ROLE OF PULSE CYCLOPHOSPHAMIDE IN CHILDREN WITH FREQUENTLY RELAPSING NEPHROTIC SYNDROME (FRNS) AND STEROID DEPENDENT NEPHROTIC SYNDROME (SDNS)
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Abstract: Background: Oral cyclophosphamide (OCP) in the treatment of frequently relapsing (FR) and steroid dependent (SD) idiopathic nephrotic syndrome (INS) poses problems of compliance, side effects and infections. Therefore, cyclophosphamide pulses given intravenously may provide an option that maintains remission with less-frequent side effects. Aim: To assess the usefulness of Intravenous Cyclophosphamide (IVCP) in FRNS and SDNS. Method: We retrospectively evaluated the usefulness of IVCP in children with FRNS and SDNS. Thirty children were included in this study of whom 17 were FRNS and 13 were SDNS. IVCP was administered in a dose of 500mg/m2/month for 6 months after achieving a steroid induced remission. During this period, patients were maintained on low dose oral steroids (5mg/day). We retrospectively analyzed patients for compliance with therapy, remission rate, maintenance of remission, occurrence of relapse and side effects during this period and for an additional 6 months after withdrawal of cyclophosphamide. Results: At the end of 6 months treatment period 19 patients (63.3) were in remission. Number of persistent remission at the end of one year was 15 (50%). Vomiting was seen in 4 patients (13.2). Two patients (6.6) developed pneumonia. Leucopenia was seen in 3 patients (9.9) which were transient. No incidence of haemorrhagic cystitis. Notably treatment adherence was 100. No incidence of severe bone marrow depression and alopecia. Conclusion: IVCP has comparable efficacy with oral cyclophosphamide therapy in SDNS and FRNS with less cumulative dose, fewer complications and good adherence.

Key words: Intravenous cyclophosphamide, Steroid dependent, frequently relapsing, remission

Introduction:
Most of the children with idiopathic nephrotic syndrome respond to corticosteroids with a complete remission. However, a significant number (40%-50%) of these will either be frequent relapsing nephrotic syndrome (FRNS) with or without steroid dependent nephrotic syndrome (SDNS) 1. Although corticosteroids are effective, they also have serious side effects when given for a prolonged period in children. Many adjunct therapies like cyclophosphamide, cyclosporine 2, tacrolimus 3 and mycophenolate mofetil 4 have been studied with variable beneficial effects. Intravenous cyclophosphamide (IVCP) has been used in lupus nephritis and various vasculitis disorders and has been shown to be an effective form of therapy with significantly fewer side effects than oral cyclophosphamide 5.

Materials & methods:
This is a retrospective study and the study period was from January 2010 to December 2012. We analyzed 30 children admitted in our institute of child health, Chennai. Inclusion criteria were FRNS or SDNS status in the age group of 1-14 years. Exclusion criteria was history of previous use of cytotoxic drugs. SDNS is defined as the occurrence of complete remission on steroids but relapse upon withdrawal or within 2 weeks after withdrawal of steroid treatment. FRNS is defined as more than two relapses in 6 months period 6. IVCP was started in a dose of 500mg/m2/month for 6 months after achieving a steroid induced remission. The drug was dissolved in 300ml of 0.9% NaCl and infused over 3 hours under supervision. None of these patients received MESNA. After achieving steroid induced remission, these patients were maintained on minimal dose of steroid (5mg/day) throughout the treatment period. The children were followed up monthly for the first 6 months and thereafter once in every 3 months. On each visit the child was evaluated clinically for evidence of disease activity and complications. Urine albumin and creatinine in a spot sample, serum protein, albumin, creatinine, hemoglobin, and total leukocyte count were carried out in each visit. Remission was defined as urine albumin nil or trace (or proteinuria <4mg/m2/hr) in consecutive early morning specimens, for 3 days. Relapse was defined as urine albumin >3+ or proteinuria of >4mg/m2/hour for three consecutive early morning specimens, having been in remission previously 6.

Evaluation of response to IVCP:
The response to IVCP was evaluated in terms of 1. Non responders: (Persistence of FR/SD status) during IVCP therapy, 2. Change in steroid responsive status a) from SDNS in to FRNS b) from FRNS in to Infrequent relapse, 3. Sustained remission after 6 months of the last dose of cyclophosphamide, 4. Complications, 5. Compliance.

Statistical analysis:
Statistical analysis was done with SPSS statistical version 17 software. Descriptive statistics were used to describe the data. Continuous variables are expressed as mean +/- SD. Categorical variables are expressed as absolute frequencies (%).

Results:
A total of 30 children with either FR or SD INS were included in this study. Of these 13 were SDNS and 17 were FRNS. The baseline clinical profile was shown in Table 1.
At the end of 6 month after starting the IVCP therapy, the following results were obtained. Among the 13 SDNS patients 7 (53.8%) showed remission and 2 patients (15.2%) showed improvement into infrequent therapy in the study population. At the end of 6 months after completing the last dose of IVCP therapy, 3 patients in FRNS and 1 patient in SDNS went for relapse. There was no remission noted from the initial nonresponder patients. So persistent remission at two years was seen in 2 (6.6%) patients, which were seen only in a transient period. Respiratory tract infection was seen in 2 (6.6%) patients and they were treated successfully. None of our patient developed hemorrhagic cystitis. All the patients completed the course of IVCP without fail and the compliance rate was 100%.

**Discussion:**

Alkylation agents have been used in childhood NS since the 1960s. They lead to a depletion of immune competent cells but the exact mechanisms of action in Steroid sensitive nephritid syndrome (SSNS) are not known. Side effects include bone marrow suppression with leucopenia, alopecia, hemorrhagic cystitis, gonadal toxicity and rarely malignant transformation.

The most common complication was nausea and vomiting (13.2%, 4 out of 30 patients). Leucopenia was seen in 3 patients (9.9%) which were seen only in a transient period. Respiratory tract infection was seen in 2 (6.6%) patients and they were treated successfully. None of our patient developed hemorrhagic cystitis. All the patients completed the course of IVCP without fail and the compliance rate was 100%.

**REFERENCES:**


**Table 1**

- **Age (years) (means+/-SD):** 7.38+/-2.44
- **Total number of male patients:** 18
- **Total number of female patients:** 12
- **No. of SDNS patients:** 13 (8M + 5F)
- **No. of FRNS patients:** 17 (10M + 7F)

**Table 2**

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug</th>
<th>Route of administration</th>
<th>Dose</th>
<th>Duration</th>
<th>Cumulative Dose</th>
<th>Possible Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oral cyclophosphamide</td>
<td>2 mg/kg/day</td>
<td>60 days</td>
<td>3.15 kg</td>
<td>Poor compliance</td>
<td>Alopecia, leukopenia</td>
</tr>
<tr>
<td>2</td>
<td>Intravenous cyclophosphamide</td>
<td>500 mg/m²/2</td>
<td>6 pulses</td>
<td>435 mg</td>
<td>Good compliance, prolonged remission</td>
<td>Alopecia, leukopenia</td>
</tr>
<tr>
<td>3</td>
<td>Tacrolimus</td>
<td>0.1 mg/kg</td>
<td>6 months to 15,000 mg</td>
<td>1 year</td>
<td>Good response</td>
<td>Cholestasis, nephrotoxicity, hypertension, growth retardation, weight loss, leukopenia</td>
</tr>
<tr>
<td>4</td>
<td>Cyclosporin</td>
<td>2.5 mg/kg</td>
<td>2-3 months</td>
<td>56,000 mg</td>
<td>Variable responses</td>
<td>Nephrotic syndrome, growth retardation, weight loss, leukopenia</td>
</tr>
<tr>
<td>5</td>
<td>Mycophenolate sodium fumarilate</td>
<td>2.5 mg/kg</td>
<td>1 year</td>
<td>16,000 mg</td>
<td>Steroid sparing, decrease in relapse</td>
<td>Nephrotic syndrome, growth retardation, weight loss, leukopenia</td>
</tr>
</tbody>
</table>

**Table 2 show the comparative data of adjunctive therapy in Steroid dependent nephritic syndrome (for a 15 kg child)20**

**CONCLUSIONS:**

To conclude, our study showed good response to IVCP therapy with a reasonable remission rate which is comparable with OCP treatment in the historical controls. It is well tolerated by our children with minimal side effects and good compliance.
20. Dalip Kumar and Kothapalli Sharadha. Day care intravenous Cyclophosphamide therapy in Steroid Dependent Nephrotic Syndrome. IJHS ISSN 2349-7033