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Older boys benefit from higher initial prednisolone therapy for nephrotic syndrome

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Older boys benefit from higher initial prednisolone therapy for nephrotic syndrome.

Background. A long course of the initial prednisolone therapy has been shown to be more effective than standard-course therapy in reducing relapse rates in children with idiopathic nephrotic syndrome, but it is commonly accompanied by corticosteroid toxicities. There has been no study on prednisolone dosage for the effective treatment of nephrotic syndrome.

Methods. Sixty-eight children (42 boys and 26 girls) with an initial attack of nephrotic syndrome were randomly allocated into two different long-course treatment groups. Patients in Group 1 received a daily prednisolone dose of 60 mg/m^2 for six weeks, followed by an alternate-day dose of 40 mg/m^2 for six weeks. Patients in Group 2 had a daily dose of 40 mg/m^2 instead of 60 mg/m^2.

Results. Four children in each group did not respond within six weeks. Group 1 was associated with a significantly earlier response but more frequent corticosteroid toxicities than Group 2. Boys in Group 1 had a higher rate of sustained remission than boys in Group 2 ($P = 0.0073$), especially boys four years old or more ($P = 0.0027$), but girls did not show a significant difference ($P = 0.863$). Boys four years old or more in Group 1 had a course of frequent relapsing less often than those in Group 2 (2 of 13 vs. 6 of 8, $P = 0.0075$).

Conclusion. These findings indicate that efficient prednisolone doses may vary between sexes and ages, and that a higher initial prednisolone therapy may be of greater benefit to older boys.

Approximately 80% of idiopathic nephrotic syndrome in childhood is ascribed to minimal-change nephrotic syndrome [1, 2]. Almost the same percentage of children with idiopathic nephrotic syndrome respond to corticosteroid therapy [3]. Corticosteroid responsiveness is known as a better predictor of a good prognosis of renal function than renal histology in children with idiopathic nephrotic syndrome [4]. Corticosteroids are therefore administered to these nephrotic children without histologic examination whose proteinuria usually disappears within four weeks after initiation of corticosteroid therapy [1]. However, these steroid-responsive nephrotic children often have relapses and develop corticosteroid toxicities. Therefore, it is desirable to determine a more ideal corticosteroid dosage that is effective enough to prevent relapses and also have the least amount of toxicity. To date, control studies on prednisolone dosages are limited, so the most efficient prednisolone regimens are yet to be established.

The prednisolone regimen proposed by the International Study of Kidney Disease in Children (ISKDC; daily prednisolone of 60 mg/m^2 or 2 mg/kg for four weeks followed by alternate-day prednisolone of 40 mg/m^2 for four weeks) is the standard regimen popularly used as an initial prednisolone therapy for children with newly onset idiopathic nephrotic syndrome [2]. Recent controlled studies have demonstrated that long-course prednisolone regimens had a longer sustained remission with fewer children having frequent relapses than with the standard

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Key words: corticosteroid toxicity, nephrotoxicity, idiopathic nephrotic syndrome, gender and ESRD, proteinuria, frequent relapse of nephrotic syndrome, dose of prednisolone.

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regimen [5–8]. However, long-course prednisolone regimens have been more frequently associated with corticosteroid toxicities than the standard-course regimen [7].

Whether a standard daily dose of 60 mg/m^2 is required for sufficient therapeutic efficacy remains to be studied. On this point, it should be mentioned that adults with minimal-change nephrotic syndrome are usually treated with lower doses of prednisolone (1 mg/kg/day [9] or 30 to 60 mg/day [10, 11]) than children, and they have a comparable, good response to corticosteroids. These findings suggest that lower daily doses of prednisolone may also be effective for children with idiopathic nephrotic syndrome and are associated with less corticosteroid toxicity. Some authors also observed that nephrotic children of young age at the onset of the disease or of male sex frequently have relapses [12, 13]. These findings also raise the possibility that the most efficient dose for management of the disease may vary considerably with sex and age.

We investigated, in a multicenter randomized controlled study, whether the daily dose of prednisolone in the intensive long-course regimen (60 mg/m^2 for six weeks) used in Ehrich and Brodehl's study could be lowered to 40 mg/m^2/day with sufficient effectiveness for the management of idiopathic nephrotic syndrome in children [7]. We also analyzed differences in the efficacy of the two regimens between sexes and ages.

METHODS

The subjects comprised 42 boys and 26 girls, aged 1.5 to 14.4 years, who had had an initial attack of idiopathic nephrotic syndrome between December 93 and August 96. The study protocol was in accordance with the standards of the ethics committee at each center, and all parents of these patients gave informed consent. Children were allocated at random into two groups. Group 1 received a daily dose of 60 mg/m^2 in three divided doses (maximum dose 80 mg/day) for six weeks, followed by the alternate-day, single morning dose of 40 mg/m^2 (maximum dose 60 mg/day) for six weeks. Children in Group 2 were treated with a daily dose of 40 mg/m^2 in three divided doses (maximum dose 60 mg/day) for six weeks, followed by an alternate-day, single morning dose of 40 mg/m^2 (maximum dose 60 mg/day) for six weeks. Patients and their parents were informed about the adverse side effects of corticosteroid treatment and were advised to restrict their salt intake to below 1 g/day until remission, and between 1 and 5 g/day together with avoidance of caloric overintake after remission, until the completion of the prednisolone therapy. Remission was defined as the disappearance of proteinuria [urinary protein <4 mg/h/m^2 or albusticks $(-)$ or $(\pm)$] for at least three consecutive days [14, 15]. Patients were admitted to the hospital during treatment, at least while they were given a daily prednisolone dose. Corticosteroid toxicity symptoms, including moon face, obesity, glaucoma, cataracts, hypertension, striae, psychological disturbance, hirsutism, steroid acne, and others, were regularly checked during and at completion of corticosteroid administration.

Relapse was diagnosed when proteinuria of 2+ or more continued for three consecutive days. Patients of both groups who relapsed after two months or more following completion of the previous prednisolone course were treated with the moderate regimen. Relapses within the first two months after completion of the previous prednisolone treatment were treated with the long-term prednisolone regimen, since children with early relapses tend to have frequent relapses [5]. The long-term prednisolone regimen comprised a daily dose of 40 mg/m^2 given for four weeks, tapering by 25% every two weeks with a total daily course of 12 weeks, followed by the alternate day dose of 40 mg/m^2 for six months with a tapering dose over another three months. In the present study, frequent relapsers were defined as those who had relapses two or more times consecutively within the first two months after completion of the previous prednisolone therapy, and steroid dependence was defined as those who had relapses two or more times consecutively during the prednisolone treatment or within the first two weeks after completion of the previous prednisolone therapy [5], since patients were treated longer in the present study than in that of the ISKDC [2, 15]. All patients except one completed a two-year follow-up period from the end of the initial treatment. One girl in Group 2 became a frequent relapser and could not be followed up subsequently because she moved, receiving medical care in another place.

Clinical characteristics at onset, the days required for remission with the initial prednisolone regimen, and the rates of sustained remission (defined as having no relapse) after completion of initial daily prednisolone course were compared between the two groups. Corticosteroid toxicities were compared between the two groups according to the incidence of individual toxicity symptoms and also the total number of toxicities that developed. Differences in effectiveness between the two regimens were also analyzed for each sex and then for two subgroups in boys (<4 years and ≥ 4 years) [13]. The statistical methods used were the unpaired *t*-test, chi-square test, Fisher's exact probability test, the Mann–Whitney test, and the Kaplan–Meier life table method using a log rank test. A two-tailed *P* value of less than 0.05 was taken as the level of significance.

RESULTS

There were no differences in clinical characteristics at onset of the nephrotic syndrome between groups 1 and 2, as shown in Table 1.

The same percentage of children (30 of the 34 chil-

Table 1. Clinical characteristics of the patients at onset of the nephrotic syndrome in Groups 1 and 2

	Group 1	Group 2
Number of patients	34	34
Male/female	21/13	21/13
Age *years*	6.4 ± 3.4	7.1 ± 4.0
Serum albumin *g/dL* (normal, 4.6 ± 0.7 g/dL)	1.8 ± 0.6	1.7 ± 0.5
Serum total cholesterol *mg/dL* (normal, 170 ± 25 mg/dL)	472 ± 133	474 ± 130

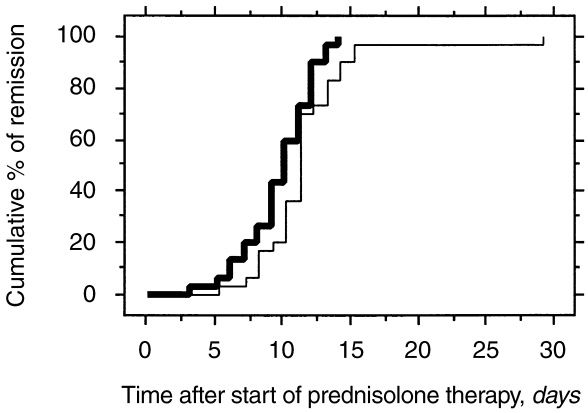

Fig. 1. Cumulative percentage of patients with remission of nephrotic syndrome on days after beginning prednisolone therapy. Data are presented for 60 of 68 children who responded to steroids. The days required for remission were significantly longer in Group 2 (thin line, $N = 30$) than in Group 1 (thick line, $N = 30$). $P < 0.05$, log rank test.

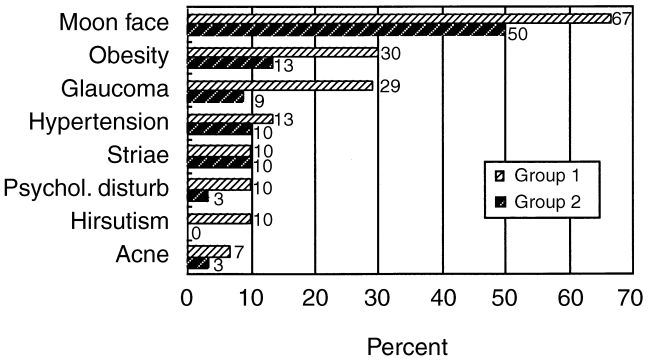

Fig. 2. Incidence of corticosteroid toxicities between Groups 1 (▨) and 2 (▨) during the initial prednisolone therapy in 60 patients who responded to the prednisolone therapy.

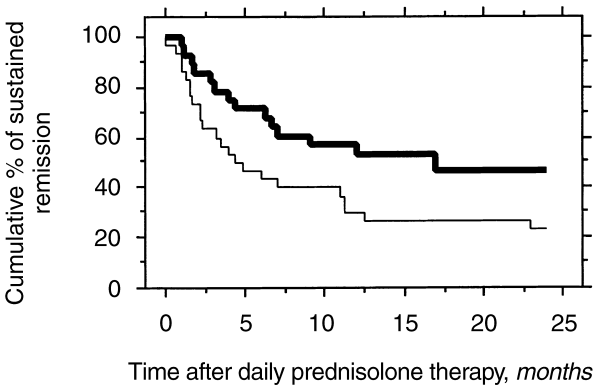

Fig. 3. Cumulative rate of the children with sustained remission two years after completion of the initial daily prednisolone in Groups 1 (thick line; $N = 30$) and 2 (thin line; $N = 30$). Group 1 had a higher cumulative rate of children with sustained remission than Group 2 ($P = 0.046$, log rank test).

dren) in the two groups responded to the prednisolone course within six weeks. Four children in Group 1 showed partial response, whereas two of the four children in Group 2 showed no response, and the others had a partial response.

The days required for remission were significantly longer in Group 2 than in Group 1 ($P < 0.05$, log rank test), with an average of 11.4 ± 4.0 versus 9.6 ± 2.6 days (SD), respectively (Fig. 1). There was no difference in the days required for remission between sexes or the two age subgroups (<4 years and ≥4 years) at onset of the disease (data not shown).

In 2 of the 34 children in Group 1, daily prednisolone was withdrawn in five weeks because of hypertension or elevated serum LDH levels. These two children were treated following the protocol except for the initial daily prednisolone course. Both relapsed, one in 9 months and the other at 15 months after completion of the initial daily prednisolone course and did not have frequent relapses. Figure 2 shows the incidence of corticosteroid toxicities during the initial prednisolone regimens in 60 patients who responded to prednisolone. Children in Group 1 were accompanied by a higher incidence of glaucoma (intraocular pressure >20 mm Hg) than those in Group 2 ($P < 0.05$, chi-square test). Although there was no significant difference in the incidence of each of the other corticosteroid toxicities between the two regimens, the total number of toxicities appearing in Group 1 was greater than in Group 2 (2.0 ± 1.2 vs. 1.1 ± 1.1, $P < 0.01$, unpaired *t*-test). The side effects were usually transient and did not require medical intervention. No patients developed cataracts in either group.

Group 1 had a higher cumulative rate of children with sustained remission than Group 2 during the two years after completion of the initial daily prednisolone course ($P = 0.046$, log rank test; Fig. 3). An analysis between the two treatment groups in each sex revealed a definite difference with a high level of significance in boys but not in girls: Boys sustained remission more frequently in Group 1 than in Group 2 ($P = 0.007$, log rank test), but the two treatment groups of girls showed no difference ($P = 0.863$, log rank test; Fig. 4). Further analysis between the two treatment groups in each age subgroup of the 36 boys showed a definite difference with a high

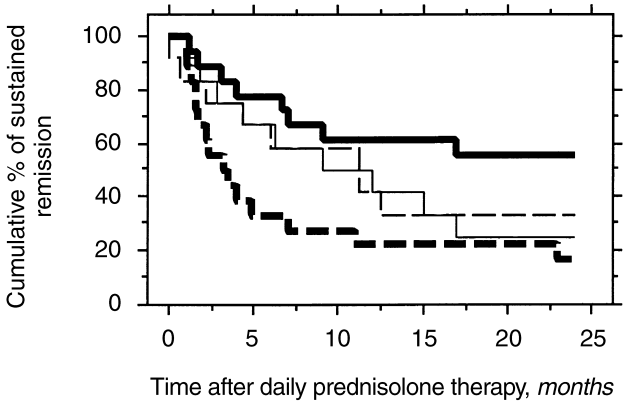

Fig. 4. Comparison of the cumulative rate of the children with sustained remission between Groups 1 and 2 in each subgroup of boys and girls two years after completion of the initial daily prednisolone. A definite difference was observed in boys ($P = 0.0073$) between the two regimens, but not in girls ($P = 0.863$). Symbols are: (solid thin line) Group 1 girls, $N = 12$; (dashed thin line) Group 2 girls, $N = 12$; (solid thick line) Group 1 boys, $N = 18$; (dashed thick line) Group 2 boys, $N = 12$.

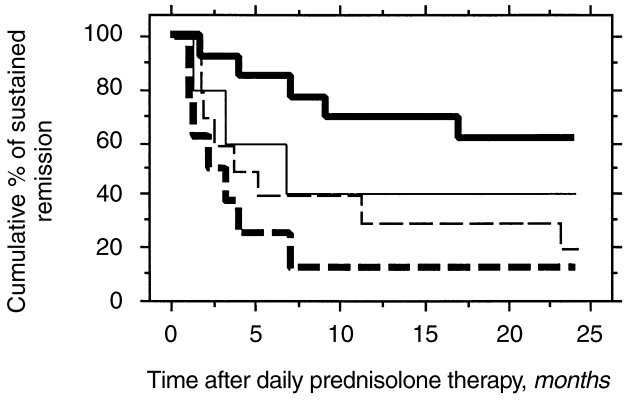

Fig. 5. Cumulative rate of the boys with sustained remission between Groups 1 and 2 in each subgroup of younger (<4 years old) and older (≥4 years old) boys two years after completion of the initial daily prednisolone. A definite significant difference was found in older boys ($P = 0.0027$), but not in younger boys ($P = 0.578$). Symbols are: (solid thin line) Group 1, age <4 years old, $N = 5$; (dashed thin line) Group 2, age <4 years old, $N = 10$; (solid thick line) Group 1, age ≥4 years old, $N = 13$; (dashed thick line) Group 2, age ≥4 years old, $N = 8$.

level of significance in older boys, but not in younger boys. Boys aged four years or more had a higher rate of sustained remission in Group 1 than in Group 2 ($P = 0.003$, log rank test), whereas comparing the two prednisolone treatment groups of boys under four years revealed no different rate of sustained remission ($P = 0.578$, log rank test; Fig. 5).

Boys in Group 1 sustained remission more frequently than boys in Group 2 at six months after completion of the initial daily prednisolone course (12 of 18 vs. 5 of 18, respectively, $P = 0.044$, Fisher's test), while girls in Groups 1 and 2 did not show the difference (8 of 12 vs. 7 of 12, respectively, $P > 0.999$, Fisher's test; Table 2). Boys aged four years or more in Group 1 had a much higher rate of sustained remission than those in Group 2 (10 of 13 vs. 1 of 8, respectively, $P = 0.0075$, log rank test), while boys less than four years of age did not show a difference between the two prednisolone dose groups ($P > 0.999$; Table 2).

Table 2. Incidence of six-month remissions between Groups 1 and 2 in sex subgroups and boys aged <4 and ≥4 years

	Sex		Boys	
	Boys	Girls	<4 years	≥4 years
Group 1[a]	12/18[b]	8/12	2/5	10/13[c]
Group 2[a]	5/18	7/12	4/10	1/8

[a] Number of patients who remained in remission at six months after cessation of the initial daily prednisolone course/number of patients who responded to steroids
[b] $P = 0.044$ vs. Group 2 (Fisher's probability test)
[c] $P = 0.0075$ vs. Group 2 (Fisher's probability test)

Table 3. Incidence of patients with frequent relapses in the total subjects who responded to steroids and in boys aged four years or older between Groups 1 and 2

	Total subjects		Boys ≥ 4 years	
	Group 1	Group 2	Group 1	Group 2
Number of patients	30	30	13	8
Patients with frequent relapses[a]	9	13	2[b]	6

[a] Frequent relapsers or steroid-dependent patients
[b] $P = 0.018$ vs. Group 2 (Fisher's probability test)

Nine (32%) of Group 1 and 13 (43%) of Group 2 patients had frequent relapses (frequent relapsers or steroid-dependent patients) during the follow-up period of 33.0 ± 8.1 months (mean ± SD, $P = 0.544$, chi-square test; Table 3). Boys aged four years or more in Group 1 less often had frequent relapses than those in Group 2 (2 of 13 vs. 6 of 8, respectively, $P = 0.018$, Fisher's test; Table 3).

DISCUSSION

The Group 2 regimen in the present study seemed effective in resolving idiopathic nephrotic syndrome in children, since the Group 2 regimen induced remission in the same proportion of children as the Group 1 regimen. The lower daily dose of prednisolone in Group 2, however, required a statistically significantly longer time than the standard daily dose of prednisolone in Group 1 for remission of the disease. The previous study by Imbasciati et al observed that more intensive initial immunosuppressive therapy using pulse methylprednisolone doses required less time until remission than the standard oral prednisolone doses [16]. On the other hand, adults with minimal change nephrotic syndrome, who are usu-

ally treated with a lower daily dose of prednisolone per body mass than children, require a longer time than children to attain remission with prednisolone therapy [10, 11]. These findings indicate that the days required for remission may depend on the intensity of the immunosuppressive therapy.

The percentage of children with sustained remission after the initial treatment in Group 2 was approximately one half that of Group 1. These results were almost similar to those in the Ehrich and Brodehl study, which compared a standard-course regimen (the standard regimen in ISKDC) and a long-course regimen (the same as the Group 1 regimen in the present study) [7]. For maintaining remission, the Group 2 regimen in the present study had comparable efficacy to the standard-course regimen in Ehrich and Brodehl's study. This may be explained by the same cumulative daily doses of prednisolone in the two regimens: 40 mg/m^2/day for six weeks vs. 60 mg/m^2/day for four weeks, respectively.

It should be noted that the advantage of the Group 1 regimen over the Group 2 regimen in sustaining remission was remarkable in boys in the present study, whereas the advantage was not observed in girls. It is also striking that the Group 1 regimen especially benefited boys aged four years or more at onset for sustaining remission more than the Group 2 regimen did. Boys, especially older boys, in Group 1 less often had relapses within six months after the initial treatment than those in Group 2. Relapses in this period have been found to be a predictor of subsequent frequent relapses [5, 15]. A smaller portion of older boys in Group 1 had a course of frequent relapsing than in Group 2. The difference in effectiveness between the two prednisolone regimens was, thus, most striking with a high level of significance in older boys. Previous studies of ISKDC found no difference in the incidence of frequent relapsers between sexes or age levels at onset of the disease [14], whereas others found a higher incidence of frequent relapsers in boys or younger children [12, 13]. Findings in the present study indicate that the influence of sex and age at onset of the disease in the incidence of frequent relapses may depend on prednisolone dosage in the initial therapy.

Adverse side effects were more frequent in Group 1 than in Group 2, although these side effects were mostly mild and transient. It should be noted that striae, one of the most significant, was only rarely observed in either group. The incidence of obesity and striae in Group 1 in the present study was approximately half of that in patients treated with the same regimen in Ehrich and Brodehl's study [7]. Differences in the genetic and sociocultural backgrounds of patients involved in the two studies possibly may explain the different incidence of these side effects. It seems, in addition, likely that recommendation to avoid caloric overintake was effective in reducing the incidence of these side effects in the present study.

There are several prednisolone regimens with varying doses for treatment of children with initial and relapsing nephrotic syndrome [5, 6, 8, 14]. The treatment of the idiopathic nephrotic syndrome has a threefold objective: (*1*) quick induction of remission of the disease, (*2*) prevention of relapse, and (*3*) avoidance of drug side effects [17]. The Group 2 regimen in the present study was actually effective in inducing remission, but required a longer time until remission with a lower rate of sustained remission in comparison to the Group 1 regimen. On the other hand, the Group 1 regimen was accompanied by more corticosteroid toxicities than the Group 2 regimen. Some authors prefer intensive regimens because of less subsequent relapses, while others choose a standard regimen because of less corticosteroid toxicities. Regimens for frequent relapses such as immunosuppressive agents as well as prednisolone have attracted much attention and have been investigated to reduce relapsing as well as adverse side effects [16, 18–24]. The present study indicates that prednisolone dosage for initial onset nephrotic syndrome also affects the subsequent relapse rate, and that intensive initial prednisolone therapy appears to be of greater benefit in older boys.

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