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The treatment of relapsing primary nephrotic syndrome in children

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Abstract: Objective: To explore better therapy and reduce the rate of re-relapse of primary nephritic syndrome in children who had been treated with corticosteroids but relapsed. Methods: Eighty relapsers were enrolled from Jan. 1994 to Apr. 2000, who were randomly divided into two groups. The treatment group (n=39) had been treated with tripterysium glucosides for three months, with the control group (n=41) members were treated with cyclophosphmide (CTX) by intermission intravenous pulse, with total dose of CTX not being more than 150 mg/kg. Prednisone, meanwhile, was given to both groups. The total treatment period of prednisone was prolonged by 12−18 months. Results: After following up for 3−7 years, the re-relapse rates of both groups were observed. The re-relapse rate of the treatment group was 28.2% to 29.3% in the CTX-controlled group. The re-relapse rates between two groups were almost similar, and with no observed significant difference (P>0.05). The side effect of tripterysium glucosides was less than that of CTX. Conclusion: For the treatment of relapsing nephritic syndrome in children, the combination of tripterysium glucosides and prolonged corticosteroid therapy is as effective as the regimen of CTX plus prolonged use of prednisone.

Key words: Primary nephrotic syndrome, Relapse, Tripterysium glucosides, Prednisone
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INTRODUCTION

Primary nephrotic syndrome is the most common renal disease in children. Most children with nephrotic syndrome respond to corticosteroids (Hodson *et al*., 2000). However, 71.2% of children experience a relapsing course with recurrent episodes of edema and proteinuria within two years after 6~9 months treatment of corticosteroids (Yang, 2000). The relapse of primary nephrotic syndrome in children after treatment and remission is a common phenomenon. In order to reduce the re-relapse, from January 1994 to April 2000 we adopted different schemes to research treatment. Tripterysium glucosides was produced by abstracting from the wood core part of tripterysium, a Chinese medicine celastraceace plant. It has been proved that tripterysium glucosides have anti-inflammatory and immunosuppressive effects. Tripterysium glucosides may have effect by suppressing the production of interleukin-2 and its receptor effect, inducing activated lymphocytes apoptosis, interfering with the lymphocytes cell cycle, decreasing lymphocytes proliferation, and suppressing the activation of nuclear factor-kappa B (Liu *et al*., 1999; Qiu and Kao, 2003). We compared the effects of tripterysium glucosides plus prolonged use of prednisone with that of CTX plus prolonged use of prednisone. Now we report the outcome as follows.

PATIENTS AND METHODS

Eighty cases in the research met the criteria of the Association Group of Science and Research of the National Children's Nephropathy in 1981. The so called relapse means: the proteinuria was changed from negative to positive, there were signs of ++ for three times in one week, or the amount of protenuria

is equal to or greater than 50 mg/kg in 24 h. The frequent relapse means: the times of relapse in half a year are equal to or more than 2, or the times of relapse in one year are equal to or greater than 3. In clinical practice, we often classify primary nephrotic syndrome into clinical simple type and nephritic type. The clinical simple type means that the patients have four features including proteinuria (urinary protein excretion greater than 50 mg/(kg·d)), hyperlipidemia, hypoalbuminemia and edema. The nephritic type means that the patients have one of the follow situations, besides the above four features: (1) hematuria (more than 10 red blood cells per high power field in centrifuged urine three times within two weeks); (2) hypertention (except for the influence of prednisone); (3) increased serum levels of creatinine and urea nitrogen (except for hypovolemia); (4) hypocomplementemia 3.

The patients were randomly divided into two groups. One group is the treatment group. In this group, there were 39 cases: male 31 cases, female 8 cases. The age was from 1 to 13 years old. The mean age was 4.99 years old. There were 35 cases of the clinical simple type, 4 cases of the nephritic type; 29 cases of non-frequent relapse type, and 10 cases of frequent relapse type. The other group was the control group. In this group, there were 41 cases: male 33 cases, female 8 cases. The age was from 1.5 to 12 years old. The mean age was about 4.37 years old. There were 32 cases of the clinical simple type, 9 cases of the nephritic type; 23 cases of non-frequent relapse type, and 18 cases of frequent relapse type (Table 1).

Fifteen cases of frequent relapse were renal biopsied, in which 7 cases were included in the treatment group, 8 cases in the control group. The histopathologic changes showed that there were 6 cases of minimal change, 4 cases of mesangial proliferative glomerulonephritis from minor to medium level, one case of IgA nephropathy, 3 cases of IgM nephropathy, one case of focal segmental glomerulosclerosis.

Sufficient dose (1.5–2.0 mg/(kg·d), not to exceed 60 mg/d) of prednisone was given to both groups. When remission occurred within 4 to 8 weeks of therapy, the dose of prednisone was decreased. At the first time, one third of total dose was deducted, and it was given in each morning for 3–4 weeks. Then 5 mg was deducted every other day every two weeks, and the dose of prednisone was gradually changed to alternate-day doses in the morning. About 2–3 months were needed in this period. After the above period, the dose of prednisone was about 0.5–1.0 mg/kg every other day, which was given in 6 months or longer period of time. The total treatment period was about 12–18 months.

Tripterysium glucosides were added in the treatment group, 1 mg/kg each day. The total dose each day was not be over 30 mg, which was given orally 2 or 3 times. The total treatment period was about 3 months. Tripterysium glucosides were used for 10 cases in the initial treatment period, for 29 cases in the last 3 months before completion of the prednisone treatment when two kinds of medicines were simultaneously not used anymore.

The dose of prednisone for the control group was the same as that of the treatment group, and cyclophosphamide (CTX) was applied by intermission intravenous pulse, at dose 10 mg/kg each day, with 0.9% normal saline being added in the vein injection given for two days as treatment and repeated each 2–4 weeks. About 7 treatment periods in average were needed, with the total dose of CTX not being more than 150 mg/kg within 3–6 months.

Comparisons between the two groups were analyzed. Statistical analysis was performed using χ^2-test and Fisher-exact probabilities. Differences were considered significant at $P<0.05$.

RESULTS

The relapse of both groups: after following up for 3–7 years, mean of about 4.9 years. There were 11 relapse cases (about 28.2% re-relapse rate) in the

Table 1 Clinical characteristics of the two groups

Groups	Cases	Male/female	Mean age (year)	Clinical simple type	Nephritic type	Non-frequent relapse	Frequent relapse	Renal biopsy
Tripterysium group	39	31/8	4.9	35	4	29	10	7
CTX group	41	33/8	4.4	32	9	23	18	8
Total	80			67	13	52	28	15

treatment group, in which there were 7 cases of non-frequent relapse, 4 cases of frequent relapse. There were 12 relapse cases (about 29.3% re-relapse rate) in the control group, in which there were 7 cases of non-frequent relapse, 5 cases of frequent relapse. The re-relapse rates between the two groups were almost similar, with no significant difference observed (P>0.05) (Table 2).

The numbers of children who relapsed 6 months after the end of therapy comprised 3 cases in the treatment group, one case in the CTX group. By 12 months there were 3 relapse cases in the treatment group, 2 cases in the CTX group. By 24 months there were 3 relapse cases in the treatment group, 4 cases in the CTX group. There were 2 cases in the treatment group who relapsed after ceasing therapy 2~4 years, 5 cases in the CTX group (Table 3).

Regarding the side effects of the medicine: there was one case rising GTP in the treatment group, one case of transient leukocytopenia. They were all back to normal after stopping the medicine. As for the control group, there was one case of rising of GTP, 3 cases of transient leukocytopenia, 11 cases of alopecia to different extent, 6 cases of the reaction of gastrointestinal tract. The above situation was changed to normal after stopping the medicine. The long-term side effect should be observed during further follow up.

DISCUSSION

The relapse of primary nephrotic syndrome in children may result in the change of histopathologic type, which would cause difficulty in the treatment, and even affect children's future (Yap *et al.*, 2001). Many factors may cause the relapse of primary nephrotic syndrome, including too short steroid treatment period, rapid tapering off the dose of prednisone, infections, etc. The most important factor is too short prednisone treatment period, so we adopted prolonged prednisone treatment plus tripterysium glucosides therapy. The prolonged period during which 0.5~1.0 mg/kg prednisone was given on alternate days for about six months or longer. This therapy strengthened the treatment effect of prednisone, but the adverse effect of prednisone did not increase. Some patients had tripterysium glucosides added to their medication for three months during the initial prednisone treatment period, but most patients received it during the last three months of prednisone therapy. Children who are steroid sensitive and have relapsing nephrotic syndrome are more likely relapse during withdrawal of prednisone or after the end of prednisone treatment, so during the last three months of predinsone therapy we added tripterysiun glucosides in order to strengthen the treatment and reduce the re-relapse.

Currently it is commonly thought that combining with CTX, especially intravenous intermission pulse treatment can certainly reduce the relapse of the illness (Mendoia and Tune, 1995; Takcda *et al*., 2001). With the same treatment scheme of prednisone, the writers added tripterysium glucosides and compared the results with the CTX-controlled group. After following up for 3~7 years, the re-relapse rate of the treatment group was 28.2%, 29.3% in the CTX-controlled group. The total re-relapse rates between two groups were almost similar, and there were no significant differences (P>0.05). In addition,

Table 2 Comparison of the re-relapse rate of the two groups

Group	Cases	Re-relapse	No-relapse	Re-relapse rate
Tripterysium group	39	11	28	28.2%
CTX group	41	12	29	29.3%
Total	80	23	57	

χ^2=0.011; P>0.05

Table 3 Re-relapse numbers of two groups after the end of therapy by 6, 12, 24 months or longer

Group	Cases	<6 months	6–12 months	12–24 months	2–4 years
Tripterysium group	11	3	3	3	2
CTX group	12	1	2	4	5
Total	23	4	5	7	7

in this study we observed the re-relapse numbers of children who had relapsed by 6, 12, 24 months or longer period after the end of therapy. The result suggested that CTX-controlled patients have more stable long-term remission compared with tripterysium glucosides group.

In this randomized CTX-controlled clinical study, the numbers of two groups were not equivalent because two patients of the treatment group were lost from the follow-up. This study's results suggested that the effect of intermission intravenous pulse CTX plus prednisone on the frequent relapse nephrotic syndrome may be better than that of tripterysium glucosides plus prednisone. Further observation is needed.

In conclusion, for the treatment of relapsing nephrotic syndrome in children, the combination of tripterysium glucosides and prolonged corticosteroid therapy is as effective as a regimen of CTX plus prolonged use of prednisone. The side effect of tripterysium glucosides was less than that of CTX, and worth being further studied and applied.

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