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Original Article

Analysis of the Efficacy of Cyclophosphamide in Frequently Relapsing and Steroid Dependent Nephrotic Syndrome

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Abstract

Background: Idiopathic nephrotic syndrome (NS) is one of the common causes of pediatric ward admissions. Although majority of children do not relapse frequently, significant percentage of children with NS goes either for frequent relapses or steroid dependence. Various immunomodulators are used in the treatment of these children including cyclophosphamide.

Objectives: To analyze and compare the efficacy of oral and intravenous cyclophosphamide therapy in children with frequently relapsing and steroid dependent NS and also recording the side effects.

Materials and Methods: Prospective interventional study on 27 children admitted with a history of frequent relapsing and steroid dependent NS was randomized to receive either oral or intravenous cyclophosphamide, and the results were compared. The study period was 2 years.

Results: The mean proteinuria free days with oral and intravenous cyclophosphamide were 180 and 285, respectively. 14.8% of the children developed nausea and vomiting and 3.7% developed alopecia. None developed either leucopenia or hemorrhagic cystitis.

Key words: Children, Cyclophosphamide, Frequent relapse, Nephrotic syndrome, Proteinuria, Side effects, Steroid dependence

INTRODUCTION

Nephrotic syndrome (NS) is one of the common syndromes in the world. Idiopathic NS has a reported incidence of 2-7 cases per 100,000 children.[1] Dossier *et al.* describe an annual incidence of 3.35 per 100,000.[2]

NS is characterized by (a) Heavy proteinuria – spot protein creatinine ration >2, early morning urine protein 3+/4+ on dipstick, and urine albumin excretion >40 mg/m^2/h, (b) hypoalbuminemia (serum albumin <2.5 mg/dl), (c) hyperlipidemia (serum cholesterol >200 mg/dl), and (d) edema.

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Definitions in NS

Remission

- Urine albumin nil or trace in three consecutive early morning samples
- Proteinuria <4 mg/m^2/h.

Relapse

Urine albumin 3+ or 4+ (or proteinuria >40 mg/m^2/h) in three consecutive early morning samples having been in remission previously.

Frequent Relapse

- Two or more relapses in initial 6 months
- Four or more relapses in any 12 months.

Steroid Dependence

Two consecutive relapses when on alternate day steroid or within 14 days of its discontinuation.

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Steroid resistance

Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg/day for 4 weeks.

The universal impression is that the NS is a self limiting and generally benign disease. The tendency toward relapses decreases with time and the number of children who eventually fail to respond to therapy is quite small. Approximately 20% will never have a relapse following the first episode while 20-30% will have only infrequent relapses. Children who continue to have multiple and frequent relapses despite prolonged or repeated courses of steroid therapy represent 20-40% of the nephrotic population and constitute a difficult problem. First episode of NS is treated with prednisolone at a dose of 2 mg/kg/day (maximum 60 mg/day) in single or divided doses for 6 weeks followed by 1.5 mg/kg/day (maximum 40 mg/day) as a single morning dose on alternate days for next 6 weeks therapy and discontinued.[3]

In the case of infrequent relapses, prednisolone is administered at a dose of 2 mg/kg/day in single or divided doses until urine protein is nil or trace for 3 consecutive days. Subsequently, prednisolone is given in a single morning dose of 1.5 mg/kg/day on alternate days for 4 weeks and then discontinued.[3]

In case of frequent relapses and steroid dependence, after giving the usual daily and alternate day treatment for relapse, prednisolone instead of abrupt discontinuation is gradually tapered by 0.15-0.25 mg/kg/day every 4 weeks to maintenance of 0.5-0.7 mg/kg/day which is administered for 9-18 months (Figure 1).[3]

Multiple and frequent recurrences of proteinuria place undue pressure on both physicians and parents to intensify their struggle to eliminate proteinuria often using more and more steroids for longer and a longer period to serious and unacceptable steroid toxicity. A close monitoring of growth, blood pressure and other features of steroid toxicity is essential. If the prednisolone threshold to maintain remission is higher or if features of corticosteroid toxicity are seen the additional use of immunomodulators such as cyclophosphamide, levamisole, cyclosporine, tacrolimus, and mycophenolate mofetil are suggested.[3]

The objectives of the study are to compare the efficacy of intravenous and oral cyclophosphamide in steroid dependent and frequently relapsing NS and to evaluate the side effects of the drug in the study population.

MATERIALS AND METHODS

Study Center

This study was conducted in Pediatric Unit of a Tertiary Care Centre in Tamil Nadu over a period of 2 years.

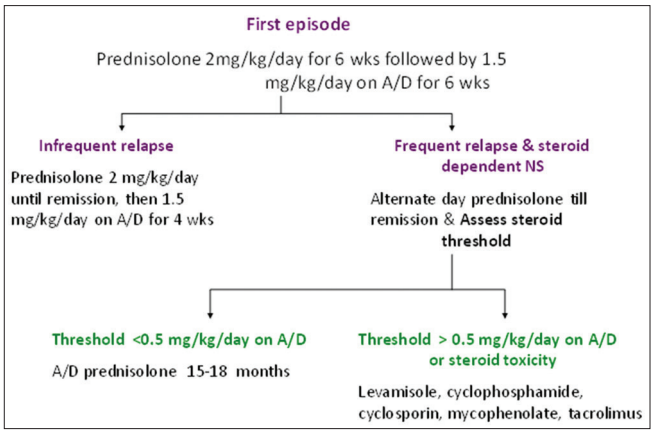

Figure 1: Treatment of steroid-sensitive nephrotic syndrome

Sampling

A total of 27 children who satisfied the criteria for steroid dependent and frequently relapsing NS were included in the study. They were randomized to receive either oral cyclophosphamide at a dose of 2 mg/kg/day for 12 weeks in Group 1 or intravenous cyclophosphamide at a dose of 500 mg/m^2/month for 6 months in Group 2 after achieving steroid remission. Both intravenous and oral cyclophosphamide groups received oral prednisolone as – 1.5 mg/kg/day on alternate days for 4 weeks, 1 mg/kg/day on alternate days for 8 weeks, 0.75 mg/kg/day on alternate days for 4 weeks, 0.5 mg/kg/day on alternate days for 4 weeks and tapered and stopped over a period of 4 weeks.

The demographic data, biochemical profile, and duration of follow-up in two groups were similar (Table 1 and Figure 2). The two groups did not differ significantly in the age of onset of disease, duration of NS before cyclophosphamide therapy (Table 2 and Figure 3). All patients were followed for a minimum of 18-24 months after cyclophosphamide therapy.

The response was evaluated in terms of proteinuria free days. The proteinuria free days before and after starting cyclophosphamide were compared between both groups. Of the total 27 children enrolled for study, 12 were given oral cyclophosphamide, and 15 were given intravenous cyclophosphamide. Total leukocyte counts were monitored every 2 weeks in both the study groups. Other side effects such as alopecia, vomiting, and hemorrhagic cystitis were also monitored. The results were analyzed using the R Software (Version 2.2.1) and also with tabular columns.

RESULTS

Among the total 27 children, 29.62% of the children were below 5 years of age, 48.15% between 6 and 10 years of age and 22.22% were between 10 and 12 years of age (Table 1).

Table 1: Age-wise distribution of the disease

Age group (in years)	Frequency (%)
<5	8 (29.62)
6-10	13 (48.15)
>10	6 (22.22)

Table 2: Gender wise distribution of the disease

Gender	Frequency (%)
Male	18 (66.77)
Female	9 (33.33)

Table 3: Comparison of proteinuria free days in oral and intravenous cyclophosphamide

Route	Number of children	Proteinuria free days		Mean±standard deviation
		Minimum	Maximum	
Oral				
Before Rx	12	17	40	22±6.86
After Rx	12	90	222	180±41.5
Intravenous				
Before Rx	15	17	40	26±5.89
After Rx	15	120	370	285±90.45

Table 4: Adverse effects after oral/intravenous cyclophosphamide

Side effects	Frequency (%)
Nausea and vomiting	4 (14.8)
Alopecia	1 (3.7)
Leukopenia (<4000 cells/mm^3)	0
Hemorrhagic cystitis	0

About 66.7% of the study population were males, and the remaining 33.33% were females (Table 2).

The mean proteinuria free days in children before receiving treatment with oral and intravenous cyclophosphamide were 22 and 26, respectively. The mean proteinuria free days in children after receiving oral and intravenous cyclophosphamide therapy were 180 and 285 days, respectively. There was a significant treatment effect for both intravenous and oral cyclophosphamide with a $P < 0.01$. There is a significant difference between intravenous and oral route where intravenous route achieves more proteinuria free days than the oral route (Table 3).

Regarding the side effects of cyclophosphamide in both our study groups, 14.8% ($n = 4$) developed nausea and vomiting and this is the most common side effect in our study. 3.7% ($n = 1$) developed alopecia, and none developed leukopenia or hemorrhagic cystitis (Table 4 and Figure 4).

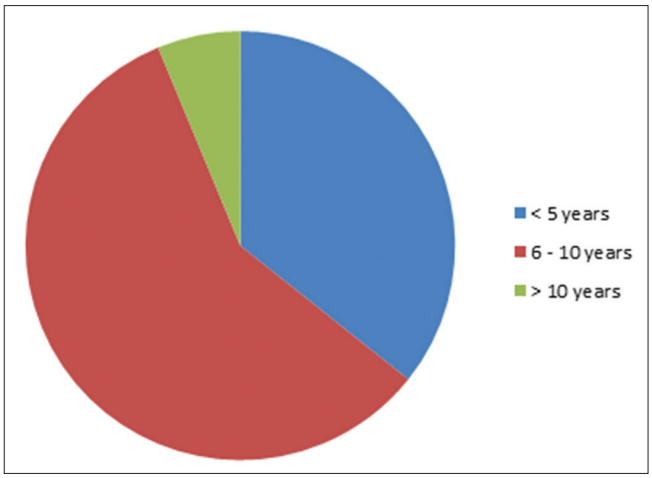

Figure 2: Age-wise distribution of the disease

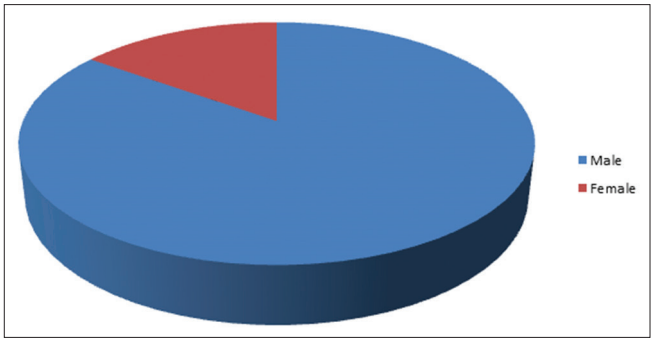

Figure 3: Gender wise distribution of the disease

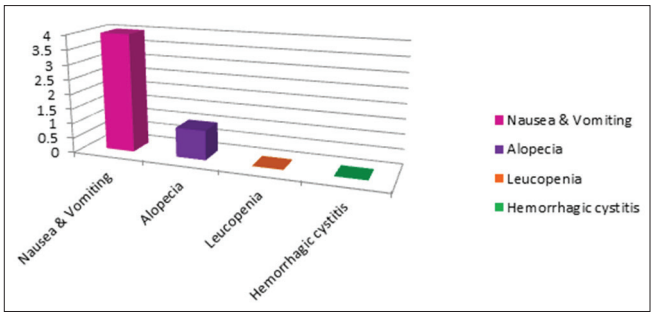

Figure 4: Side effects of oral/intravenous cyclophosphamide

DISCUSSION

In our study, mean proteinuria free days were 29 ± 6.86 days before initiating oral cyclophosphamide therapy, and after therapy, the results were 180 ± 41.5 days. With intravenous cyclophosphamide therapy, the proteinuria free days were 26 ± 5.89 days and 285 ± 90.4 days before and after treatment, respectively. Mean proteinuria free days were more in intravenous than oral cyclophosphamide group. Hence in our study overall improvement is better with intravenous than oral cyclophosphamide.

Narayan *et al.* in their study had documented the mean proteinuria free interval of 96 ± 8 days after oral and

360 ± 8 days after oral and intravenous cyclophosphamide therapy and also found out that the remission rate attained in patients treated with the intravenous route is 88% compared to 57% in oral cyclophosphamide group.[4]

In a study by Gulati *et al.*, where 51 children were studied among whom 22 frequent relapsers and 29 steroid dependent children, they claim that the improvement was statistically significant for intravenous cyclophosphamide with the mean proteinuria free days before and after therapy was 19.9 ± 3.5 and 1256 ± 167 days, respectively. The *P* value is very significant (<0.00001).[5,6] The cumulative remission rate was 49% at 5 years.

A study conducted by Bircan and Kara on 19 children with frequently relapsing and steroid dependent NS where 10 were given intravenous and 9 were given oral cyclophosphamide documents less annualized relapse rate and longer subsequent relapse time is intravenous than the oral cyclophosphamide group.[7]

In a study conducted by Pennisi *et al.* in which 53 children with steroid dependent NS were enrolled, cyclophosphamide was given either for 8 weeks (short course) or 12 weeks (long course) after randomization. The relapse rate was lower (8%) in long course than short course (30%).[8]

Ponticelli *et al.* in their study on the role of oral cyclophosphamide in frequently relapsing and steroid dependent NS concluded that 63% had not had any relapse in their follow-up period of 2 years.[9]

In our study, we also found that the complications with cyclophosphamide both with oral and intravenous cyclophosphamide are less. Out of 27 patients, 4 (14.8%) developed nausea and vomiting, and only 1 (3.7%) developed alopecia and none developed leukopenia and hemorrhagic cystitis. Bircan and Kara report nil complications in both oral and intravenous cyclophosphamide groups.[7]

Hence, cyclophosphamide is not only a drug that causes a significant reduction in the relapse rate in both frequent relapsing and steroid dependent NS but also a safe drug.

CONCLUSION

Both intravenous and oral cyclophosphamide therapy increases the proteinuria free days in children with frequent relapsing and steroid dependent NS reducing the morbidity. Intravenous cyclophosphamide therapy has a long lasting effect with lower annualized relapse rate and longer subsequent relapse time compared to oral cyclophosphamide group. Intravenous cyclophosphamide is the preferable treatment in non-compliant patients, and the follow-up is simple and inexpensive. And also it is a safe drug with lesser frequency of side effects.

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