

## RELAPSE RATE IN DAILY SINGLE-DOSE PREDNISOLONE THERAPY FOR CHILDREN WITH PRIMARY NEPHROTIC SYNDROME

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### ABSTRACT

Most current references recommend divided doses of prednisolone for the initial treatment of idiopathic minimal change nephrotic syndrome in children, with relapse occurring in the majority of them, but there is little experience concerning single-dose prednisolone therapy, especially considering the relapse rate. In this prospective study on 36 consecutive children with primary nephrotic syndrome, prednisolone (2 mg/kg/day) was used as a single daily dose in 17 patients (SD group), or divided into 3 doses in 19 cases (DD group) who were randomly selected, and relapse rates were compared.

The mean age of the patients was 6 years (range 15 months-13 years) and there was no statistically significant difference between the two groups considering age, sex, clinical presentation, laboratory findings at the time of admission and prednisolone side effects.

After 4 weeks of full dose prednisolone therapy, the drug was changed to 2 mg/kg as a single dose every other day in both groups, irrespective of the response. During the third month of therapy, the drug was reduced to 1 mg/kg every other day and it was discontinued after 4 weeks.

Relapse rate was compared in steroid responsive patients in both groups (14 in the SD and 11 in the DD group) who were matched for age, sex and paraclinical findings. During the first year of follow-up, in those who were initially steroid responsive, 2 patients in the SD and 6 in the DD group had no relapse. The number of total relapses/year in the SD and DD group were 19 for 12 patients and 8 for 5 patients respectively ( $p < 0.02$ ).

In conclusion, daily single-dose prednisolone therapy in childhood nephrotic syndrome can be effective for induction of remission and is tolerated well by patients but increases the relapse rate significantly.

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**Keywords:** Prednisolone, single daily dose, nephrotic syndrome, relapse.

## INTRODUCTION

Prednisolone is effective in the treatment of minimal change nephrotic syndrome and represents the mainstay of current therapy.<sup>1-3</sup> Most reference sources currently recommend initial therapy by prednisolone 60 mg/m<sup>2</sup> or 2 mg/kg daily in divided doses for 4 weeks.<sup>1,3-5</sup> Although it is usually effective for induction of remission, the major problem is the tendency to relapse. Recent data suggest relapse rates of 76 to 97% and about 50% in the form of frequent relapses.<sup>6</sup> There are no clinical predictors of the subsequent relapse rate just after the initial remission,<sup>7</sup> but in a recent study, young age and a low serum level of total protein at the time of diagnosis were the only risk factors for relapse.<sup>8</sup> The number of relapses within the first 6 months of presentation is highly predictive of the subsequent course.<sup>9</sup>

There is little information about single dose therapy, especially considering the relapse rate. This study was undertaken to compare the remission and relapse rates of divided- and single-dose prednisolone therapy.

## PATIENTS AND METHODS

In this prospective study (from 1992-1994) a total of 42 consecutive children with age ranging from 15 months to 13 years (mean: 5.65 years), admitted in Shiraz University Hospitals with their first attack of documented primary nephrotic syndrome were selected. They were randomly divided in 2 groups based on the order of admission.

The mean age of patients in the SD group was 5.53 years compared to 5.76 years in the DD group. Male to female ratio was 0.63 (in SD: 0.9 and in DD: 0.46,  $p = 0.324$ ). After excluding the steroid resistant group, this ratio was 0.55 and 0.57, respectively.

Gross hematuria was present in 17.6% of SD and 26.3% of the DD group ( $p=0.695$ ). Systolic and diastolic hypertension at the time of admission was detected in 35.2% and 23.2% in SD and 26.3% and 26.3% in the DD group, respectively ( $p = 0.82$ ). No statistically significant difference was observed considering history, physical examination or laboratory findings between the two groups upon admission. One patient in each group had an initial serum creatinine level of 1.1 mg/100 mL while in all other cases it was less than 1 mg/100 mL.

One group was administered prednisolone (2 mg/kg/day, maximum 60 mg) divided in 3 doses (DD), and the second group was given the same daily dose, but as a single dose (SD) each morning, for 4 weeks. After 4 weeks of prednisolone therapy in both groups, irrespective of the response, the drug was changed to 2 mg/kg as a single dose every other day for 4 weeks and with half of this dose for the third month. In patients who were in remission, prednisolone was discontinued at the end of the third month.

Patients with secondary nephrotic syndrome, renal failure

or severe hypertension were not included in this study.

After discharge from the hospital the patients were visited in the nephrology clinic at short intervals and urine was checked for protein and blood by tape test.

Two months after starting prednisolone therapy, serum albumin, triglyceride, cholesterol, blood sugar and erythrocyte sedimentation rate (ESR) were checked and all patients were visited by an ophthalmologist for evaluation of prednisolone side effects.

During the follow-up, 6 patients were not cooperative and were finally excluded. Of the 36 remaining patients, 17 cases were treated by SD and 19 by DD method.

Relapse of the disease in either group was treated as the initial therapy in that group, but prednisolone dosage was changed to every other day 3 days after disappearance of proteinuria.

Statistical analysis was performed using the chi-square and Fisher exact test.

Definitions used in this article are as follows:

**Primary nephrotic syndrome:** Proteinuria >50 mg/kg/day, ESR >20 mm/hour, serum albumin <3 g/100 mL, edema with or without hyperlipidemia, but with no identifiable cause.

**Remission:** Urine free of protein for 5 days and disappearance of edema.

**Relapse:** Reappearance of proteinuria (>2+) for 3 consecutive days.

**Steroid resistant:** No remission after 8 weeks of prednisolone therapy.

**Steroid dependent:** Relapse of nephrotic syndrome during tapering or up to 2 weeks of discontinuation of prednisolone therapy, repeated in 2 consecutive courses of treatment.

**Infrequent relapses:** <2 relapses/6 months.

**Frequent relapses:** >2 relapses during 6 months or >3 relapses per one year.

## RESULTS

The pattern of prednisolone response is shown in Table I with no significant difference in the two groups. Duration of prednisolone therapy before remission was 14.3 days (range 8-28 days) in the SD and 13.8 days (range 10-26 days) in the DD group.

All steroid responsive patients, while in remission (2 months after starting prednisolone therapy) had normal serum albumin, cholesterol, triglyceride, creatinine, blood urea nitrogen, sugar and ESR values.

Table I. Pattern of prednisolone response in 2 groups of nephrotic children.

Study group	Prednisolone response no. (%)				
	CR with NR	IR	FR	SDP	SR
SD	2 (11.76)	7 (41.17)	3 (17.46)	2 (11.76)	3 (17.64)
DD	6 (31.57)	3 (15.78)	0	2 (10.52)	8 (42.1)

CR: Complete remission

DD: Divided doses

IR: Infrequent relapse

NR: No relapse

SD: Single dose

SDP: Steroid dependent

SR: Steroid resistant

FR: Frequent relapse

Table II. Number of relapses in 2 groups of children with nephrotic syndrome.

Study group	First year relapses		Total relapses in one year	Total steroid responsive cases who relapsed (%)
	First 6 months	Second 6 months		
SD	8	11	19	12 (85.7)
DD	4	4	8	5 (45.4)

DD: Divided doses

SD: single dose

Prednisolone side effects observed in both groups in order of decreasing frequency were: cushingoid facial appearance (100%), polyphagia (72%), hypertension (41%), hirsutism (22%) and heart-burn (11%) with no statistically significant difference.

Only one patient (in the DD group) developed cataract. Mean height growth in the SD group was 7.31 centimeters/year, compared to 6.62 centimeters in the other group. A total of 23 episodes of infection were detected in the SD and 26 episodes in the DD group. About 75% of the infections were limited to the upper respiratory tract, but chickenpox (3 patients) and urinary tract infection (2 patients) were only detected in the DD group.

All patients were followed for at least 12 months and the number of relapses are shown in Table II with a statistically significant difference ( $p < 0.02$ ). The subsequent relapse rate in each patient with first relapse was 1.6 in both groups during the first year of follow-up.

The time interval between starting prednisolone and disappearance of proteinuria for the first relapse was 13.2 days (range 10-30 days) in SD and 15 days (range 14-30 days) in the other group.

In 11 patients (30.5%) who remained steroid-resistant, hypertension was detected in 83% and all of them had hematuria (67% gross) at the time of admission. The mean age of these patients was 5.62 years in the SD and 5.81 years in the DD group.

No mortality occurred during one year of follow-up.

## DISCUSSION

Despite the fact that prednisolone is the drug of choice for treatment of idiopathic nephrotic syndrome in children, <sup>5,7</sup> specific pharmacokinetic studies to define the duration of its action have not been possible, because the mechanism of action in this disease is not definitely known.<sup>7,10</sup>

We found that single-dose daily administered prednisolone therapy is effective for the initial management of idiopathic nephrotic syndrome in children. All steroid resistant patients in the SD group were proven to be resistant to the other potent immune-suppressive drugs later on, so they were expected to be steroid resistant irrespective of the mode of prednisolone therapy. In analysis of 22 patients previously reported, about 77% were responsive to single daily dose prednisolone therapy, but in the absence of a control group they could not compare the side effects or relapse rate by this method of therapy.<sup>10</sup>

Our observation that a single daily dose of prednisolone is enough to induce remission in nephrotic patients would not have been predicted on the basis of values for plasma half-life which is about 2 hours and are not different in nephrotic children compared to other patient groups.<sup>11</sup>

The mean response time at disease onset (14.3 days) and that for treatment of first relapse (13.2 days) compare favorably to those previously reported for divided-dose prednisone regimens. The International Study of Kidney Disease in Children reported a mean response time at disease onset of 13.3 days<sup>12</sup> and for treatment of relapse 11.4 days.<sup>13</sup>

## Single-Dose Prednisolone in Primary Nephrotic Syndrome

In steroid-responsive children, relapse was observed in 85.7% of 14 patients in the SD and 45.4% of 11 patients in the DD group, respectively, which is statistically significant, although the subsequent relapse rate per each patient with the first relapse was equal in both groups. We can conclude that single daily dose prednisolone therapy can be effective for induction of remission in idiopathic nephrosis of childhood, but relapse rates will significantly increase with this method.

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