Original Article

Management of steroid resistant nephrotic syndrome in children with cyclosporine - a tertiary care centre experience

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Objective: To observe the response and adverse effects of cyclosporine in combination with oral steroids for management of idiopathic steroid resistant nephrotic syndrome in pediatric patients.

Methodology: It was an observational study conducted at Children's Hospital, Lahore, Pakistan from March 2014 to June 2015. Forty normotensive patients of idiopathic steroid resistant nephrotic syndrome between one and twelve years of age with normal renal function were included in the study. Patients were prescribed cyclosporine with prednisolone and were followed to see the response and adverse effects of drugs.

Results: Out of 40 patients, 20(50%) were males and 20(50%) females. Mesangioproliferative glomerulonephritis was found in 27(67.5%) patients followed by Focal segmental glomerulosclerosis in 9(22.5%) patients. Complete response was observed in 32(80%) children while partial response in 8(20%) patients at the end of six months. The most common adverse effects were cushingoid features seen in 26(65%) and cyclosporine related hypertrichosis in 34(85%).

Conclusion: Management of idiopathic steroid resistant nephrotic syndrome in children with a combination of cyclosporine and prednisolone provided good results as response to treatment was seen in 80% patients. (Rawal Med J 201;40:379-382).

Key words: Steroid resistant, Mesangioproliferative glomerulonephritis, Focal segmental glomerulosclerosis, cyclosporine, nephrotic syndrome.

INTRODUCTION

Steroid Resistant Nephrotic Syndrome (SRNS) is defined as failure of response to treatment with adequate dose of prednisone for four weeks.[1]. It accounts for about 10-15% of pediatric Idiopathic Nephrotic Syndrome (INS).[2] It is a variety of INS which represents a heterogeneous group of kidney disorders which are mostly resistant to immunosuppressive drugs.[3] Different gene mutations expressed by glomerular podocytes in SRNS are NPHS1, NPHS2, WT1, CD2AP and ACTN4 genes, which are located on different chromosomes.[4] The management of SRNS is a challenge for pediatric nephrologists, as remission is difficult to achieve and patients have significant risk of progression to end stage renal disease (ESRD).[5] The prognosis is guarded in case of failure and persistence of proteinuria.[6] The goal of treatment in these patients is to achieve complete/partial remission as the most important predictor of disease outcome is proteinuria.[7]

The histopathological spectrum of idiopathic SRNS includes focal segmental glomerulosclerosis (FSGS), Mesangioproliferative glomerulonephritis (MesangioPGN) and minimal change disease (MCD) in most patients. During the last few decades, there is increase in incidence of FSGS all over the world.[8] Though rare, yet FSGS is one of the important causes of progression to ESRD in about 50% of pediatric patients over a period of 5-10 years.[9] Cyclosporine, a calcineurin inhibitor, has shown favorable results in combination with steroids.[10,11] Besides immunosuppressants, Rituximab in another treatment option in SRNS.[12] The aim of this this study was to observe the response and adverse effects of treatment with cyclosporine in combination with oral steroids in idiopathic SRNS in pediatric patients.

METHODOLOGY

This was an observational study and was conducted in the Department of Pediatric Nephrology at Children's Hospital and Institute of Child Health, Lahore, Pakistan from March 2014 to June 2015. After approval from ethics committee, 40 normotensive patients of idiopathic SRNS of either gender between one and twelve years of age with normal renal function at presentation were included in the study. Patients were diagnosed as SRNS when they failed to achieve remission after four weeks treatment of oral prednisolone in terms of clearance of urine protein. Patients who were already on cyclosporine were also included in study. Patients with biopsy-proven MCD, FSGS and MesangioPGN were selected. Children with Membranoproliferative glomerulonephritis, Systemic Lupus Erythematosis and secondary nephrotic syndrome were excluded from the study.

The subjects were prescribed oral steroids in a dose of 30 mg/m^2/day in 3 divided doses for initial 4 weeks. Afterwards, steroids were given on alternate day in once daily dose in morning for 4 more weeks and then tapering started. Cyclosporine was given in dose of 150-200 mg/m2/day in 2 divided doses. Parents/patients were educated for monitoring of proteinuria by boiling/dipstick methods in order to assess the response to treatment. The first morning urine sample was also advised for protein to creatinine ratio, value in between 1.0 - 2.0 was considered as partial response while ratio less than 1.0 was taken as complete remission.

The subjects were followed monthly for six months after initiation of treatment. When there was no response to treatment in first three months, the treatment regimen was changed. Blood pressure was monitored on each visit and in case of hypertension, antihypertensive agents were added. Renal function tests, liver function tests, blood sugar, serum electrolytes, magnesium and uric acid was monitored. Patients who developed cyclosporine induced nephrotoxicity were dropped from the study. Data regarding the age of presentation, age of diagnosis, spectrum of histopathology, serum cholesterol and albumin levels, follow-up duration, drugs used for treatment and response to treatment was recorded. The data analysis was done by SPSS version 20.0 and $p< 0.05$ was considered statistically significant.

RESULTS

Out of 40 patients, 20(50%) were males and 20(50%) were females. The age range was 1.25 - 12 years (mean 5.23±3.20 years). The weight varied from 9.20-41 kg (mean18.73±7.39 kg). The descriptive statistics are given in Table 1 and 2. Microscopic hematuria was present in 10(25.0%) patients only.

Table 1. Descriptive statistics (n=40).

Variable	Mean±SD
Urea (mg/dl)	27.88±15.139
Creatinine (mg/dl)	.6350±.29747
Cholesterol (mg/dl)	396.4000±111.04210
Albumin (mg/dl)	2.3042±.45511
Cyclosporine drug level (ng/ml)	183.41±63.38

The most common histological pattern of SRNS was MesangioPGN, which was present in 27(67.5%) patients followed by FSGS found in 9(22.5%) subjects while MCD was seen in 4(10%) children only. Complete response was observed in 32(80%) patients whereas partial remission was achieved in 8(20%) children at the end of the trial. The whole blood cyclosporine trough levels were in the range of 85.20-319.30 ng/ml (mean 183.41±63.38 ng/ml). The relation between response to cyclosporine and trough levels was not significant (p=0.979).

Table 2. Blood pressure during treatment (n=40).

BP	Mean±SD
Systolic (mm Hg)	103.1000±8.92073
Diastolic (mm Hg)	69.9000±7.44139

The most common adverse effect encountered was cushingoid features seen in 26(65%) patients. Among cyclosporine related side-effects, hypertrichosis was observed in 34(85%) subjects while gingival hypertrophy was present in only 3(7.9%) patients. Hypertension and nephrotoxicity were noticed during treatment in two patients each.

Hyperuricemia was detected in 1(2.6%) child whereas other adverse effects like hypomagnesaemia, hyperkalemia and hyperglycemia were not observed in any of the patients.

DISCUSSION

In this study, we observed the response to treatment for six months after initiation of treatment and complete remission was achieved in 32(80%) patients while partial response was seen in 8(20%) children; no patient failed to show response. A similar study by Hamasaki et al[13] found MCD to be the most common histological diagnosis (23 patients), as compared to our study showing MCD in 4(10%) subjects only; they observed MesangioPGN in 5 and FSGS in 7 patients while in our study MesangioPGN and FSGS were seen in 27(67.5%) and 9(22.5%) children respectively. Their results revealed complete response occurring in 88.6% patients, which was not very different from our study (80%); partial response was seen in 2.8% subjects in contrast to our study showing partial response in 20% patients. None of the children failed to show response in our study while Hamasaki et al had 3(8.5%) patients without response.

The results of another trial by Klaassen et al[14] showed that 23(64%) patients with SRNS were confirmed as FSGS on histopathology and 53% patients achieved complete remission; partial response was seen in 28% patients while 19.4% patients showed no response. Niaudet et al[15] reported that the response to cyclosporine was minimal when used alone (only 7% patients achieved complete remission) as compared to when administered along with steroids (complete response was seen in 57.14% subjects). Another study included 65 patients with SRNS and were treated with cyclosporine along with steroids revealed 45 patients with MCD and 20 with FSGS - 27 patients obtained complete response (48% children with MCD and 30% of FSGS), 4 patients went into partial remission while no response was seen in 34 patients.[16] The most recent recommendation for management of SRNS by Metz et al[17] includes cyclosporine with possible adverse effects of nephrotoxicity and cosmetic effects in form of hypertrichosis. In our study, 85% of patients developed cyclosporine induced hypertrichosis while 5% had nephrotoxicity.

Cyclosporine is the most common drug used in management of SRNS with good results but monitoring for drug toxicity is essential.[18,19] In a randomized control trial by Plank[20] et al response to cyclosporine was compared with cyclophosphamide pulse therapy. A better response to cyclosporine was observed and it was recommended that cyclosporine be the first line medication in management of SRNS. Ponticelli et al[21] also showed that remission was achieved with cyclosporine in 60% of patients with SRNS. There are current recommendations of Kidney Disease Improving Global Outcome (KDIGO) that calcineurin inhibitors should be used as initial therapy for SRNS.[22] As presence of mutations in NPHS2 encoding podocin is a poor prognostic indicator, identification of the mutation can help in management of patients with SRNS in order to avoid unnecessary use of immunosuppressant medications on trial basis.[23]

Though the exact definition of SRNS varies in literature, patients in our study were defined as SRNS when they failed to show response to induction dose of prednisolone given for four weeks.[1] In contrast, some pediatric nephrologists administer three pulses of intravenous methylprednisolone on alternate days following completion of induction therapy in case of failure to achieve remission.[24] There is no definite therapy proposed for management of SRNS as it is a chronic disease with poor outcome.[25] Limitations in our study include cyclosporine drug level performed only once in each patient and short duration of follow-up of six months which, cannot determine the optimum duration of cyclosporine therapy in management of patients with SRNS.

CONCLUSION

Though management of SRNS in pediatric patients is difficult, it can be achieved with cyclosporine along with steroids as response to treatment was seen in 80% of patients. Normotensive patients with SRNS, who have normal renal function, can be prescribed combination of both these drugs with drug adverse effects in consideration.

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