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A STUDY OF EFFICACY OF LEVAMISOLE IN CHILDREN WITH FREQUENTLY RELAPSING AND STEROID-DEPENDENT NEPHROTIC SYNDROME

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ABSTRACT

Objectives: To assess the efficacy of levamisole in frequently relapsing nephrotic syndrome and steroid-dependent nephroticsyndrome.
Study Design: Retrospective analysis of hospital case records.
Participants: 62 children with frequently relapsing nephroticsyndrome and 35 children with steroid-dependent nephroticsyndrome.
Methods: Case records of children who were diagnosed assteroid-dependant or frequently-relapsing nephrotic syndrome, were reviewed. Levamisole was given daily (2 mg/kg/d) along with tapering doses of alternate daysteroids after remission on daily steroids.
Results: Levamisole was effective in 77.3% children with a better(80.6%) efficacy in frequently relapsing nephrotic syndrome. Atotal of 34 children completed 1 year follow-up post levamisoletherapy. The cumulative mean (SD) steroid dose 1-year beforetherapy was 4109(1154) mg/m2 and 1-year post therapy was 661(11) mg/m2 (P<0.001). The relapses were also less during theperiod of post-levamisole therapy.
Conclusion: Levamisole is an effective alternative therapy infrequently relapsing and steroid-dependent nephrotic syndrome.

INTRODUCTION

The most commonly used drugs in the treatmentof nephrotic syndrome (NS) are steroids.Children exposed to steroids for a prolongedperiod may experience adverse effects such asgrowth failure, infections, hypertension and osteoporosis.

In order to reduce steroid toxicity, alternative drugs suchas cyclophosphamide,cyclosporine and levamisole areused [1,2]. Levamisole is an immunomodulator that hasbeen used for more than two decades, and is often used asthe first option in the treatment of steroid-dependent orfrequently relapsing NS in children. Its major advantagesare steroid-sparing property and less toxicity incomparison to the other immunosuppresants [3]. Thisstudy was conducted to evaluate the efficacy oflevamisole in steroid-dependent nephrotic syndrome(SDNS) and frequently relapsing nephrotic syndrome(FRNS) in children. The specific objectives were: (a) todetermine the efficacy of daily levamisole in SDNS andFRNS children; (b) to compare the efficacy of levamisolebetween SDNS and FRNS children; and (c) to evaluatethe response of levamisole in SDNS/FRNS children postcyclophosphamidetherapy.

METHODS

The records of children, who attended the Pediatrics Department at Darbhanga Medical College & Hospital, Laheriasarai, Bihar were analyzed retrospectively. Children aged 1-18 years receiving levamisole for at least six months for treatment of SDNS or FRNS were included. Infantile NS,congenital NS and NS secondary to systemic illnesseswere excluded. SDNS was defined when there were twoconsecutive relapses while on alternate day steroids orwithin 14 days of their discontinuation. FRNS wasdefined by two or more relapses in six months or morethan three relapses in any twelve months. Relapses weretreated according to Indian Pediatric Nephrology Groupguidelines [4]. Levamisole was started in SDNS/FRNSchildren daily at a dose of 2 mg/kg/day at the end of twoweeks of daily steroids on inducing remission.
Prednisolone was given at a dose of 1.5 mg/kg everyother day for 4 weeks and then gradually tapered to amaintenance dose of 0.5 mg/kg every other day at 6months and 0.25 mg/kg every other day at end of 1 year.

All children were monitored every three months forresponse and side effects; urinalysis, total and differentialblood cell counts, and liver enzymes were done. At the end of one year, serum albumin, serum cholesterol andurine albumin were checked, and if under remission, prednisolone was discontinued. Levamisole was stopped at the end of two years and these children were followed up for at least one year following cessation of therapy.

Levamisole was considered effective, if the children were able to maintain remission when steroids were tapered and stopped. It was considered ineffective if child developed two or more relapses while on every other day steroids or when steroids could not be withdrawn. Levamisole was stopped when it was considered ineffective. Children in post-immunosuppressive therapy (cyclophosphamide), presenting with SDNS/FRNS were included and their response to levamisole was analyzed. Statistical analyses were done using Repeated measures ANOVA, F-test, and Chi-Squared test. P<0.05 was taken as significant.

RESULTS

A total of 97 children (53 boys) completed 6 months of levamisole therapy; 62 (64%) of these were FRNS. None of the children had renal failure, hypertension or gross hematuria. The baseline characteristics at the start of levamisole therapy are shown in TableI.

The duration of levamisole therapy ranged from 6 to 24 months with a mean (SD) duration of 18.7 (6.4) months. Levamisole was effective in 77.3% children, was stopped in 15 (15.5%) children as it was ineffective, and 7 (7.2%) children were lost to follow-up. Frequent relapsers showed a better efficacy to levamisole in comparison to steroid-dependent NS (80.6% vs. 71.4%; P=0.001).

Prednisolone was tapered to 0.5 mg/kg/day at the end of 6 months with a mean (SD) duration of 5 (1.1) months. Sixty-five children completed one year of therapy and prednisolone was stopped with a mean (SD) duration of 11.84 (1.3) months. Mean (SD) serum albumin at the start of therapy was 2.32 (0.5) g/dL and at completion of therapy was 4.12 (0.3) g/dL.

At the end of 24 months, 40 children completed therapy and these children were kept under surveillance for at least a year. A total of 34 children were followed-up for 1 year post-therapy and the cumulative steroid dose and relapse rates are shown in TableII. The steroid dose and relapse rates were significantly less after levamisole therapy. Relapse free period was observed in 25 (73.5%) children during therapy and in 22 (64.7%) children during the one year period of post-levamisole therapy.

Before the administration of levamisole, 7 SDNS children had

received cyclophosphamide. Renal biopsy was performed in all these children. Four children had minimal change disease and 3 had diffuse mesangial proliferation by histopathology. Levamisole therapy was effective in 5 children.

TABLE I BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	*SDNS*	*FRNS*	
No. (%)	35 (36.1%)	62 (63.9%)	
Male gender, n (%)	18 (51.4%)	35 (56.5%)	
Age at diagnosis, y	2.5 (1.1)	3.1	(1.8)
Age at beginning of therapy, y	3.9 (1.7)	4.8	(2.3)

SDNS -– Steroid-dependent nephrotic syndrome; FRNS – Frequently relapsing nephrotic syndrome; * Values in mean (SD).

TABLE II CUMULATIVE STEROIDS AND RELAPSE RATES IN CHILDREN WITH FRNS/SDNS

Duration of follow up	*Dose of steroids (mg/m^2)mean (SD)*	*No. of relapses mean (SD)*
1 y before levamisole	4109.29 (1154)	2.41 (0.5)
During levamisole	2491.8 (694)	1.3 (0.7)
1 y after levamisole	660.7 (10.7)	0.48 (0.8)

DISCUSSION

In this retrospective study of 97 children with SDNS or FRNS, levamisole was found to be effective in majority (77.3%), with a better efficacy in children with FRNS as compared to those with SDNS.

In our study, levamisole was administered in daily dosing schedule based on personal experience; most guidelines suggest alternate day therapy in nephrotic syndrome. Fu, et al. [5], in a comparative study between daily and alternate day levamisole usage in children with FRNS and SDNS, reported that daily levamisole usage can be considered when response to alternate day usage is unsatisfactory. We did not have any comparison group as this study was a retrospective analysis.

Madani, et al. [6] evaluated the efficacy of levamisole among 304 children and demonstrated that it was effective in children with both SDNS and FRNS. In their study, the relapse rates reduced by about one-half after levamisole therapy. Alsaran, et al. [7] documented response in 90.6% children with FRNS/SDNS. Sumegi, et al. [8] followed 34 children for a duration of 5–36months and documented a reduction in relapse rate after levamisole therapy. Our results are in concordance with the above studies. In children with effective therapy, we were able to taper and stop steroids in majority of patients. Bagga, et al. [9] also showed that levamisole was effective in children with SDNS. In a meta-analysis of randomized controlled trials [10], Durkan, et al. showed that prolonged course of levamisole reduces the incidence of relapses.

Various studies have reported side effects while on alternate day levamisole schedule, though these were not life-threatening and were reversible on discontinuing levamisole [6,7,9,11]. We did not observe any side effects, even in those who completed 2 years of daily levamisole therapy.

CONCLUSION

To conclude, daily levamisole along with initial low dose steroid therapy can be effective in children with FRNS/SDNS with a better efficacy in children with FRNS. It significantly reduces the cumulative dose of steroid intake and relapse rates. Levamisole can be used as an effective steroid-sparing agent in children with frequently-relapsing and steroid dependent nephrotic syndrome.

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