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Efficacy of Cyclophosphamide versus Cyclosporine in Frequent Relapse Nephrotic Syndrome – A Hospital Based Study

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Introduction: The clinical outcome of patients with Frequent Relapse Nephrotic Syndrome (FRNS) or Steroid Dependent Nephrotic Syndrome (SDNS) treated with cyclophosphamide or cyclosporine (CsA) is yet to be established. This study was carried out to compare the efficacy of CsA with cyclophosphamide in patients with FRNS or SDNS.
Materials and Methods: A total of 54 FRNS or SDNS children were randomly enrolled in this prospective study from August 2013 to July 2014. All the study subjects were treated with prednisolone 60 mg/m^2 /day until the patients were in remission for three consecutive days. The patients were then randomly divided into two groups (Group-A & Group-B). Group-A was treated with cyclophosphamide at a dose of 2.5 mg/kg/day for 60 days, along with tapering dose prednisolone for 8 weeks. The Group-B study population was treated with cyclosporine at a dose of 3 mg/kg/day for 6 months or longer along with tapering dose of alternate day prednisolone for the initial 8 weeks. Four patients in Group-B and one patient in Group-A did not continue the treatment. So, we followed-up 49 children during this period.
Results: The efficacy of both drugs was good after 6 months of treatment. Remission was observed in 80% of the cases in Group-A and 79% of the cases in Group-B. Even after 6 months of treatment 6.7% and 10.5% of the patients with SDNS in Group-A and Group-B needed to continue corticosteroid therapy, respectively. The side effects of immunosuppressive therapy were more frequently observed in Group-B patients. On the other hand, the mean serum creatinine level after 6 months therapy was 0.55±0.21mg/dl in Group-A and 0.84±0.43 mg/dl in Group-B. The difference between the two groups was statistically significant ($p<0.05$).
Conclusions: This study showed that both drugs were effective in FRNS and SDNS.

Keywords: Child; Nephrotic syndrome; Cyclophosphamide; Cyclosporine.

Running Title: Cyclophosphamide versus Cyclosporine in Nephrotic Syndrome

Introduction

Nephrotic syndrome is the commonest form of renal disease in children [1]. Most of the cases of childhood nephrotic syndrome are steroid sensitive [1]. It is estimated that 80% to 90% of the children with steroid sensitive nephrotic syndrome will experience one or more relapses. Among them, 35% to 50% of the individuals relapse frequently [2,3]. Patients in this group

remain in remission for several weeks following discontinuation of treatment but experience frequent relapses. If relapses occur 4 or more times during 12 months or 2 or more times during 6 months, these patients are referred to as having frequent relapse nephrotic syndrome [2-4]. In childhood nephrotic syndrome, whether in the initial or relapsed case, corticosteroid is the mainstay of treatment [1-4]. However, because of its potential side effects, the need for an alternative immunosuppressive treatment is evident. The first line immunosuppressive treatment in frequent relapse nephrotic syndrome in children is still open to discussion. So, different corticosteroid sparing agents, mainly cyclophosphamide [5,6] and cyclosporine A, are used to reduce the relapse rate of frequent relapse nephrotic syndrome as well as to reduce adverse effects of corticosteroids [8]. However, their relative effectiveness in maintaining remission remains controversial. Their use in our country usually depends on their availability and the patient's and physician's preferences. Most of the previous studies [8-12] have shown different results in favor of these two drugs. Podracka et al [13] in a retrospective study showed that cyclophosphamide therapy was more effective in maintaining long-term remission than cyclosporine A treatment. In a prospective study, Ponticelli reported both treatments were effective and well tolerated but patients given cyclophosphamide had stable remissions [11,14]. On the other hand, Durkan et al demonstrated no significant difference between the two drugs [9]. Both cyclophosphamide and cyclosporine have some adverse effects, as well. Cyclophosphamide may potentially be responsible for infections, malignancies, and reduced fertility and abnormal gonadal function in men. On the other hand, adverse effects of cyclosporine are significant with hypertension, gum hypertrophy, reduced renal function, and hirsutism [15,16].

So, we conducted this prospective observational study to compare the efficacy and safety of cyclophosphamide versus cyclosporine A as the initial therapy of children with frequent relapse and steroid dependent nephrotic syndrome.

Materials and Methods

Total 54 steroid sensitive frequent relapse or steroid dependent nephrotic syndrome patients, age 2-15 years of both sexes were randomly enrolled in this prospective observational study after obtaining informed written consent. The study was conducted in the Pediatric Nephrology Department, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka from July 2013 to September 2014. All the children with frequent relapse and steroid dependent nephrotic syndrome were evaluated with history, physical examination and relevant investigations that includes- a) Complete blood count, b) Urine R/E and C/S, c) Blood Culture (If needed), d) Chest X-ray, f) Spot urinary protein creatinine ratio, g) Serum Creatinine, h) Serum Albumin and i) Serum Electrolytes. Those patients had infections were treated either oral or parenteral antibiotic as per need. Prior to start cytotoxic therapy all the study subjects were treated with prednisolone 60 mg/m^2/day until the patients were in remission for three consecutive days. After achieving remission the patients were randomly divided into two groups (Group-A & Group-B). Group-A was treated with Cyclophosphamide at a dosage of 2.5 mg/kg/day for 60 days, along with prednisolone (40 mg/m^2) for 4 weeks in every alternate day followed by tapering dose for another 4 weeks. The Group-B study population was treated with Cyclosporine-A, at a dosage of 3-5 mg/kg/day (two divided doses 12 h apart) for 6 months or longer along with tapering dose of alternate day prednisolone for initial 8 weeks. Cyclosporine – A trough level was monitored to adjust the dose of the drug at least one or two times because of financial constraint during initial 6 months study period. The dose was adjusted to maintain a whole blood trough level of 150–200 ng/ml. During second 6 months period, the patients were followed up to see the number of relapses, complications of diseases and side effects of drugs.

Four patients from Group-B were not included in the study due to discontinuation of treatment (because of financial constraint) or could not be followed up for 6 months. One patient from Group-A developed severe leucopenia and could not complete the treatment. So we followed-up 49 children during this period by both clinical (weight, height, vital signs, any side effects of the drugs) and laboratory investigations like, complete blood count, s. creatinine, s. electrolytes.

Results

In this study, 54 steroid sensitive frequent relapse or steroid dependent nephrotic syndrome patients aged 2-15 years of both sexes were initially enrolled randomly. Because of different

issues as mentioned above, only 49 patients were studied. Among them, 30 patients were in Group – A and 19 were in Group – B. The age range of the study population was 2 – 15 years. The mean age of onset of nephrotic syndrome was 39.37±28.65 months in Group-A and 48.90±25.65 months in Group-B. The mean age at the initiation of steroid sparing agents was 74.43±43.51 and 88.16±41.65 months in Group-A and Group-B, respectively (Table 1).

Table I. Characteristics of the study population (n=49)

	Drugs		p value*
	CPM (n=30)	CS (n=19)	
Age during initial episode (month)	39.37±28.65	48.90±25.65	0.244
Age during starting treatment (month)	74.43±43.51	88.16±41.65	0.280
Sex (Male/Female)	18/12	13/6	
Duration of illness (month)	40.26±26.82	38.40±35.62	0.846
SDNS (%)	14 (46.7%)	9 (47.37%)	
FRNS (%)	16 (53.33%)	10 (52.63%)	
Histopathological evaluation			
Minimal change disease (%)	Not done	12 (63.16%)	
Others (%)	Not done	7 (36.84%)	
S. Albumin	13.18±3.85	12.32±3.35	
S. Creatinine	0.50±0.16	0.56±0.16	

CPM: Cyclophosphamide CS: Cyclosporine
*Unpaired t-test was done to measure the level of significance.

The patients who could be followed up for at least 6 months were included in this study. In these two groups, 14 (46.7%) children had SDNS in Group-A and 9 (47.37%) in Group-B. Renal biopsy was performed only in Group-B before starting cyclosporine. Of these 19 patients, 12 (63.16%) children had minimal change disease. The efficacy of both drugs was good after 6 months of treatment. Remission was observed in 80% of the cases in Group-A and 79% of the participants in Group-B (Table 2, 3, 4). After 6 months of treatment, the mean number of relapse was 1.57±1.25 and 1.89±1.37 in Group-A and Group-B, respectively. In Group-A, 6.7% of the children with SDNS and 10.5% of the children in Group-B required to continue corticosteroid therapy. The side effects of immunosuppressive therapy were more frequently observed in Group-B patients. Hematuria, leucopenia, and alopecia were seen in 2 patients within 7-10 days of the initiation of cyclophosphamide and necessitated temporary discontinuation of the treatment; the treatment restarted successfully in one patient after some time. Hypertrichosis was more frequently (6/19) observed in Group-B. Hypertension was detected in 2 patients who were treated with angiotensin receptor blocker and calcium channel blocker. One patient needed to reduce the cyclosporine dose because of renal dysfunction (Table 5). The mean serum creatinine level after 6 months therapy was 0.55±0.21mg/dl in Group-A and 0.84±0.43 mg/dl in Group-B. The difference between the two groups was statistically significant ($p<0.05$).

Table 2. Outcome of cyclophosphamide treated patients (n=30)

	Before treatment	6 month after treatment	P value
No of relapses/6 months	3.3±0.79	1.57±1.25	0.0001
S. Albumin	13.18±3.85	28.28±8.09	0.0001
S. Creatinine	0.50±0.16	0.55±0.21	0.32
Prednisolone required in SDNS (%)	14(46.7%)	2(6.7%)	
Remission		24(80%)	

*Paired t-test was done to measure the level of significance.

Table 3. Outcome of cyclosporine treated patient (n=19)

	Before treatment	6 month after treatment	P value
No of relapses/6month	2.95±0.62	1.89±1.37	0.004
S. Albumin	12.32±3.35	28.68±8.37	0.0001
S. Creatinine	0.56±0.16	0.84±0.43	0.0116
Prednisolone required in SDNS (%)	9(47.3%)	2(10.5%)	
Remission		15(79%)	
Cyclosporine requirement		2(10.5%)	

*Paired t-test was done to measure the level of significance.

Table 4. Clinical and biochemical differences between Group-A and Group- B after 6 months of treatment

	CPM (n=30)	CS (n=19)	p value*
No of relapses	1.57±1.25	1.89±1.37	0.4044
Prednisolone required in SDNS (%)	2(6.7%)	2(10.5%)	
Remission	24(80%)	15(79%)	
S. Albumin	28.28±8.09	28.68±8.37	0.8698
S. Creatinine	0.55±0.21	0.84±0.43	0.0028

CPM: Cyclophosphamide CS: Cyclosporine
*Unpaired test was done to measure the level of significance.

Table 5. Adverse effects during therapy

	CPM (n=30)	CS (n=19)
Alopecia	1	
Bone marrow suppression	1	
Haemorrhagic cystitis	2	
Gum hyperplasia		2
Hypertension		2
Hypertrichosis		6
Renal dysfunction		1

CPM: Cyclophosphamide CS: Cyclosporine

Discussion

Steroid sparing agents can effectively reduce the relapse rate in frequent relapse and steroid dependent nephrotic syndrome. These agents are usually indicated in children who have significant adverse effects from corticosteroid therapy. Cyclophosphamide and levamisole are commonly used as initial agents and cyclosporine is reserved for children who continue to have frequent relapses despite receiving these agents. However, most previous studies [5-8] clearly mentioned different results in favor of these two drugs. To date, no report has been published on the differences in efficacy between cyclophosphamide and cyclosporine among Bangladeshi children. Therefore, we performed this randomized study to compare the efficacy of cyclophosphamide and cyclosporine. There is a lack of consensus among different centers to provide a uniform treatment protocol for frequent relapse and steroid dependent nephrotic syndrome patients. It is believed that this study may be helpful to decrease the controversy of using steroid sparing agents.

The two groups were well balanced at presentation. Four patients in Group-B and one patient from Group-A did not continue the treatment. So, 49 children were analyzed. The benefit of either treatment was evaluated regarding the remission rate, need of prednisolone, and renal outcome. In this study, it was found that both cyclophosphamide and CsA were effective in maintaining remission in frequent relapse and steroid-dependent patients. The number of relapses and the need of prednisone were significantly lower in either treatment group.

In one study, Ponticelli et al. (1993) found that after 9 months of treatment, 74% of CsA treated and 64% of cyclophosphamide treated patients were in complete remission [11]. In this study, after 6 months of treatment, 80% of the cyclophosphamide treated and 79% of cyclosporine treated patients were in remission. Here, we obtained more favorable results in cyclophosphamide treated patients in contrast to the study conducted by Ponticelli, which may be because of treating the patients with cyclophosphamide for 12 weeks instead of 8 weeks. APN also suggested the benefit of cyclophosphamide treatment for 12 weeks [18].

In general, long term cyclosporine is recommended, but we introduced short course cyclosporine with a whole blood trough level of 150–200 ng/ml. In long term studies, remissions of 1 and 2 years are achieved in 60% and 40% of the children, respectively [18]. Higher remission rates could be achieved when the CsA is administered in combination with steroids despite adequate whole blood levels of cyclosporine [19]. Our observational period was at least 6 months. We found 15 (79%) patients were in remission after 6 months of cyclosporine therapy. Among them, 10.5% required to continue steroid and cyclosporine. On the other hand, only 6.7% of the patient required to continue steroid in the cyclophosphamide treated group.

The side effects of immunosuppressive therapy were more frequently observed in Group-B patients. It could be because of the high target trough level or less frequent monitoring of the trough level. Hino et al. found CsA related nephrotoxicity in 15% of their patients with minimal change SDNS [20]. Most of the previous studies revealed that these CsA related complications can be reverted after completion of cyclosporine therapy. Hypertrichosis and gum hyperplasia were more frequently observed in our study. We did not need to discontinue cyclosporine because of hypertension and renal dysfunction. Hypertension and renal function were controlled by reducing the dose of cyclosporine and adding angiotensin converting enzyme inhibitor. One of our cyclosporine treated patients required cyclosporine dose adjustment due to renal dysfunction.

All the patients were treated on an out-patient basis. Only two patients in Group–A required hospitalization for hematuria and leucopenia; one patient was excluded from our study because of discontinuation of treatment. So, we did not consider hospitalization as a variable to differentiate these two groups.

The strength of this study includes its prospective nature of random data collection and the evaluation of Bangladeshi children that has not been previously described in the literature.

Despite these strengths, this study is limited by being a single center study with a relatively small sample size and short duration of observational period.

Conclusions

In this study, two drugs of different pharmacological groups were used in FRNS and SDNS patients with different modes of action, recommended duration of therapy, and side effects. Although cyclophosphamide and cyclosporine were used in separate groups of age and sex matched FRNS and SDNS patients, both agents showed equal efficacy during the study period with insignificant side effects. So, it can be concluded from this study that both drugs can be used safely in FRNS and SDNS patients.

Conflict of Interest

None declared

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