Original Article

Pulse Cyclophosphamide Therapy in Steroid Resistant Nephrotic Syndrome Associated with Mesangial Proliferative Glomerulonephritis

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ABSTRACT. High proportion of patients with mesangial proliferative glomerulonephritis (MesGN) is steroid resistant. We report the response of ten children with steroid resistant MesGN treated with intravenous pulse cyclophosphamide (IVCP) together with oral prednisone. All patients were treated with pulse IVCP 500 mg/m² per month for six months; oral prednisolone was given concurrently at a dose of 60 mg/m² per day for four weeks, then 40 mg/m²/per alternate day for another four weeks, which was tapered over the following eight weeks. All the patients were followed up for four years after treatment. All the patients became steroid responsive after the completion of IVCP therapy; nine patients were weaned of steroids and one patient could not. Seven patients showed early response to IVCP; they had no proteinuria after the 2nd dose of IVCP. Three patients had complete remission and never had any relapses over four years of observations. By the end of the observation period, there were six patients who achieved complete remission and they were off steroid, while four patients remained steroid dependent. None of the patients developed any significant side effects. We believe that IVCP is a safe and effective therapeutic modality in children with steroid resistant MesGN.

Key Words: Nephrotic syndrome, Mesangial proliferative glomerulonephritis, Steroid resistant, Pulse cyclophosphamide, Children.

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Introduction

Mesangial proliferative glomerulonephritis (MesGN) occurs in 3-5% of childhood idiopathic nephrotic syndrome. Many terms have been used for this disease entity, including diffuse mesangial hypercellularity,
pure diffuse mesangial proliferations \(^4\) and mesangial proliferative glomerulonephritis. \(^5\) Though still debated, many studies suggest that MesGN is a heterogeneous disease entity including minimal change nephrotic syndrome (MCNS) variant and focal segmental glomerulosclerosis (FSGS) variant. \(^1\)\(^-\)\(^3\)\(^,\)\(^6\)-\(^9\) The high proportion of non-responders to steroid therapy among patients with MesGN suggest that these patients differ clinically as well as histopathologically from those with MCNS. \(^1\)\(^-\)\(^3\)

Approximately, 46% patients with MesGN in the international study of kidney disease in children (ISKDC) did not respond to steroid therapy but showed a protracted course. \(^1\)

In the steroid resistant nephrotic syndrome, children usually suffer from consequences of unremitting disease such as chronic edema and susceptibility to infection. \(^10\) In addition, there may be transition from MesGN to FSGS \(^9\) with risk of renal failure. \(^9\)\(^,\)\(^10\)

The beneficial effect of the cytotoxic treatment with oral cyclophosphamide in steroid sensitive nephrotic syndrome has been established. \(^11\)\(^,\)\(^12\) A number of treatments have been tried for steroid resistant nephrotic syndrome, including CPO and cyclosporin without any sustained benefit. \(^10\)\(^,\)\(^13\) Intravenous cyclophosphamide (IVCP) has been used extensively in lupus nephritis and has been shown to be an effective form of therapy with significantly fewer side effects than oral cyclophosphamide. \(^14\)\(^-\)\(^16\) Further studies demonstrated beneficial role of IVCP in steroid resistant MCNS disease \(^13\) and steroid resistant FSGS. \(^17\)

We conducted a clinical trial in children with steroid resistant MesGN to investigate the efficacy of IVCP in this group of patients. The patients had long-term follow-up for four years after the treatment.

**Patients and Methods**

All patients included in this study had initial or late steroid resistant nephrotic syndrome. Initial steroid resistance was defined as failure to respond to treatment with oral prednisolone at a dose of 2 mg/kg/day given for four weeks. The patients who responded to such therapy initially, but failed to respond to daily oral prednisolone in a subsequent relapse, were diagnosed as having late steroid resistance. We performed renal biopsy for all patients with steroid resistant nephrotic syndrome. Between 1995 and 1997, 13 patients with steroid resistant nephrotic syndrome were diagnosed histopathologically as MesGN; the renal biopsies were examined by two independent pathologists who reported the findings on light and electron microscopy, and immunofluorescence. In order to diagnose MesGN the biopsies should show an increase in the mesangial matrix associated with hypercellularity and patent capillary lumina with thin capillary wall. The presence of IgM was determined by immunofluorescence. The glomeruli were characterized by the variable degrees of increased cellularity of the mesangium affecting all lobules. The hypercellularity was defined as mild with 4 to 5 nuclei in the mesangial zone, moderate with 5 to 7 nuclei and severe with more than 7 nuclei.

The IVCP was refused by only three parents. There were four patients with initial steroid resistant nephrotic syndrome and six with late steroid resistant nephrotic syndrome. There was no history of prior use of cytotoxic drugs in the ten patients who had IVCP. Prior to the treatment, all the patients had no history of hypertension or gross hematuria and their renal function was normal.
The patients were given pulse IVCP 500 mg/m$^2$ per month for six months. The cyclophosphamide was mixed with 250 ml of normal saline and infused slowly over 3-4 hours in order to reduce the risk of nausea and vomiting. A high oral fluid intake was encouraged for the following 24 hour period to promote frequent voiding of dilute urine in order to minimize the risk of hemorrhagic cystitis. To reduce further bladder toxicity, the patients received 2-mercaptoethane sulfonate sodium (MEZNA) during the first 12 hours after cyclophosphamide infusion. The patients received concurrently 60 mg/m$^2$ of oral prednisolone daily for four weeks and then 40 mg/m$^2$ per alternate day for four weeks, which was tapered over the following eight weeks, unless patient showed dependency. Complete remission following IVCP therapy was defined as qualitative resolution of proteinuria (negative or trace protein by dipstick method and normal albumin:creatinine ratio in the morning urine sample), normal serum cholesterol and triglyceride levels and serum albumin $\geq$ 3.5 g/dL. Patients were considered resistant to IVCP if they fail to respond after the 6th dose of the drug.

The parents were given instructions to do urine dipstick at home once a week. The children were followed up monthly for the first six months and thereafter once every 3 months. On each visit, the children were evaluated clinically for evidence of disease activity and complications. In addition, the follow-up investigations included albumin and creatinine in a spot urine sample; serum total protein, albumin, creatinine, hemoglobin and total leukocyte count, and lipid profile. The children were monitored for infection, leucopenia and alopecia. In the presence of infection or leucopenia, the next dose of IVCP was delayed until complete recovery from infection and/or normalization of leukocyte count. All the patients had a minimum follow-up of four years after stopping treatment. After completion of IVCP, the time of the first relapse was investigated as well as the subsequent clinical course including the development of steroid dependency. The proteinuria free period post IVCP was calculated from the time of completion of IVCP protocol to the occurrence of the first relapse.

**Results**

All the 10 patients completed the full trial, and become steroid responsive after the completion of IVCP therapy (Table 1).

Seven patients responded after the 2nd dose of IVCP; three of them sustained complete remission with no relapses over the four years observation period. These three patients had mild mesangial hypercellularity with no IgM deposition.

In the other extreme, there was one patient who could not be weaned from steroids and showed late response to IVCP. This patient had moderate mesangial hypercellularity with no IgM deposition and continued to be steroid dependent (prednisone 0.5 mg/kg per alternate day) until the end of the observation period.

Another two patients showed relatively late response to IVCP (No. 1 and 5 on Table 1); they developed early relapses, became steroid dependent (prednisone 0.3 mg/kg alternate day) by the end of the 1st year of follow-up and had moderate mesangial hypercellularity; one of them had 1+ IgM deposition.

There was one patient (No. 7 on Table 1) who could not be weaned off steroids after the 2nd relapse in the 2nd year of follow-up and continued to be steroid dependent; he had mild hypercellularity with 2+ IgM deposition.

The duration of resistance to steroids before IVCP therapy was not significantly related to the response to steroids after it. It is
obvious from the study that five out of six patients who achieved complete remission by the end of the study had mild mesangial hypercellularity and only one of them had a significant IgM deposition. It is interesting to see all the four girls in the study having complete remission and all the steroid dependent patients were males.

The side effects to IVCP were minimal; two patients developed nausea and vomiting during the infusion of IVCP. Alopecia, cystitis were not seen, leucopenia was not observed in any of the ten patients. The renal function was normal in all the patients by the end of the observation period. None of the patients had hypertension.

**Discussion**

Minimal change nephrotic syndrome, mesangial proliferative glomerulonephritis and focal segmental glomerulosclerosis account for the majority of the idiopathic nephrotic syndrome in children. Such children are usually treated by steroid and/or cyclophosphamide. The nephrotic syndrome due to MesGN tends to be associated with relatively high incidence of steroid resistance and progression to renal insufficiency.

Though the international study of the kidney disease in children (ISKDC) and the southwest pediatric nephrology study group investigated the clinical disease conditions in relation to MCNS and FSGS, the heterogeneity of the disease entity and its morphologic significance are still debated. This may explain the paucity of information in the literature regarding the use of cytotoxic drugs in the steroid resistant MesGN.

In the report of the Southwest pediatric nephrology study group, 12 of the 24 patients with mesangial hypercellularity treated with steroids had complete remission and three had partial remission. Of the nine patients resistant to steroid therapy, six received chlorambucil or cyclophosphamide but none responded. Resistance to steroid was associated with the most severe mesangial hyperplasia.

In our study, IVCP was found to be an effective therapy for children with MesGN; mild mesangial hypercellularity was associated with early response to IVCP, the majority was in complete remission after four years of the last dose of the drug. The patients with moderate mesangial hypercellularity had late response to IVCP with early relapse and steroid dependency. Hymes treated seven patients with MesGN with cyclosporin; one patient developed renal failure and only two patients had complete remission.

The presence of positive IgM deposit in the mesangium was not related to the eventual response to IVCP. This was comparable to the results of other studies that could not find clear correlation between the mesangial IgM deposits and the response to corticosteroid therapy or clinical outcome.

Ellence et al induced sustained remission by IVCP in children with MCNS who were steroid resistant; the results indicated a better outcome than prolonged management with oral cyclophosphamide. Later, Rennert et al reported 70% remission rate in patients with FSGS by using the same protocol. Our study extends the experience gained from patients with steroid resistant MCNS and FSGS as 100% of our patient sustained remission; our follow-up period was also longer than these two studies and confirmed the efficacy of IVCP in the long-term outcome.

None of our patients suffered from complications related to IVCP apart from mild nausea and vomiting in two patients. This may correlate to the lower cumulative dose than oral cyclophosphamide. The infusions were well tolerated and were administered in a day care setting. The possibility of non-compliance, which might occur with oral therapy, was negated.
In conclusion, we believe that IVCP is an effective and safe therapeutic modality in the steroid resistant MesGN.

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References

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<th>No.</th>
<th>Age (Year)</th>
<th>Sex</th>
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<th>Mesangial Cellularity</th>
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<th>Response to IVCP</th>
<th>Time of response after IVCP</th>
<th>Time of first relapse after last dose IVCP</th>
<th>No. of relapses over 4 years</th>
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