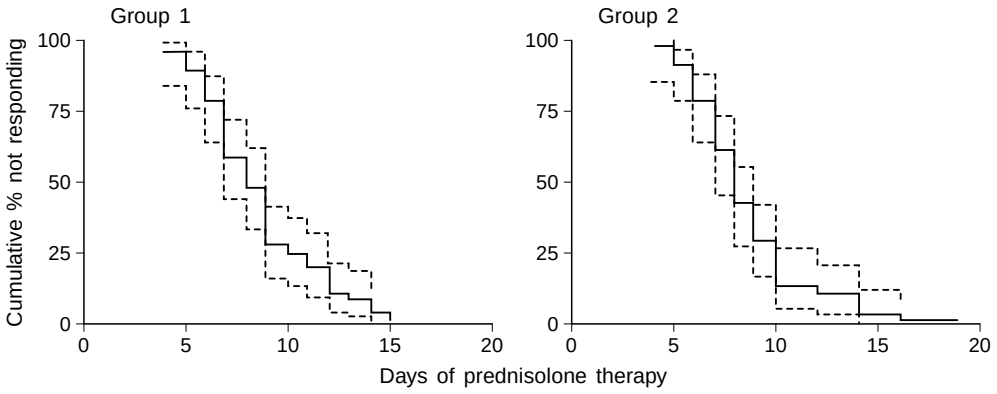

Fig. 1. Cumulative percentage of patients not in remission (*bold line*) with 95% confidence limits (*broken lines*) in the two prednisolone regimens (group 1 = single dose, group 2 = divided dose; $P = 0.7$, log rank test)

the results in a diary. Remission was defined as absence of proteinuria for 3 consecutive days. The duration between initiation of treatment and achievement of remission was recorded. The duration of daily prednisolone therapy was increased to 4 weeks in patients who did not achieve remission at the end of 2 weeks; those not responding despite 4 weeks of daily treatment were removed from the study. Following daily treatment, patients in both groups received 1.5 mg/kg prednisolone as a single morning dose, on alternate days for 4 weeks, after which it was discontinued.

The patients were followed at 3- to 4-week intervals for the next 9 months. Subsequent relapses were treated using the same regimen in which the patient was initially randomized. The number of relapses and the cumulative dose of prednisolone received was recorded. The side effects of steroid treatment, including hypertension [9], obesity (weight exceeding 120% of that expected for height [10]), presence of cushingoid features, serious infections, and cataracts, were noted.

Statistical tests. We assumed that a difference of 30% in the days to achievement of remission in the groups would be clinically significant. For a power of 80% and a two-tailed test performed at a 0.05 significance level, 45 patients were required in each group. Chi-squared test, unpaired Student's *t*-test, and Wilcoxon rank sum test were used for statistical analysis.

Results

Of 106 patients with steroid-responsive nephrotic syndrome, 52 and 54 were randomized to receive single- or divided-dose prednisolone, respectively. These patients were on regular follow-up of the pediatric nephrology clinic of this hospital for a period ranging from 4 to 36 months. Eleven children (5 in the single-dose, 6 in the divided-dose groups) did not report for follow-up and were excluded. One patient in the divided-dose group did not

Table 1. Important characteristics of patients prior to inclusion[a, b]

Characteristic	Single dose ($n = 47$)	Divided dose ($n = 47$)
Age at onset (years)	3.7 ± 2.3 (0.8–11)	3.1 ± 2.2 (1–11)
Age at inclusion (years)	5.6 ± 2.8 (2–17)	6.6 ± 3.4 (1.3–16)
Male : female	32 : 15	31 : 16
Weight (kg)	18.3 ± 5.8	21.5 ± 9.3
Height (cm)	106.8 ± 16	107.0 ± 23.8
Systolic blood pressure (mmHg)	101.9 ± 7.5	105.6 ± 12.3
Diastolic blood pressure (mmHg)	70.2 ± 8.5	72.1 ± 11.1
Relapses (preceding year)	1.7 ± 1.0 (1–4)	1.9 ± 1.3 (1–4)
Serum creatinine (mg/dl)	0.3 ± 0.3 (0.2–0.9)	0.4 ± 0.4 (0.3–1.1)
Serum albumin (g/dl)	1.5 ± 1.4 (1.2–4.2)	1.6 ± 1.2 (1.1–4.8)
Serum cholesterol (mg/dl)	169.4 ± 174.3 (144–584)	179.0 ± 242.8 (127–669)

[a] Values represent mean ± standard deviation
[b] Figures in parentheses indicate range

Table 2. Response to single- and divided-dose prednisolone treatment[a, b]

Parameter	Single dose ($n = 47$)	Divided dose ($n = 47$)	P value
Time to remission (days)	8.6 ± 2.8 (4–15)	8.5 ± 2.9 (2–19)	0.94
Duration of first remission (weeks)	22.5 ± 13.0 (1–36)	23.7 ± 13.3 (2–48)	0.64
Relapse (in 9 months)			
None	18	20	0.33
Two or less	22	19	0.50
Three or more	7	8	0.33
Relapse rate (/patient per 9 months)	1.7 ± 1.1 (0–4)	1.9 ± 1.1 (0–4)	0.85
Cumulative prednisolone (mg/kg per 9 months)	90.3 ± 49.0 (30.4–226.9)	92.1 ± 54.2 (26.9–222.9)	0.86

[a] Values represent mean ± standard deviation
[b] Figures in parentheses indicate range

show remission, despite treatment with daily prednisolone for 4 weeks, and was also excluded.

The important clinical and laboratory characteristics of patients in the two groups were comparable (Table 1). The frequency of relapses in the two groups was also similar. Treatment with immunosuppressive drugs (cyclophosphamide in 9, levamisole in 2) had been previously given for treatment of frequent relapses, in 5 and 6 patients in the single- and divided-dose groups, respectively. Renal biopsy in 9 patients in the single-dose and 10 of the 12 patients in the divided-dose groups showed minimal change; 2 in the latter had mild mesangial proliferation. The mean duration between onset of relapse and initiation of steroid therapy in the single-dose and divided-dose groups was 7.8 ± 6.3 days and 7.3 ± 6.9 days, respectively ($P > 0.05$).

The mean duration of prednisolone therapy before remission occurred was 8.6 days in the single-dose and 8.5 days in the divided-dose group (Table 2). Two patients in each group had remission after 2 weeks of daily prednisolone treatment. Figure 1 shows that the time to occurrence of remission was similar in the two groups. There was also no significant difference in the duration of remission following therapy in either group. During follow-up, the frequency of relapses and the cumulative dose of prednisolone received in the two groups were also comparable (Table 2). During the following 9 months, 40 patients in the single-dose and 39 in the divided-dose group had two or fewer relapses; 7 and 8 patients in the single-dose and divided-dose groups, respectively, had three or more relapses.

Two patients each in both groups developed serious infections. Obesity was seen in 2 patients in the single-dose and 5 in divided-dose groups. There were no other significant side effects of steroid therapy.

Discussion

The International Study of Kidney Diseases in Children (ISKDC) [1] and Arbeitsgemeinschaft fur Paediatrische Nephrologie [2] recommend treatment of relapses of nephrotic syndrome with prednisone in three divided doses until remission of proteinuria. Prednisone is then administered either intermittently [1] or on alternate days [2] for another 4 weeks. Although these recommendations are widely followed, some workers have suggested that other prednisone regimens are as effective in inducing remission.

Choonara et al. [11] showed that prednisolone administered at a dose of 30 mg/m^2 once daily led to remission in almost all patients with steroid-responsive nephrotic syndrome. Warshaw and Hymes [6] successfully treated 31 of 32 patients with prednisone given at a single dose of 2 mg/kg per day. Comparing their results with those reported by ISKDC [1], they found that the time taken to achieve remission was similar in patients receiving prednisone in either single or divided doses. Similar observations were made by Lee and Lee [7] in 23 patients; patients receiving prednisone in a daily dose had also less adrenocortical suppression and fewer side effects.

The present study is the first prospective randomized controlled trial comparing single daily-dose and divided-dose prednisolone for the treatment of relapses of nephrotic syndrome. We found that treatment with single-dose prednisolone was as effective as divided doses in inducing remission. The power of this study to show that the two regimens were comparable was 96%. The mean time to remission in patients receiving single and divided doses was 8.6 and 8.5 days, respectively; similar durations varying from 6 to 11.5 days have been reported previously [1, 2, 6, 7]. Administration of prednisolone in a single dose daily thus induces remissions in a similar time frame compared with divided doses.

Administration of the total prednisolone dose in the morning may cause less adrenocortical suppression [3, 4], which is important since adrenocortical suppression has been reported to increase the risk of relapse in patients with nephrotic syndrome [12]. We found no significant differences in side effects in patients treated with prednisolone in single or divided doses. The degree of adrenocortical suppression was, however, not measured. The duration of first remission, relapse rate, and cumulative dose of prednisolone after 9 months' follow-up was also similar in the two groups.

In summary, we observed that prednisolone administered in a single daily dose was effective in the treatment of relapse of nephrotic syndrome. Such a regimen has the obvious advantages of compliance and convenience, and may reduce the intensity of adrenocortical suppression.

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