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Original Article

Safety and efficacy of intravenous pulse cyclophosphamide therapy in children with steroid-dependent nephrotic syndrome

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ABSTRACT

Background: Cyclophosphamide (Cyp) is a well-known alternative agent to spare the use of steroids and avoid the side effects that result from long-term steroid therapy in children with idiopathic nephrotic syndrome (NS). Use of Cyp typically reduces the risk of relapse in comparison with prednisolone by about 50%. **Objective:** To study the safety and efficacy of intravenous pulse Cyp (IV Cyp) therapy in children with steroid-dependent NS (SDNS). **Materials and Methods:** This was a retrospective single-center analysis from a large government hospital in South India. The data were retrieved from the records of children attending the pediatric nephrology clinic between 2005 and 2016. Children with SDNS who received the complete schedule of IV Cyp were included in the study. Children who received other alternate drugs were excluded. **Results:** Fifty patients with SDNS were treated with IV Cyp, seven patients did not complete the treatment and were excluded from the analysis. 24 (56%) of the 43 patients stayed in remission throughout the course of Cyp treatment and prednisolone could be stopped and were considered as Cyp responsive. The remaining 19 (44%) children had relapsed while on Cyp therapy (Cyp resistant) and required treatment with alternate immunosuppressant drugs. 19 of the 24 Cyp responsive patients were in remission 6 months after stopping Cyp treatment (Cyp sensitive) while the remaining five patients relapsed within 6 months of stopping Cyp treatment (Cyp dependent). 9 children (20.9%) were relapse-free till the time of last follow-up with a median follow-up of 2.1 years. Among 24 children, 13 (30.23%) who responded were infrequently relapsing NS and 2 (4.5%) children were frequently relapsing NS.

Key words: *Nephrotic syndrome, Cyclophosphamide, Relapse*

The first-line treatment for children presenting with idiopathic nephrotic syndrome (NS) is oral corticosteroids. Although the majority of children respond to steroids, 80% of children experience a relapsing course and among these half relapse while on reducing doses of corticosteroids or within 2 weeks of completion of steroid therapy (steroid-dependent NS [SDNS]) [1]. These children with SDNS need long-term steroid usage to maintain sustained remission and hence are at risk of steroid toxicity such as hypertension, obesity, cataracts, psychosis, striae, and growth failure [2,3]. In addition, relapses may continue into adulthood. Hence, SDNS is not regarded as a benign condition, even though the renal function is not compromised [4,5].

Cyclophosphamide (Cyp) is a well-known alternative agent to spare the use of steroids and avoid the side effects that result from the long-term steroid therapy. Use of Cyp typically reduces the risk of relapse in comparison with prednisolone by about 50% for 1 year during and after the treatment. Many studies have shown that treatment with Cyp reduces the risk of relapse at 6, 12, and 24 months when compared to placebo or prednisolone alone [6-10]. Cyp may be given orally or as monthly pulse intravenous (IV) therapy. However, there is no consensus on the route of administration of Cyp in children with SDNS. The potential advantages of monthly IV therapy include better compliance, avoidance of frequent blood sampling to monitor lymphopenia which may be a challenge in younger children and use of lesser cumulative dose as compared to oral Cyp which may result in lesser toxicity.

The cumulative dose is higher in the oral group when compared to the IV group. Infections are significantly more common in children treated with oral Cyp compared with IV therapy. The other side effects seen with IV Cyp are bone marrow suppression, alopecia, hemorrhagic cystitis, and vomiting [11]. There are very few studies that reported the utility of IV pulse Cyp in SDNS. Hence, this study was undertaken to determine the efficacy and safety of IV Cyp in children with SDNS.

MATERIALS AND METHODS

This was a retrospective single-center study undertaken in a large government hospital in South India. The data were retrieved from the records of children attending the pediatric nephrology clinic between 2005 and 2016. Children with SDNS who received the complete schedule of IV Cyp were included in the study. Children

who received other alternate drugs such as calcineurin inhibitors or mycophenolate mofetil (MMF) before receiving IV Cyp were excluded. Age at onset of disease, clinical characteristics of initial episode of NS, renal histology if available, number of relapses, use of other immunosuppressive treatments (e.g., levamisole, long-term steroid treatment) were recorded. Treatment duration and cumulative dose of Cyp were calculated. Height and weight were recorded at diagnosis of NS, at start of Cyp, at first relapse after Cyp, and at last follow-up visit. IV Cyp therapy was given once a month for 6 months. Adequate hydration was ensured during and post-IV infusion. Cyp was started at dose of 500 mg/m^2 and increased to maximum dose of 750 mg/m^2. Oral prednisolone 1.5 mg/kg was given alternate day for 4 weeks, then tapered by 0.25 mg/kg every month and subsequently stopped. Children were initially followed up monthly for the first 6 months and then quarterly. At each visit, they were monitored for proteinuria by dipstick and side effects of Cyp and prednisolone. The drug was withheld if total white cell count was <3000 cells/mm^3 or if the platelet counts were <50000/mm^3. Following treatment with IV Cyp and after prednisolone has been stopped, relapse of NS was treated with standard treatment guidelines, and the course of NS was followed up and labeled as infrequently relapsing NS (IFRNS) and frequently RNS (FRNS) according to standard definitions. Permission and ethical clearance have been obtained from the hospital ethical committee to publish the data.

Definitions Used in the Study

SDNS

SDNS is defined as 2 consecutive relapses, when on alternate day steroids or within 14 days of its discontinuation. Relapse was defined as urine albumin 3+ to 4+ or 2+ with edema was considered as relapse. Remission was defined as urine albumin nil or traces for 3 consecutive days [12]. A sustained remission was defined as a relapse-free period for 6 months or more. In addition, in those whose steroid response category was changed to infrequently relapsing or frequently relapsing were considered as responders. Those children who continued to be dependent on prednisolone were considered as non-responders.

Statistical analysis was done using Epi Info™ for Windows software. The mean relapse rates (RR) and prednisolone dose (PD) before and after Cyp were calculated using paired *t*-test.

RESULTS

Fifty patients with SDNS were treated with IV Cyp, seven patients did not complete the treatment and were excluded from the analysis. Baseline characteristics of patients are shown in Table 1. The median period of follow-up in these children was 4 years (interquartile range [IQR] = 2.1- 5.5 years), the maximum follow period being 11 years with the maximum period of remission being 8 years. The median age of children in our study at the time of last follow-up was 11 years with IQR of 7.2–14.5 years.

Only two patients had kidney biopsy before starting treatment with IV Cyp, the indication being the presence of atypical features, one had minimal change NS (MCNS) and other patient had mesangioproliferative NS. After treatment with IV Cyp, seven patients among the non-responders underwent biopsy before starting with tacrolimus, five had MCNS, one patient had focal segmental glomerulosclerosis (FSGS) and one had C1Q nephropathy. Overall, only the child with mesangioproliferative glomerulonephritis responded to IV Cyp and six children with MCNS and one each with FSGS and C1Q nephropathy did not respond.

The overall response to IV Cyp is shown in Table 2. 24 (56%) of the 43 patients stayed in remission throughout the course of Cyp treatment and prednisolone could be stopped and were considered as Cyp responsive. The remaining 19 (44%) children had relapsed while on Cyp therapy (Cyp resistant) and required treatment with alternate immunosuppressant. Nine were given a trial of levamisole, nine children were started on tacrolimus, out of which two patients later required MMF and rituximab, one patient was lost for follow-up. 19 of the 24 Cyp responsive patients were in remission 6 months after stopping Cyp treatment (Cyp sensitive) while the remaining five patients relapsed within 6 months of stopping Cyp treatment (Cyp dependent). Of the 24 children who responded, 9 children (20.9%) were relapse-free till the time of last follow-up and the median follow-up in these children was 2.1 years (IQR of 0.95-2.9 years). The exact follow-up period in these nine children were 5 months, 10 months, 1 year, 1 year 7 months, 2 years 2 months, 2 years 6 months, 2 years 9 months, 3 years, and 5 years. 13 (30.23%) children out

Table 1: Baseline characteristics in the study

Age at onset of NS (in years)	Median age 2.5yrs (IQR 1.5-6yrs)
Male : Female	22:21
Duration of NS in years before starting therapy with cyclophosphamide	Median age 3 yrs (IQR 1-5yrs)
Age at initiation of cyclophosphamide therapy (in yrs)	Median age 6yrs (IQR 3-11yrs)
Cumulative dose of cyclophosphamide (mg/kg)	Median dose 150mg/kg (IQR 125-159mg/kg)
Number of patients treated with levamisole before cyclophosphamide	16 (37.2%)

Table 2 : Response to cyclophosphamide therapy

Cyp resistant	19 (44.1%)
Cyp responsive	24 (55.8%)
No relapse	09 (20.9%)
IFRNS	13 (30.23%)
FRNS	2 (4.6%)
Mean Relapse rate (RR per year) (In Cyp responsive patients)	
Before cyclophosphamide	3.10±2.21
After cyclophosphamide	0.99±2.02 P value <0.001
Mean Prednisolone dose (PD in mg/kg) (In Cyp resistant patients)	
Before cyclophosphamide	1.16±0.42
After cyclophosphamide	0.54±0.33 P value <0.001

of 24 who responded were IFRNS and 2 (4.5%) children were FRNS. The mean RR was calculated for those children who responded and was 3.10 ± 2.21 and 0.99 ± 2.02 before and after treatment with Cyp, respectively, $p < 0.001$. The mean PD for the non-responders with $p < 0.001$ before and after treatment with Cyp was 1.16 ± 0.42 and 0.54 ± 0.33, respectively.

Side effects of Cyp were documented during Cyp therapy, none of the children in our study had hemorrhagic cystitis, 3 (6.9%) developed alopecia, 3 (6.9%) children had leukopenia, 4 (9.3%) children developed headache, and vomiting after the pulse doses of Cyp which subsided with simple supportive measures. 6 (13.9%) had lower respiratory tract infection, 8 (18.6%) had upper respiratory tract infection (URTI), 2 (4.6%) had candidal skin infection, 1 (2.3%) each had acute gastroenteritis, measles, spontaneous bacterial peritonitis, and non-bullous impetigo.

DISCUSSION

Cyp has been used in childhood NS since 1960s. Oral Cyp has been widely used and most of the studies have been on oral Cyp. In our study, we tried to evaluate the efficacy and side effects of IV Cyp in SDNS. The mean age of onset of NS in our study was 4.05 ± 3.3 years. Srivastava *et al*. in their study found that in majority of children with NS, the onset of disease occurs before the age of 5 years [13]. The mean age of initiation of Cyp therapy was 7.4 ± 4.7 years, whereas in the study by Prasad *et al.,* it was similar being 7.6 ± 5 years. Our primary objective was to evaluate the efficacy of IV Cyp in SDNS in the form of change in steroid response category.

In our study, nine patients underwent renal biopsy as described in the results section and there was no correlation between response to IV Cyp and histopathology with only child with mesangioproliferative glomerulonephritis responding to therapy. In the study by Prasad *et al.*, among the 14 children biopsied, nine had MCNS and five had FSGS. They have not mentioned about the correlation of histopathology and response [14].

In this study, 24 (55.8%) of the 43 children studied responded to IV Cyp, and steroids could be stopped, 19 (44.1%) continued to be on steroids and were labeled as Cyp resistant. Out of the 24 children who responded (Cyp responsive), 9 (20.9%) of them were in remission and off steroids till their last follow-up (median follow-up 2.1 years, IQR of 0.95–2.9 years). Prasad *et al.* in their study compared IV with oral Cyp and found that IV Cyp was more effective than oral Cyp. In 26 children who received IV Cyp, 15 (57.7%) had sustained remission for 6 months.

5 (19.2%) were infrequent relapsers, 3 (11.5%) were frequent relapsers, and 3 (11.5%) continued to be steroid dependent [14]. The overall improved category in their study was 88.5% when compared to 55.1% in our study. This difference may be due to higher number in our study and also, it has been showed in a study that certain genetic polymorphisms of glutathione-S-transferase may predict a better response to IV pulse Cyp treatment and in the same study Sharda *et al.* also reported a benefit in 50% of patients after IV Cyp, but they presented no exact outcome data. 37 of the 74 patients showed response, but this study included both steroid sensitive and steroid-resistant NS [15]. In a prospective study, by Bhagwani and Sharada 16 children with SDNS were treated with IV pulse Cyp and followed up for 2 years. After 2 years of follow-up, 9 children (56.25%) had sustained remission, 4 (26%) were infrequently relapsing, 1 (6.25%) was FRNS, and 2 (12.5%) continued to be SDNS [16]. In our study, 19 of the 43 children continued to be dependent on prednisolone and were labeled as CPA resistant and the dependent dose of prednisolone was significantly reduced after Cyp therapy. The median cumulative dose of Cyp was 150 mg/kg, compared to 100 mg/kg in the Prasad *et al.* study.

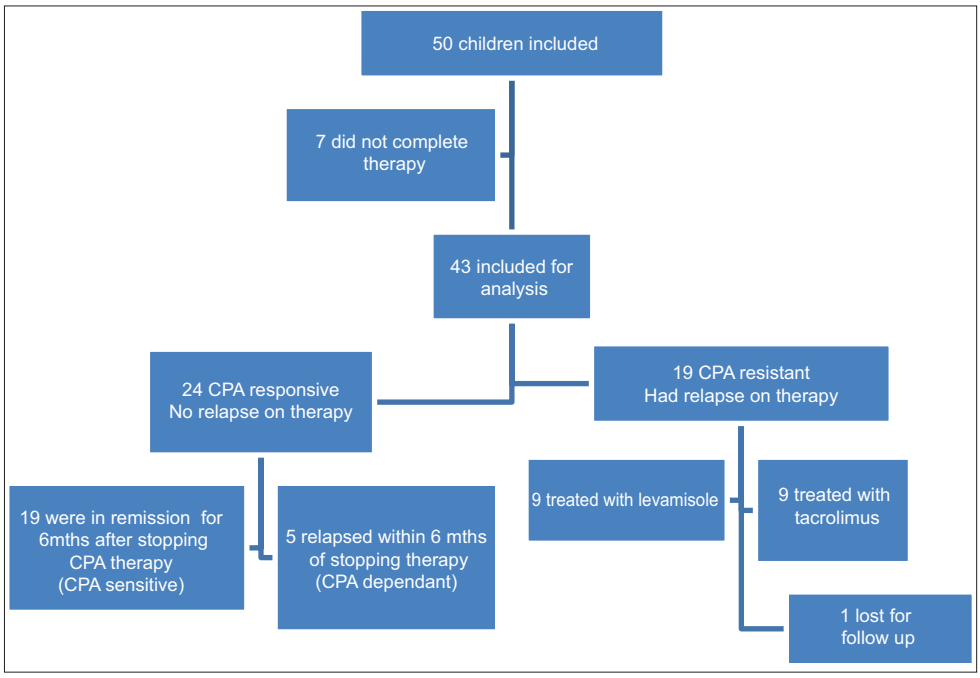

Figure 1: Flow diagram of the study

The side effects were documented and none of them had serious side effects requiring discontinuation of Cyp therapy. Therapy was deferred till they recovered from leucopenia or infections. In the study by Prasad *et al.,* out of 26 children, two developed leucopenia, three had alopecia. One had pneumonia and two had nausea and vomiting which were comparable with our study except for the higher incidence of infection in our study, which may be partly related to the low socioeconomic status of the patients in our study. Furthermore, in their study, side effects were significantly more in children treated with oral Cyp. In the study by Bhagwani and Sharada, out of 16 patients, two had nausea and vomiting, one had alopecia, one had thrombocytopenia, five had mild URTI and one developed chickenpox. None of the children developed hemorrhagic cystitis.

Ours being a resource-poor country, cost and affordability also play an important role in the treatment of these children. When we compared the cost between IV Cyp, tacrolimus, and MMF, it was found that the cost of tacrolimus and MMF was about 30 and 60 times that of IV Cyp (considering a 30 kg child with a body surface area of 1 m2 , 6 doses of IV Cyp would cost about Rs. 1000, tacrolimus (0.1 mg/kg/day for 1 year) costs Rs. 30,000, and MMF (1000 mg/m^2/day for 1 year) would cost around Rs. 60,000. These drugs sometimes have to be continued for 2–3 years that would further increase the cost proportionately and obviously cost will play an important role in the compliance to treatment.

The limitation of our study was that this was a retrospective study including patients treated over the last 10 years; hence, we did not have uniform follow-up period for all patients which would have provided better interpretation. Our sample size was small with only 43 patients in the study, and also comparison with oral Cyp would have given us better idea about the advantages of IV Cyp over oral Cyp.

CONCLUSIONS

Our study, there was fairly good response to IV Cyp with 55.8% response rate. About 21% of children did not have any relapse and 30% were infrequent relapsers, which are quite acceptable considering the low cost of Cyp which is about 30 and 60 times cheaper when compared to tacrolimus and MMF, respectively. Hence, although not an ideal option, IV Cyp can be tried as the initial alternative immunosuppressant in SDNS, particularly in the resource-poor countries.

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