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Original Article

# Nephrotic syndrome in children- Role of intravenous cyclophosphamide in comparison with oral cyclophosphamide in frequently relapsing or steroid dependent cases

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**Abstract:**

**Introduction: Nephrotic syndrome in children is a disease of relapse and remission. The treatment of frequently relapsing (FR) and steroid dependent (SD) idiopathic nephritic syndrome(INS) with oral cyclophosphamide creates problem like side effects, infections and compliance.**

**Methods: A prospective study was conducted among 27 patients selected consecutively selected, of them 19 were FR and 8 were SD idiopathic nephritic syndrome. Fourteen children were treated with Intravenous Cyclophosphamide (IVCP) at a dose of 500mg/m$^2$/month for 6 months after achieving a steroid induced remission. Thirteen children were treated with Oral Cyclophosphamide(OCP) 2mg/kg/day for 12 weeks in case of SD and 3mg/kg/day for 8 weeks in case of FR nephritic syndrome. The response of IVCP & OCP were evaluated in terms of remission, change in steroid response status of the patient, duration of remission(ie. proteinuria free days), side effects & compliance with therapy.**

**Results: The mean proteinuria free days (243.5 # 108.9 days in IVCP group *vs* 136.3# 73.3 days in OCP group) which was highly significant (p=0.004). The cumulative remission in the IVCP group 71.4% at one year follow up and was comparable to that of OCP group which was 46.2% at a 40% lower cumulative dose.**

**Conclusion: Monthly intravenous cyclophosphamide pulse therapy causes prolonged remission with negligible side effect in frequently relapsing and steroid dependent idiopathic nephritic syndrome in children**

## Introduction:

Nephrotic syndrome is one of the most common renal diseases in children [1]. Incidence is much higher in Africa and Asia [2, 3]. Steroid sensitive nephrotic syndrome is more common in people of Indian subcontinent [4, 5]. The disease is unusual in the first year of life where as highest incidence is within 2-6 years of age in children [6]. Moreover, about 95 percent cases of nephrotic syndrome is due to primary glomerular abnormality [7]. It is also known that most common (80%) primary nephrotic syndrome in children is minimal change nephrotic syndrome (MCNS) also known as idiopathic childhood nephrosis, nil disease, foot process disease, lipoid nephrosis or minimal change nephropathy [7, 8]. whereas in adults minimal change consists of only 15% of the primary nephrotic syndrome [9].

Steroid is the treatment of choice in children with nephrotic syndrome [10]. Alkylating agents such as cyclophosphamide and chlorambucil have the advantages of minimizing these problems and of successfully inducing longer lasting remissions in many children [11, 12, 13]. The study will compare the effectiveness of intravenous pulse cyclophosphamide and oral cyclophosphamide in frequently relapsing and steroid-dependent nephrotic syndrome in children.

**Rationale of the study:**

There is no controlled studies has performed to comparing pulse IVCP with OCP in the treatment of frequently relapsing and steroid-dependent nephrotic syndrome in children. In this study, it could observe in children with frequently relapsing and steroid-dependent nephritic syndrome can be achieved by intravenous cyclophosphamide therapy

**Aim and objectives:**

The aim of the study is to compare the effectiveness of intravenous pulse cyclophosphamide and oral cyclophosphamide in frequently relapsing and steroid-dependent nephrotic syndrome in children.

**Methodology:**

A prospective clinical trial was conducted in a tertiary hospital, in the Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), in between August/2006 to April/2008. We selected 27 children purposively who fulfil the inclusion criteria. Of them, every alternate patient was taken for group I (IVCP) & for group II (OCP). Some inclusion and exclusion points were set for enrolling the children for the study were as follows:

**Inclusion criteria:**

Children with idiopathic nephrotic syndrome who were-

1. Age group 1-16 years.
2. Frequently relapsers (FR )[i.e. two or more relapses in a 6-month period following cessation of steroid therapy] or steroid-dependent(SD)[at least two consecutive relapses during a period of steroid tapering or within 2 weeks of stopping steroid therapy]
3. Presence of at least two of the following features of steroid toxicity like hypertension, growth suppression, cushingoid appearance, hirsutism cataract, psychosis and diabetes.
4. The qualifying period for the diagnosis of FR or SD should be six months preceding the enrollment into the study.

**Exclusion criteria:**

1. Age – below 1 year or above 16 years.
2. Steroid resistant nephrotic syndrome
3. Presence of systemic diseases(SLE, HSP)
4. History of previous use of cytotoxic drugs (Cyclophosphamide, cyclosporine, mycophenolate mofetil).
5. Presence of congenital renal diseases.
6. First attack nephrotic syndrome.

Consecutive children were selected who fulfill the inclusion criteria and every alternate patient for IVCP group(15) and for OCP group(15). Detailed history was taken and physical examination for each patient was done by the investigator and informed written consent was taken from parents or attendants of each patient The toxicity and side effects about cyclophosphamide were clearly explained to the parents/attendants.

**Procedure:**

For group I, 14 patients were given cyclophosphamide therapy monthly for 6 months at a dose of 500mg/$m^2$. IV pulse cyclophosphamide(200mg, 500mg, 1gm, powder for injection preparation, Baxter, Germany) was given with adequate hydration by 500 ml of 5% dextrose in ½ strength normal saline or 5% dextrose over a period of 6 hour with antiemetics and also MESNA(Sodium 2-mercaptoethane sulfonate) to combat hemorrhagic cystitis(1.5 times of the cyclophosphamide dose). One third amount of the total dose of MESNA were given along with cyclophosphamide and two third amount were given with the rest of fluid.

For group 2, 13 patients of the study population were selected for oral cyclophosphamide(50mg tablet preparation, Baxter, Germany) therapy. For steroid-dependent children a 12 weeks course at a dose of 2 mg/kg/day and for frequently relapsing children a 8 weeks course at a dose of 3mg/kg/day were given daily morning with plenty of water by mouth.

Both groups of children were done urinary remission by prednisolone (oral or intravenous methylprednisolone)

for consecutive 3 days before the introduction of cyclophosphamide therapy. Thereafter alternate day prednisolone single morning dose at a rate of 40mg/$m^2$ for 4 weeks was continued. Both groups were maintained on a salt restricted diet and were given diuretics as needed. Patient suffering from any infection from either group was treated with proper antibiotics and albumin or fresh frozen plasma were given where indicated.

Baseline investigations were done before introduction of cyclophosphamide therapy. Complete blood count, serum albumin, serum cholesterol, serum creatinine, serum ALT, serum ANA, serum C3, C4, serum HBsAg, Mantoux test, urine microscopy and culture with colony count, 24-hours urinary total protein and chest X-ray and sometimes renal biopsy were done when needed.

Follow-up were done in each group of patients during therapy with cyclophosphamide and after therapy for a period of one year. In Group I, monthly follow up were done in first 6 months during treatment period then 3 monthly for next 1 year. In Group II, monthly follow up were done for first 2 or 3 months during treatment period then 3 monthly for next 1 year. Parents were instructed to examine the urine for protein by heat coagulation test daily morning during treatment period and every alternate day morning during remission. Other routine investigations were also performed accordingly. Data were collected using a pre-designed semi-structured questionnaire and were analysed using the x2-square test and the paired and unpaired student's t-test. The analysis was carried out using SPSS statistical software (SPSS Inc., Chicago, IL, USA, 1998, version 15). All values are in mean ±SE.

**Results:**

Among two groups of children, mean age of children in group I was 103.8±44.4 where as in group II was 69.9±26.6. Majority of the children are male, 8 (57.1%) and 9 (69.2%) in group I and II respectively. Most of the children's age at initial attack was > 36 months in group I and group II it was 25 – 36 months of age [table-1]. Baseline physical findings were measured which was quite similar except height, weight and blood pressure, which was statistically significant ($p<0.05$) [table-2]. Bio chemical investigations also found almost similar in two groups [table-3]. Group I was treated with Intravenous cyclophosphamide (IVCP) and Group II was treated with Oral cyclophosphamide (OCP) and it was found that The mean duration of urinary protein free days was 243.5±108.9 days in group I and 136.3±73.3 days in group II which is statistically significant ($p=0.004$) [figure-1] where as, higher sustained remission was found in group I (71.4 %) than that of group II (46.2 %) [Figure-2].

**Discussions:**

The age of onset of minimal change nephrotic syndrome is between 2-6 years whereas other than minimal change disease are often present at later age usually after 8 years [14, 15,16]. In our study, the mean age at initial attack was 70.7± 43.3 months in IVCP group where as in OCP group was 34.8± 14.8 months. The male female ratio was 1.3:1 and 2.2:1 respectively. An overall male preponderance was identified in this study like many other studies [15, 17].

During treatment with intravenous Cyclophosphamide (IVCP) in group I, 71.4% of the children attained a sustained remission which is comparable to the previous study done by Gulati et al.(2001). While, in OCP group, 46.2% of the children attained sustained remission was found in another study was 61% [18]. Among the study children, intravenous cyclophosphamide causes a prolonged remission than that of oral cyclophosphamide. Urinary protein-free time after IVCP was 243.5±108.9 days *vs* 136.3±73.3 days following OCP therapy, which was statistically significant ($p=0.004$). This result was comparable with the work conducted by Prasad et al.(2004) where the median proteinuria-free time was 360±88 days in IVCP group and 96± 88 days in OCP group [19].

Cyclophosphamide, one of the most widely used alkylating agent has been launched long ago for the treatment of idiopathic nephrotic syndrome. Recently intravenous cyclophosphamide has been used rather than oral medication as its convenient doses and drug compliance. In our study it has explored that iintravenous cyclophosphamide is a safe and more effective therapeutic modality than oral

cyclophosphamide in children with idiopathic nephrotic syndrome who are frequent relapser or steroid dependent.

### Limitation of the study:

In this study, we followed up the children for a period of one year after IVCP or OCP therapy in the treatment of frequently relapsing and steroid-dependent nephrotic syndrome. Moreover, our study represents a small number of children of 27 in number which is not representative.

### Annexure:

**Table I: Demographic characteristics of study children (N=27).**

| **Age in months** | | | | | |
|---|---|---|---|---|---|
| | Group I (n=14) | | Group II (n=13) | | p value |
| | n | % | n | % | |
| 12-60 | 4 | 28.6 | 5 | 38.5 | |
| 61-108 | 4 | 28.6 | 7 | 53.8 | |
| >108 | 6 | 42.9 | 1 | 7.7 | |
| Total | 14 | 100.0 | 13 | 100.0 | |
| Mean ± SD | 103.8±44.4 | | 69.9±26.6 | | 0.025[S] |
| **Sex** | | | | | |
| Male | 8 | 57.1 | 9 | 69.2 | |
| Female | 6 | 42.9 | 4 | 30.8 | |
| **Age at initial attack** (months) | | | | | |
| <24 | 2 | 14.3 | 3 | 23.1 | |
| 25-36 | 3 | 21.4 | 7 | 53.8 | |
| >36 | 9 | 64.3 | 3 | 23.1 | |
| Total | 14 | 100.0 | 13 | 100.0 | |
| Mean ± SD | 70.7±43.3 | | 34.8±14.8 | | 0.005[S] |
| **Diagnosis** | | | | | |
| SDNS | 4 | 28.58 | 4 | 30.76 | |
| FRNS | 10 | 71.42 | 9 | 69.24 | 0.598 NS |
| Total | 14 | 100 | 13 | 100 | |

Group I= Intravenous cyclophosphamide (IVCP)
Group II= Oral cyclophosphamide (OCP)
S= Significant, NS= Not significant
p value reached from unpaired t test

**Table II: Physical findings of the children (N=27).**

| Physical findings | Group I (n=14) | | Group II (n=13) | | p value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Puffy face | 14 | 100.0 | 13 | 100.0 | |
| Pallor | 2 | 14.28 | 3 | 23.0 | [a] 0.863 [NS] |
| Edema | 14 | 100.0 | 13 | 100.0 | |
| Proteinuria | | | | | |
| 2 + | 1 | 7.1 | 1 | 7.7 | |
| 3 + | 11 | 78.6 | 7 | 53.8 | [a] 0.343 [NS] |
| 4 + | 2 | 14.3 | 5 | 38.5 | |
| Reddish urine | 3 | 21.4 | 1 | 7.7 | [a] 0.327 NS |
| Ascities | 13 | 92.9 | 13 | 100.0 | [a] 1.000 [NS] |
| Corticosteroid toxicity | | | | | |
| Cushingoid face | 10 | 71.4 | 7 | 53.8 | [a] 0.293 [NS] |
| Mallar flush | 9 | 64.3 | 5 | 38.5 | [a] 0.179 [NS] |
| Striae | 1 | 7.1 | 1 | 7.7 | [a] 0.741 [NS] |
| Pot belly | 2 | 14.3 | 3 | 23.1 | [a] 0.500 [NS] |
| Systolic BP (mean±SD) | 96.7 | ±9.8 | 100.3 | ±13.2 | [b] 0.393 [NS] |
| Diastolic BP (mean±SD) | 64.7 | ±8.3 | 71.7 | ±9.4 | [b] 0.040 [S] |
| Height (mean±SD) | 105.3 | ±14.4 | 120.9 | ±20.7 | [b] 0.027 [S] |
| Weight (mean±SD) | 20.7 | ±6.1 | 27.6 | ±9.8 | [b] 0.030 [S] |

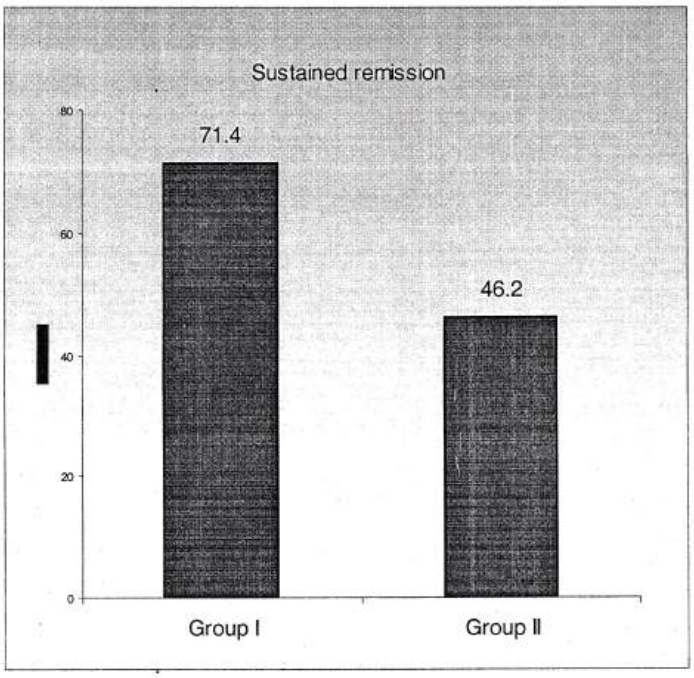
Group I= Intravenous cyclophosphamide (IVCP)
Group II= Oral cyclophosphamide (OCP)
S= significant, NS= Not significant
a= p value reached from chi square test
b= p value reached from unpaired t test

**Table III: Biochemical parameters before cyclophosphamide therapy (N=27).**

| Investigations | Group I (n=14) | | Group II (n=13) | | p value |
|---|---|---|---|---|---|
| | Mean | ±SD | Mean | ±SD | |
| Serum albumin(gm/L) | 18.6 | ±3.4 | 17.1 | ±3.2 | 0.213 [NS] |
| S. cholesterol(mg/dl) | 281.7 | ±39.7 | 295.7 | ±35.1 | 0.156 [NS] |
| Serum creatinine(mg/dl) | 0.7 | ±0.2 | 0.6 | ±0.3 | 0.289 [NS] |
| S. ALT(u/L) | 44.7 | ±7.8 | 47.2 | ±7.2 | 0.367 [NS] |
| 24 hours UTP(gm/m$^2$) | 2.47 | ±.56 | 2.62 | ±0.43 | 0.249 [NS] |

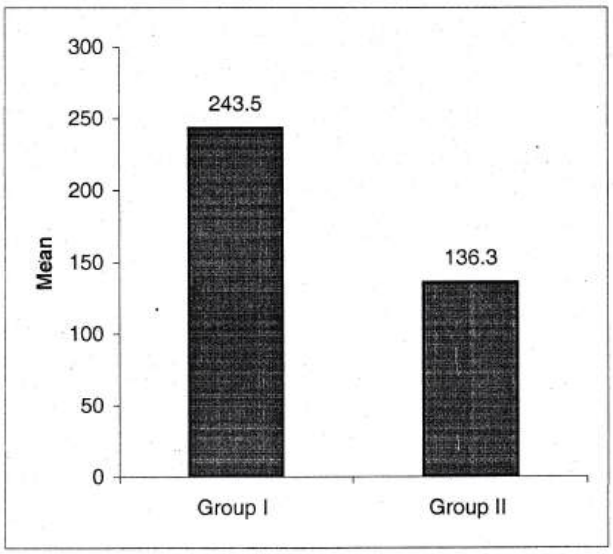
UTP = Urinary total protein, ALT= Alanine transaminase
Group I= Intravenous cyclophosphamide (IVCP)
Group II= Oral cyclophosphamide (OCP)
NS= Not significant
p value reached from unpaired t test

**Figure 1: Response after cyclophosphamide therapy (N=27).**




Above Bar diagram shows the higher sustained remission in group I (71.4 %) than that of group II (46.2 %).

**Figure 2: Urinary protein free days after cyclophosphamide therapy (N=27).**




Above Bar diagram shows the mean duration of urinary protein free days between group I (243.5 days) and group II (136.3 days) which is statistically significant (p=0.004).

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