

Effect of Levamisole in Steroid-Dependent Nephrotic Syndrome

Abbas Madani,¹ Seyed-Taher Isfahani,¹ Nahid Rahimzadeh,²
Seyed-Mohammad Fereshtehnejad,³ Rozita Hoseini,⁴
Mastaneh Moghtaderi,⁵ Parvin Mohseni,¹ Nematollah Ataiee¹

¹Division of Pediatric Nephrology, Children Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran

²Division of Pediatric Nephrology, Rasoul-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

³Firoozgar Clinical Research Development Center, Iran University of Medical Sciences, Tehran, Iran

⁴Division of Pediatric Nephrology, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁵Pediatric Nephrology

Keywords. levamisole, steroid, nephrotic syndrome, immunosuppressive agents

Introduction. Childhood idiopathic nephrotic syndrome is characterized by frequent relapsing courses or steroid dependency. Levamisole is a popular drug for treatment of these patients. The purpose of this study was to evaluate levamisole in children with steroid-dependent nephrotic syndrome.

Materials and Methods. We retrospectively studied 304 children with a diagnosis of steroid-dependent nephrotic syndrome or frequently relapsing nephrotic syndrome. The mean age at the time of diagnosis was 4.84 years. Following induction of complete remission with steroid therapy based on the International Study of Kidney Disease in Children's protocol and when they were taking alternative days of steroid, 2.5 mg/kg of levamisole was administered.

Results. The steroid dose was significantly decreased (mean reduction of 0.39 ± 0.46 g to 0.33 ± 0.38 g) after treatment with levamisole ($P < .001$). The number of relapses also significantly decreased (mean reduction of 0.92 ± 0.98 episodes to 1.07 ± 1.20 relapses per year; $P < .001$). The 14.5-month administration of levamisole had a sensitivity of 67.5% and a specificity of 71.9% to reach a dose reduction of more than 50% in steroid therapy. The duration of levamisole treatment was associated with more than 50% reduction in the number of relapses ($P < .001$). A 14.5-month treatment with levamisole had a sensitivity of 62.3% and a specificity of 63.6% to reach a relapse reduction of more than 50%.

Conclusions. Levamisole appears to be effective in prolonging the duration of remission and decreasing the steroid dose in children with steroid-dependent nephrotic syndrome.

IJKD 2010;4:292-6
www.ijkd.org

INTRODUCTION

Idiopathic nephrotic syndrome (NS) is one of the most common glomerular diseases among children, with a benign prognosis, most of which satisfactorily respond to steroid therapy. However, frequent relapses and dependency on steroid therapy are common clinical features of these patients. Prolonged steroid therapy for these children is unavoidable and imposes several complications such as systemic hypertension, obesity, short stature, infection, psychological disturbances, retrolental opacity, and osteoporosis.¹

Different kinds of other medications, such as

cyclophosphamide, cyclosporine, and levamisole, are using to avoid the complications of steroid therapy. It seems that levamisole is a suitable drug for controlling of this syndrome.^{2,3} There are several reports demonstrating significant effects of levamisole in treatment of NS in children, but the number of patients and their follow-up are limited.⁴⁻⁸ Therefore, we aimed to evaluate the effects of levamisole in 304 Iranian patients with a diagnosis of steroid-dependent NS (SDNS) or frequently relapsing NS (FRNS) referred to the Children Medical Center Hospital. We chose levamisole, because several studies showed that

levamisole was an effective steroid-sparing agent in pediatric NS, with less toxicity and it is not expensive.

MATERIALS AND METHODS

Patients

In this retrospective cohort study, 304 children with a diagnosis of SDNS or FRNS treated with levamisole were included. They had had all been referred to the Children Medical Center Hospital, Tehran, Iran between the years 1986 and 2006. Inclusion criteria were age at the onset of disease between 6 months to 16 years; initially being steroid sensitive, being steroid-dependent, or having FRNS; and a follow-up period longer than 6 months. Exclusion criteria were NS secondary to other systemic diseases or syndromes, membranoproliferative glomerulonephritis, and membranous nephropathy, according to the first kidney histology.

Definitions

Nephrotic syndrome was defined as proteinuria equal to or higher than 1 g/m², hypoalbuminemia, edema, and hyperlipidemia. Steroid-sensitive NS was defined as remission within 4 weeks after starting glucocorticoids; steroid-dependency, relapsing during steroid tapering period or within 14 days of its cessation; frequent relapsing, 4 or more relapses annually; levamisole resistance, no response to levamisole after 3 months; remission with levamisole, no relapse during 1 year of treatment with levamisole; and levamisole responder, response to levamisole after 3 months of treatment.

Treatment Protocols Assessment

Initial steroid therapy was begun based on the protocol of the International Study of Kidney Disease in Children; prednisolone, 60 mg/m²/d, up to a maximum dose of 80 mg/d was started and continued for 4 weeks. When urine was free of protein, levamisole was administered in a dose of 2.5 mg/kg every other day and continued with tapering of prednisolone to 0.15 mg/kg every 2 weeks on alternative days. Before starting therapy, informed consent was obtained from the patient and/or parents.

Follow-up assessment of the patients was made in the Pediatric Nephrology Clinic by means of

urinalysis. At the end of 1st month of therapy, cell blood count and platelet count were measured for all of the patients, as well. If levamisole resistance or occurrence of side effects with levamisole were reported, therapy would be stopped. In responders, prednisolone was continued with a dose of 0.3 mg/kg to 0.5 mg/kg for alternate days, accompanying with levamisole.

Cyclophosphamide and cyclosporine were administered separately before treatment with levamisole in some patients. Immunosuppression characteristics of the patients before and after levamisole therapy are shown in Table 1. Kidney biopsy was performed for 108 children.

Statistical Analyses

Values were expressed as mean \pm standard deviation, and the risk was expressed as odds ratio (OR) with 95% confidence interval (CI). In order to examine differences between groups, the chi-square test with Yates continuity correction and the Student *t* test were employed for categorical and parametric quantitative data, respectively. The 1-way analysis of variance and the Kruskal-Wallis test were performed to compare the mean values of different parametric and nonparametric quantitative variables between more than two groups, respectively. In addition, the paired *t* test analysis was performed to compare the differences between steroid dose before and after levamisole treatment. The Spearman correlation was also used to evaluate the relationship between quantitative variables.

To further analysis, receiver operating curve (ROC) analysis was performed to assess the predictability of duration of treatment with levamisole and more than 50% reduction in steroid dose and the number of relapses. Then the area under curve (AUC) of this variable was calculated

Table 1. Immunosuppression Characteristics of Children Before Levamisole Therapy

Immunosuppressive Agent	Patients (%)
Cyclophosphamide	
No	249 (81.9)
Dependent	17 (5.6)
Resistant	38 (12.5)
Cyclosporine	
No	282 (92.8)
Dependent	18 (5.9)
Resistant	4 (1.3)

in each analysis, and the cutoff points were determined in each ROC analysis. The diagnostic values of each cutoff point, including sensitivity and specificity, were also calculated. All *P* values were two-tailed and a *P* value less than .05 was considered significant.

RESULTS

Baseline Characteristics

A total number of 304 children with SDNS were recruited in this study. The patients were 208 boys (68.5%) and 96 girls (31.5%) with a mean age of 4.8 ± 3.1 year at the time of diagnosis (range, 1 to 16 years). Baseline characteristics of the patients are listed in Table 2.

The mean baseline steroid dose and number of relapses per year were 0.74 ± 0.38 g and 2.0 ± 1.2 , respectively. Before the administration of levamisole, 62 children (20.4%) received immunosuppressive treatments, including cyclophosphamide (18.1%) and/or cyclosporine (7.2%), while 242 patients (79.6%) were not administered any immunosuppressive drug before levamisole. In 108 patients, kidney biopsy was performed. The results of histological findings were minimal change lesion in 72 (66.7%), diffuse mesangial proliferation in 19 (17.6%), and focal segmental glomerulosclerosis in 17 (15.7%).

Follow-up Period

After receiving levamisole, the patients were followed up for 6.7 ± 3.9 years (range, 1 to 22 years). The mean time of levamisole therapy was 17.87 ± 11.22 months. The steroid dose was significantly decreased with the mean reduction

of 0.39 ± 0.46 g to reach the mean dose of 0.33 ± 0.38 g after treatment with levamisole ($P < .001$). The number of relapses was also significantly decreased with the mean reduction of 0.92 ± 0.98 episodes to arrive at 1.07 ± 1.20 relapses per year after levamisole therapy ($P < .001$). Follow-up characteristics of the patients are shown in Table 3. There was a significant correlation between duration of levamisole treatment with both dose reduction of steroid ($r = 0.428$, $P < .001$, Figure 1) and reduction of relapses ($r = 0.341$, $P < .001$, Figure 2).

The ROC analysis of the duration of levamisole treatment to reach more than 50% reduction in steroid dose is illustrated in Figure 3 (AUC, 0.734; $P < .001$). A 14.5-month administration of levamisole had a sensitivity of 67.5% and a specificity of 71.9% to reach a dose reduction of more than 50% in steroid therapy. Moreover, the ROC analysis of the duration of levamisole treatment showed to reach a significant level of more than 50% reduction in the number of relapses (AUC, 0.686; $P < .001$; Figure 4). A 14.5-month administration of levamisole had a sensitivity of 62.3% and a specificity of 63.6% to

Table 2. Baseline Characteristics of Patients*

Characteristics	Value
Number of patients	304
Mean age, y	4.84 ± 3.09
Gender	
Boy	208 (68.5)
Girl	96 (31.5)
Pathologic diagnosis	
Minimal change lesion	72 (23.7)
Mesangial glomerulonephritis	19 (6.3)
Focal segmental glomerulosclerosis	17 (5.6)
Not available	196 (64.5)
Mean baseline steroid dose, g	0.74 ± 0.38
Mean baseline episodes of relapse per year	2.02 ± 1.20

*Values in parentheses are percents.

Table 3. Follow-up Characteristics of Patients*

Characteristic	Value
Mean duration of levamisole, mo	17.87 ± 11.22
Mean reduction in steroid dose, g	0.39 ± 0.46
Mean reduction in steroid dose, %	53.24 ± 45.97
Mean reduction in relapse episodes	0.92 ± 0.98
Mean reduction in relapse episodes, %	52.22 ± 49.32
Remission, %	84 (27.6)

*Values in parentheses are percents.

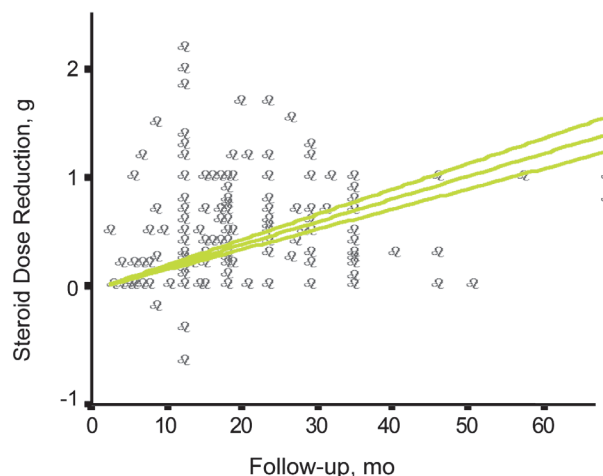


Figure 1. Correlation between duration of treatment with levamisole and reduction in dose of steroid ($r = 0.428$, $P < .001$).

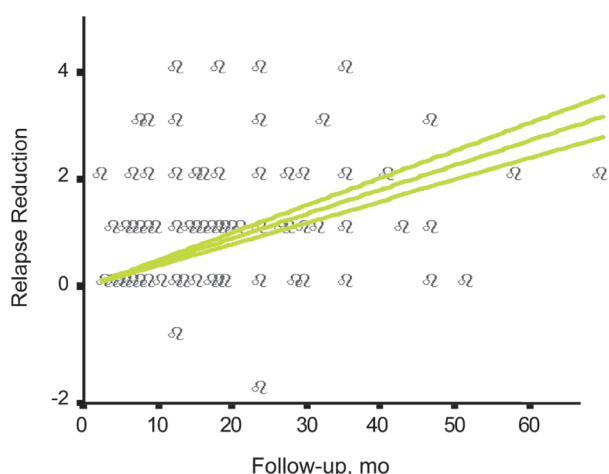


Figure 2. Correlation between duration of treatment with levamisole and reduction in relapse episodes per year ($r = 0.341$, $P < .001$).

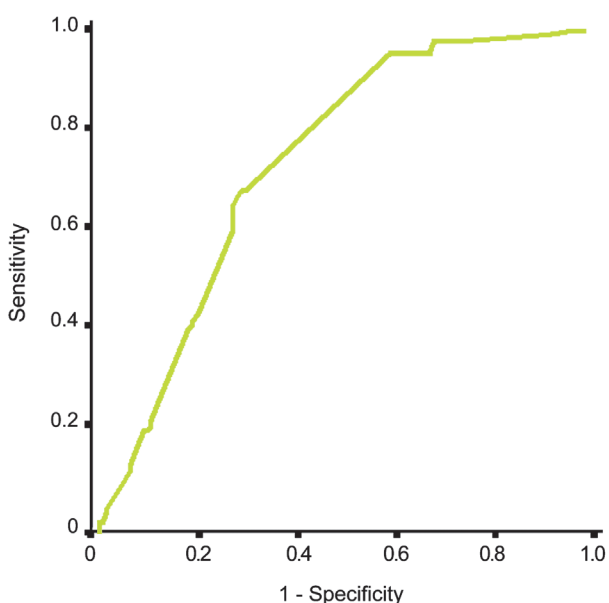


Figure 3. The receiver operating characteristics analysis of levamisole treatment to reach more than 50% reduction in steroid dose (area under the curve, 0.734, $P < .001$). A 14.5-month treatment with levamisole had a sensitivity of 67.5% and a specificity of 71.9%.

reach a relapse reduction of more than 50%.

Resistance to levamisole was seen in 104 patients (34.2%), whereas the other 200 children were sensitive to levamisole. Treatment complications with levamisole were reported in 2 cases (0.66%) including 1 patient with neutropenia and another with vertigo, both reversible after discontinuation of levamisole.

Levamisole and Immunosuppressive Agents

Immunosuppression characteristics of the

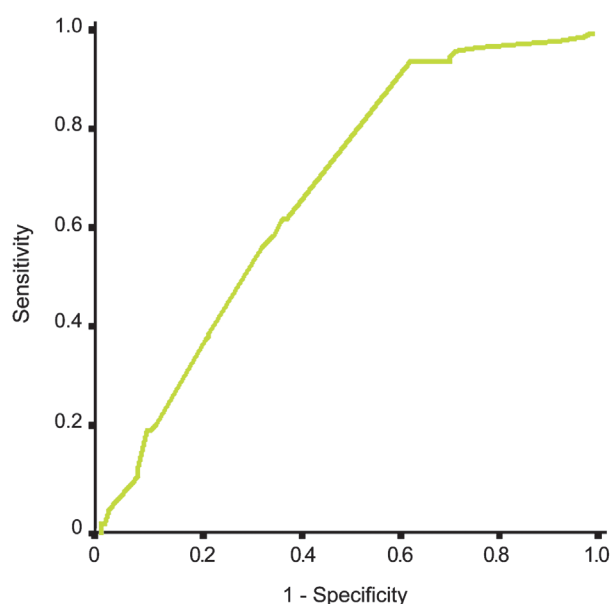


Figure 4. The receiver operating characteristics analysis of levamisole treatment to reach more than 50% reduction in relapse per year (area under the curve, 0.686, $P < .001$). A 14.5-month treatment with levamisole had a sensitivity of 62.3% and a specificity of 63.6%.

patients are shown in Table 1. As mentioned before, 242 children (79.6%) were not administered any immunosuppressive drug before levamisole. The rate of levamisole resistance was significantly higher in children who had received immunosuppressive agents before levamisole (45.2% versus 31.4%; OR, 1.80; 95% CI, 1.02 to 3.18; $P = .04$). Levamisole resistance was seen in 31.4% of children without any immunosuppressive agents (76 of 242), 42.5% of children who received cyclophosphamide (17 of 40), 57.1% of those who received cyclosporine (4 of 7), and 46.7% of patients who received both cyclophosphamide and cyclosporine (7 of 15) before levamisole treatment.

DISCUSSION

The majority of patients with steroid-sensitive NS respond to corticosteroid treatment alone, but children with SDNS or FRNS are candidates for treatment with steroid-sparing agents. Levamisole has been known as an immunostimulatory agent rather than immunosuppressive. It has been hypothesized to normalize deficient cell-mediated immunity.⁹ It enhances T-cell responses by stimulating T-cell activation and proliferation. Also it potentiates monocyte and macrophage functions, including phagocytosis and chemotaxis, and increases

neutrophil mobility, adherence, and chemotaxis.¹⁰

Sumegi and colleagues evaluated the effects of levamisole treatment on prolonged outcomes in 34 children with NS. They found that levamisole could significantly reduce both relapse rate and the cumulative steroid dose in SDNS and FRNS.⁴ Davin and Merkus treated 20 SSNS patients with levamisole for 6 months and followed them for a further 6 months. At the end of the 6-month treatment period, 10 patients (50%) were maintained remission on levamisole alone, and at the end of the 12 months, 5 patients (25%) were still in remission without another therapy.⁶ In the retrospective study of Abeyagunawardena and colleagues, levamisole was effective to induce remission in 30% of children when prescribed as the first steroid-sparing agent and 66% for postcyclophosphamide steroid dependency.⁷

Our findings demonstrated that levamisole therapy significantly reduced relapse rate and steroid dose in SDNS and FRNS. Furthermore, prednisolone could be discontinued in some patients. Our study also showed that there was a significant correlation between duration of levamisole treatment with both dose reduction of steroid and reduction of relapses. A 14.5-month use of levamisole had a sensitivity of 67.5% and a specificity of 71.9% to reach a dose reduction of more than 50% in steroid therapy and the same duration use of levamisole had a sensitivity of 62.3% and a specificity of 63.6% to reach a relapse reduction of more than 50%.

In our study, some patients had been treated with immunosuppressive drug before levamisole therapy. Results of these patients showed that the rate of levamisole resistance was significantly higher in children who received immunosuppressive agent before levamisole. Using immunosuppressive agents (especially cyclophosphamide) before levamisole treatment also had a negative effect on the dose reduction of steroid and number of relapses. This finding is in contrast with the study of Abeyagunawardena and colleagues that showed the efficacy of cyclophosphamide in maintaining remission when it began before levamisole.⁷ However, these findings need to be confirmed by larger prospective studies as double-blind clinical trials.

CONCLUSIONS

In summary, levamisole appears to be effective in prolonging the duration of remission and decreasing the steroid dose in children with steroid-dependent

or relapsing idiopathic NS, and longer treatment periods may be expected to induce remission. However, more studies are needed to assess the effects of long-term levamisole therapy.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Brodehl J. The treatment of minimal change nephrotic syndrome: lessons learned from multicentre co-operative studies. *Eur J Pediatr*. 1991;150:380-7.
2. Brodehl J. Conventional therapy for idiopathic nephrotic syndrome in children. *Clin Nephrol*. 1991;35 Suppl 1:S8-15.
3. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. *Pediatr Nephrol*. 2001;16:271-82.
4. Sumegi V, Haszon I, Ivanyi B, Bereczki C, Papp F, Turi S. Long-term effects of levamisole treatment in childhood nephrotic syndrome. *Pediatr Nephrol*. 2004;19:1354-60.
5. Bagga A, Sharma A, Srivastava RN. Levamisole therapy in corticosteroid-dependent nephrotic syndrome. *Pediatr Nephrol*. 1997;11:415-7.
6. Davin JC, Merkus MP. Levamisole in steroid-sensitive nephrotic syndrome of childhood: the lost paradise? *Pediatr Nephrol*. 2005;20:10-4.
7. Abeyagunawardena AS, Dillon MJ, Rees L, van't Hoff W, Trompeter RS. The use of steroid-sparing agents in steroid-sensitive nephrotic syndrome. *Pediatr Nephrol*. 2003;18:919-24.
8. Tenbrock K, Muller-Berghaus J, Fuchshuber A, Michalk D, Querfeld U. Levamisole treatment in steroid-sensitive and steroid-resistant nephrotic syndrome. *Pediatr Nephrol*. 1998;12:459-62.
9. Robinson RF, Nahata MC, Mahan JD, Batsky DL. Management of nephrotic syndrome in children. *Pharmacotherapy*. 2003;23:1021-36.
10. Renoux G. The general immunopharmacology of levamisole. *Drugs*. 1980;20:89-99.
11. Boyer O, Moulder JK, Grandin L, Somers MJ. Short- and long-term efficacy of levamisole as adjunctive therapy in childhood nephrotic syndrome. *Pediatr Nephrol*. 2008;23:575-80.
12. Donia AF, Ammar HM, El-Agroudy Ael B, Moustafa Fel H, Sobh MA. Long-term results of two unconventional agents in steroid-dependent nephrotic children. *Pediatr Nephrol*. 2005;20:1420-5.

Correspondence to:

Abbas Madani, MD

Division of Pediatric Nephrology, Children Medical Center Hospital, Keshavarz Blvd, Tehran, Iran

Received November 2009

Revised May 2010

Accepted June 2010