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THE LONG-TERM OUTCOME OF CYCLOPHOSPHAMIDE ORAL VERSUS INTRAVENOUS IN CHINESES CHILDREN WITH STEROID DEPENDENT NEPHROTIC SYNDROME

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ABSTRACT

Objectives: To investigate the effects of oral or intravenous cyclophosphamide with steroid dependent nephrotic syndrome(SDNS) children. **Method:** Sixty-nine SDNS children(39 girls and 30 boys) aged 1 to 14 years were treated with prednison and oral cyclophosphamide(OCP)(35cases) or with prednison and intravenous cyclophosphamide(IVCP) (34 cases). Essential investigations were done including blood count, renal function test, electrolytes, liver function test and Creatine-kinase isoenzyme(CK-Mb), Purified Protein Derivative(PPD), X-ray chest and urine analysis. Data were analyzed using appropriate SPSS 13.3 software for statistical test. **Results:** There were no statistically significant difference in children in two groups in age, sex, blood count, hemoglobin level, renal function, electrolytes, proteinuria, serum protein, albumin, cholesterol. Duration of remission were same in patients treated with IVCP and OCP. Side effects in patients treated with OCP were more than that in IVCP. **Conclusion:** The effects are similar in two groups, but side effects of OCP group are more than that in IVCP group. IVCP is a useful method for the SDNS children.

KEYWORDS: Cyclophosphamide; idiopathic nephrotic syndrome; children.

INTRODUCTION

Nephrotic syndrome, a manifestation of glomerular disease, is characterized by nephrotic range proteinuria and the triad of clinical findings associated with large urinary losses of protein: hypoalbuminemia, edema, and hyperlipidemia. Most children with nephrotic syndrome have a form of primary or idiopathic nephrotic syndrome (INS). INS is the most common glomerular diseases, with an incidence of 2-7 cases per 100,000 children. The majority of patients are steroid responsive. However, about 70% INS children are relapse or steroid dependent. Glucocorticoids are repeated or continued for a long-term in these children. The glucocorticoids have many adverse drug effects, such as obesity, growth retardation, hypertension, diabetes mellitus, osteoporosis and adrenal suppression. To reduce the steroids adverse effects, other immunosuppressive agents have been proposed to treat these children.

Cyclophosphamide (CP), a non-steroid immunosuppressive agent, has been used in the treatment of INS children for more than four decades.[1,2] CP can reduced the relapse frequency and maintain the duration of remission of INS. However, side effects of daily oral CP (OCP) treatment, including bone marrow depression, increased susceptibility to infection, haemorrhagic cystitis, alopecia, sterility or increased risk of malignancy, have been reported.

Most previous studies have discussed the short-term results of Oral and pulse introvenous CP(IVCP). Few of articles reported the long-term effects of CP in steroid-dependent INS children. In present study, we will investigate the following: 1.long-term outcome of OCP versus IVCP in children with steroid-dependent nephrotic syndrome(SDNS). 2. Side effects of OCP and IVCP in SDNS children.

PATIENTS AND METHODS

Patients

After obtaining approval from institutional review board for research, the study was carried out. Sixty-nine patients were diagnosed as SDNS from 1-14 years of age. Among them, 39 were girls and 30 were boys. 35 patients were treated with OCP and 34 patients were treated with IVCP. Inclusion criteria of patients: The patient included were steroid dependent .All investigation parameters should be within normal limits. White Blood Cell Count(WBC), Ck-Mb, Alanine transaminase(ALT), Urine examination, X-ray, PPD. Exclusion criteria of patients: Abnormal investigation

findings (WBC, CK-Mb, ALT, Urine examination, X-ray, PPD).

Table 1: Patient's characteristics of two groups at start of onset.

Groups	Oral	IV. Pulse
Cases	35	34
Age(years)	6.2(1-14)	6.3(1-14)
Female/Male	19/15	20/15
Duration of steroid treatment(months)	13.1	13.5
Maintenance of every other day steroid dose(mg/kg)	1.0	1.0
Hypertension	20	21
Cushingoid facies	18	20

Ethical consideration

Before commencing data collection for this study, a proposal was submitted to the Institutional Review Board and ethical clearance was taken. The will of parents/children was fully respected and written/verbal consent was taken after fully explaining all relevant details, its importance and implications. Those who failed to provide consent for any reason were excluded from the study.

Criteria of diagnosis

The initial treatment of SDNS was: prednisone (2 mg/kg/day) for 4-6 weeks and then 2/3rd of 2mg/kg on alternate days and then dose was tapered gradually 5mg/month. We defined remission as urine free of protein, evaluated by proteinuria ≤4 mg/ m2/h, zero or traces of albumin in dipstick probe for 3 consecutive days. Relapse was defined as a reappearance of proteinuria ≥40 mg/m2/h or Albustix 2+ or greater for 3 consecutive days. Steroid-dependency was defined as the occurrence of two consecutive relapses during alternate-day steroid treatment, or the appearance of recurrence until 14 days after its withdrawal.

Laboratory test

Prior to initiation of prednisolone, Urine investigation, PPD (Mantoux) test and X-ray, Complete blood count, CK-Mb and ALT was sent in all cases. Urine investigation and WBC count was sent weekly after starting cyclophosphamide, CK-Mb and ALT were sent monthly and monitored regularly after initiation of cyclophosphamide therapy; if any alteration in these parameters drug was withdrawn. Prior to initiation of treatment WBC count should be more than 4000/mm3, ALT should be within normal limit.

Usage of cyclophosphamide

The cyclophosphamide was introduced after the induction of remission of nephrotic syndrome by prednisolone, continued in alternate days and tapered subsequently. The oral dose of cyclophosphamide was 2 mg/kg/day for 3 months; IV dose was 10-12 mg/kg/day for 2 days and repeat dose after 15 days for 3 months, thereafter monthly for 3 months.

Statistical method

SPSS 13.0 software for windows was used for statistical calculation of data.

RESULTS

1. We compared the effects of oral and IV pulse cyclophosphamide therapy. The results were showed in table 2. All the patients were followed up for more than 10 years. There is no difference in 2 groups（p>0.05）.

Table 2: Comparison of Remission years after oral and IV cyclophosphamide.

Route	No response	＜1 yr remission	1-3 yrs remission	>3 yrs remission
Oral	4 (11.4%)	4（11.4%）	7（20.0%）	20（57.1%）
iv	3 (8.8%)	4（11.8%）	6（17.6%）	21（61.8%）

However, the side effects of two groups are different. Decreased WBC count and nausea/vomiting were very common in oral group, but less in iv group. At the sametime, the percentage of increased ALT,and CK-MB are also higher in oral group than that in iv group.

2. The side effects of oral versus IV cyclophosphamide showed in table 3.

Table 3: Comparison of side effects of oral versus IV cyclophosphamide.

Route	n	WBC↓	ALT↑	CK-Mb↑	Nausea/Vomiting	Hair loss	hematuria
Oral	35	28(80.0%)	25(71.4%)	11(31.4%)	28(80.0%)	24(68.6%)	2(5.7%)
iv	34	2(5.9%)	8(23.5%)	5(14.7%)	7(20.6%)	0	0
p		<0.001	<0.001	>0.05	<0.001	<0.001	>0.05

DISCUSSION

Most of INS children respond well to predisone therapy. In cases with steroid dependent long term use of high dose of prednisolone leads to many side effects; so low dose of steroid along with cyclophosphamide is used to reduce its complications. The present study showed that OCP therapy has more side effects in comparison of pulse IVCP therapy. The duration of remission is similar in two groups.

Approximately 90% of children with nephrotic syndrome is INS. INS in children is characterized by high sensitivity to steroids and about 77% had minimal change disease.[3] Approximately 80% of children with steroid-sensitive NS (SSNS) have one or more relapses, and about 50% have frequent relapses and/or steroid dependence[4,5,6] requiring higher exposure to steroids. INS includes multiple histologic types: minimal change disease, mesangial proliferation, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis. Minimal change disease is characterized by remitting and relapsing course and its stricking susceptibility to corticosteroid therapy. Patients who have frequent relapse or steroid dependent, it is difficult to obtain remission. Prolonged use of steroids can cause significant side-effects such as hypertension, obesity, cataracts, psychosis, striae and growth failure.[7] Long term use of steroid has so many complications so other alternative medicine has to be introduced for obtain remission. Cyclophosphamide has been chosen by many centers as first line treatment for children suffering from SDNS along with low dose of steroid to reduce complications of long term high dose of steroid. Several studies have reported prolonged remission in these cases when cyclophosphamide was given along with steroids. But there is no uniform opinion regarding the dose and duration of cyclophosphamide treatment. Also hazards like bone marrow depression, increased susceptibility to infections, haemorrhagic cystitis, alopecia, gonadal failure and malignancy are associated with daily cyclophosphamide regimen. Response to cyclophosphamide was more dependent on histopathological pattern and age of onset of cyclophosphamide treatment.[8,9] Biopsy was not a pre-requisite before starting cyclophosphamide therapy. The percentage of cumulative sustained remission was similar in children who received treatment without biopsy versus those who had prior biopsy.[10]

In a retrospective comparative study done by Sumboonnanonda[11] with 68 patients with INS with steroid-dependent, steroid-resistant or frequent relapse, Fifty-four patients (79.4%) received cyclophosphamide at a dose 2.2 ±0.5 mg/kg/d for 11.6±3.4 weeks. Enalapril was prescribed in 50 patients for 12.4±10.0 months. Thirty-six patients also received cyclophosphamide. The results of 3 regimens: cyclophosphamide, enalapril, and cyclophosphamide plus enalapril showed that Remission was significantly better in cyclophosphamide group ($p = 0.014$). Complications included hypertension (44%), cataract (40%), glaucoma (15%), short stature (17.6%), and obesity (5.9%). Recurrent infection was found in 69%, including dental caries (16.29%), urinary tract infection (14.7%), intestinal parasitic infestation (10.3%), respiratory tract infection (8.8%), and skin infection (7.4%). Chronic renal failure was found in 3 patients and portal vein thrombosis was found in 1 patient. In INS with steroid dependent, steroid resistance and frequent relapse duration of remission was prolonged in patients with cyclophosphamide in comparision to enalapril alone and enalapril with cyclophosphamide. Azib et al.[12] also reported 90 patients with SDNS with single course of oral cyclophosphamide (2 mg/kg/day for 10 to 12 weeks). Sustained remission was seen with cumulative rate of 57% at 1 year, 42% at 2 years, and 31% cases at 5 years. For the patients who relapsed, the median threshold dose of prednisone between Cyclophosphamide initiation and first relapse was significantly decreased (22.1 mg/kg/day versus 4.9 mg/kg/day, $p < 0.001$). No further immunosuppressive agent was required in 60% of all patients. Young age at OCP initiation was associated with a lower rate of sustained remission ($p<0.001$). In SDNS children, prolonged sustained remission was achieved after use of cyclophosphamide. However, young age of cyclophosphamide was associated with less sustained remission. Sumegi et al.[13] reported 22 children, group 1 (3 focal segmental glomerulosclerosis, 19 minimal-change nephrotic syndrome) were treated with cyclophosphamide orally for 2.5±0.5 months; 15 children group 2 (7 Focal segmental glomerulosclerosis, 8 Minimal change nephrotic syndrome) were treated with cyclosporine-A for 28±15 months. The relapse-free period was significantly longer in the Cyclophosphamide group (Cyclophosphamide 30 ± 21.5; Cyclosporin-A 26.2±18 months, $p < 0.001$). The relapse rate decreased significantly in both groups and remained in this lower level during the follow-up (from 3.4± 2.8 to 0.1± 0.2/year in group 1, and from 3.7 ±3.1 to 0.6± 0.8/year in group 2). At the end of the 5-year follow-up, 20/22 patients (90.9%) and 10/15 patients (66.6%) were in remission in groups 1 and 2 respectively($p < 0.05$). In INS with steroid dependent or steroid resistant cases, long term remission was sustained in cases treated with cyclophosphamide in comparision to cyclosporine-A.

In a report of Al Salloum,[14] ten patients treated with pulse IVCP 500 mg/m 2 per month for six months; with oral prednisolone at a dose of 60 mg/m 2 per day for four weeks, then 40 mg/m 2 /per alternate day for another four weeks, then tapered over the next eight weeks, all the patients became steroid responsive after the completion of IVCP therapy after four years of follow up; six patients achieved complete remission and they were off steroid; while four patients remained steroid dependent. In steroid resistant nephrotic syndrome associated with mesangial proliferative glomerulonephritis IVCP can lead to sustained remission. Bircan et al.[15] reported nineteen children with SDNS, ten children were treated with IVCP and nine with OCP, remission was then achieved with prednisolone. Dose of OCP was 2 mg/kg per day for 12 weeks. IVCP 500 mg/m2 per month (with intravenous 3500 ml/m2 per 24 h one-third saline hydration) for 6 months. Long-term complications and side-effects such as alopecia, infection and hemorrhagic cystitis were not observed in the children treated with IVCP and the number of patients in remission for 2 years was significantly higher in patients treated with IVCP

(P<0.05). It is concluded that prolonged sustained remission and fewer side effects can be achieved by IVCP in comparision to OCP in SDNS. Narayan et al.[16] also reported that forty-seven SDNS children was with OCP (2 mg/kg per dayx12 weeks) or IVCP (500 mg/m (2) per month IV for 6 months) after achieving a steroid-induced remission with prednisolone. IVCP was given to 26 children and OCP to 21 children. The sustained remission seen was 73% in IVCP compared with 38.1% in OCP at 6 months after therapy, but was almost same (18.6% in IVCP vs. 19%in OCP) after 2 years. Long term remission is similar in both IVCP and OCP in cases with SDNS.The results are similar with our study.

However, Cammas et al.[17] and Kyrieleis et al.[18] documented that long term remission was not achieved with cyclophosphamide therapy.

Our result showed fewer side effects in cases treated with pulse IV cyclophosphamide but induce similar long term remission in a patient with SDNS. It also appears that intense cyclophosphamide pulse therapy provides maximum therapeutic benefit and minimizes the toxicity compared to regimen involving daily dose of oral cyclophosphamide.

INS responds well to prednisolone therapy. But in cases with steroid dependent use of long term high dose of steroid can lead to many complications; many immunosuppressive drugs have been suggested as an alternative to this; among all cyclophosphamide is the preferred first line of treatment for many years. Both oral and IV cyclophosphamide has been used for treatment of SDNS. Pulse IV cyclophosphamide has less side effects in comparison to oral cyclophosphamide therapy and similar period of remission. IVCP is an effective form of therapy for SDNS patients. The patients receiving IVCP has a significant improvement in steroid response categories from steroid-dependent to sustained remission, infrequent relapse, and frequent relapse. Biopsy is not mandatory prior cyclophosphamide and it does not change method of treatment.

Because of retrospective study our study has its own limitation. This was carried out in limited sample size in limited period of time. The study involved the patients with wide range of age, so the complain of patient may vary in different age group. However, our result could provide a baseline data for study of oral and IV cyclophosphamide drug in children with SDNS. Further large sample studies and longer-term follow-up are indicated.

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