IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 11 Ver. 3 (November. 2018), PP 55-57
www.iosrjournals.org

Role of High Dose Methylprednisolone in Children With Steroid Resistant Nephrotic Syndrome

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Abstract: *Treatment of Steroid Resistant Nephrotic Syndrome(SRNS) imposes one of the most difficult problems on nephrologists. IntraVenous Methyl Prednisolone(IVMP) is considered as one of the treatments of choice for children with oral steroid resistant Nephrotic Syndrome. We reviewed the clinical outcome in children with SRNS not responding to Tacrolimus under intravenous methyl prednisolone treatment. A total of 32 children presented with SRNS during the period from January 2011 to December 2017. Mean age of patients was 7.9 (Range- 4 to 9 years). Renal Biopsy was done in 12 out of 32 children which showed Focal Segmental Glomerulosclerosis (FSGS) in 8 patients, 2 patients had Minimal Change Disease (MCD), another 2 had Diffuse Mesangial Proliferation (DMP). Treatment with IVMP along with oral prednisolone induced remission in 12 patients (37.5%), 4 patients had complete remission and 8 patients had partial remission. We conclude, the study shows that IV Methyl Prednisolone can be tried in patients not responding to Calcineurin inhibitors in SRNS patients.*

Key Words*: Children, IV Methyl Prednisolone, Steroid Resistance, Tacrolimus*

Date of Submission: 28-10-2018 Date of acceptance: 14-11-2018

I. Introduction

The annual incidence of nephrotic syndrome ranges from 2-7 per 100000 children and prevalence is 12-16 per 100000 [1].There is epidemiological evidence of a higher incidence of nephrotic syndrome in children from South Asia [2-4]. The condition is primary (idiopathic) in 95% cases. 10% of children with Idiopathic Nephrotic Syndrome (INS) develop steroid resistance (SRNS), and 50% of them will progress to End Stage Renal Disease (ESRD) [5]. Tune et al first showed the beneficial results of treatment in patients with SRNS with high dose IVMP, given in a tapering schedule over 30 months [6-10]. Children with SRNS maybe treated with immunosuppressive agents such as cyclophosphamide, chlorambucil, cyclosporine and mycophenolate mofetil (MMF), along with non-immunosuppressive agents such as ACE inhibitors. There are not many published studies of SRNS who have not responded with Tacrolimus or decrease in GFR with CNI being treated IV Methyl Prednisolone. The aim of the study was to analyze the response achieved by treatment of SRNS patients with intra venous methyl prednisolone who have not responded with tacrolimus.

II. Material And Methods

We retrospectively analyzed the data of 32 children with steroid resistant nephrotic syndrome, who were later treated with tacrolimus, but did not remit or had decrease in GFR following initiation of tacrolimus. These children were treated with high dose IV Methyl Prednisolone during the period from January 2011 to December 2017.

The definition and criteria for nephrotic syndrome were same as used by ISKDC. Relapse is defined as the reappearance of proteinuria (>= 40 mg/day for 3 consecutive days). Patients were considered as Steroid Resistant if remission did not occur after 4 weeks of continuous steroid (Prednisolone) treatment followed by another 4 weeks of intermittent treatment. All these children with SRNS were treated with tacrolimus for a minimum period of 6 months at a dose of 0.1 mg/kg/day. Tacrolimus was stopped after they did not remit or had a fall in GFR. Children with documented SRNS were included but those children with clinical and laboratory pointers for secondary Glomerulonephritis were excluded.

The initial attack was treated with Prednisolone 2mg/kgin 2 or 3 divided doses.Steroid resistance was defined as lack of remission despite continuing steroids for 8 weeks.

We performed renal biopsy after consent in 12 out of 32 children with SRNS. Hepatitis B and C were excluded by serological tests before treatment with Tacrolimus. These patients were not analyzed for genetic mutations.

Tacrolimus was started at a dose of 0.1mg/kg/day in 2 divided doses. The patients received oral prednisolone in combination with Tacrolimus during the period of 6 months. Prednisolone started 1 mg/kg followed by tapering doses. Those children who do not respond to both oral steroids and tacrolimus were started on IV Methyl Prednisolone pulse therapy. Methyl prednisolone was given at a dose of 30mg/kg/day (30 doses) along with oral steroids starting at 2 mg/kg rapidly tapered to 10 mg/day.

Table 1

Initial	8 doses	Alternate day
Next	7 doses	Weekly
Next	4 doses	Fort nightly
Next	7 doses	Given monthly
Last 4 doses	4 doses	Alternate monthly

Injection Methyl prednisolone is given by diluting in 0.9%normal saline solution.Complete remission was defined as Urine: Creatinine ratio< 0.3 for 3 days, while partial remission as PCR 0.3-3 or at least 50% reduction ofproteinuria.

These children were followed up at frequent intervals with monitoring of the urine protein, blood pressure, renal function and infection. Time to onset of remission and maintenance of remission were noted in every child on follow up.The primary outcome of complete and partial remission at 9 months, based on proteinuria was observed. In patients who responded to 9 months were followed to look for sustained remission at 18 months (secondary outcome).Remission status was confirmed with the defined criteria. Serum creatinine level and glomerular filtration rate(GFR) estimation was considered as an indicator of renal function.Other parameters like serum albumin,serum cholesterol was measured. Angiotensin Converting Enzyme(ACE) inhibitor given for antiproteinuric effects. Statins for hypercholesterolemia were used in patients who received IV methyl prednisolone.

III. Results

Of the 32 children included in the study, 21 were boys (66 percent) and 11 were girls(33 percent).Ten patients(31%) had their parents' consanguineous marriage.Baseline demographic and clinical characteristics given in table 2 and laboratory characteristics 3.

Table 2 Baseline demographic & clinical characteristics

Mean age at enrolment (years)	7.91
Boys/Girls	21/11
Weight (kg)	24.5
Height (cm)	119.34

Table 3 Laboratory characteristics

Serum creatinine (mg/dl)	0.5
Serum albumin (g/dl)	2.69
Serum cholesterol (mg/dl)	326.24
eGFR (ml/min/1.732 sq. metre	106.24
Urine PCR mg/mg	7.3

Consent was obtained in 12 children and renal biopsy was done for these patients.Of which 8 patients had FSGS, 2 had MCD and another 2 with DMP.32 patients were started on IV methyl prednisolone.The outcome of therapy was given in table 4 and 5.Meantime for remission with IV Methyl Prednisolone is 4.5+/-1.5 months.Complications associated with IVMP therapy is given in table 6.

Table 4 Primary Outcome (9 months)

Remission	Number of patients
Complete	4(12.5)
Partial	8(25)
Treatment Failure	Number of patients
No response	18(56.75)
Treatment Withdrawal	1 (3.12)
Serious infections	1 (3.12)

Table 5 Secondary Outcome (18 months)

Remission	Number of patients (12)
Sustained remission	10 (83)
Non-nephrotic proteinuria	1 (17)

Table 6 Complications

Hypertension	3
Stunting	6
UTI	6
URI	16
Recurrent LRI	3
Peritonitis	2
Cellulitis abdomen	1
Herpes Zoster	1
Bronchopneumonia	1
Latent tuberculosis	1

IV. Discussion

Treatment of SRNS has not substantiallychanged over the past decade.Corticosteroids and Calcineurin inhibitors remain mainstay of therapy. There were limited options for SRNS patients who have CNI regimen failure/toxicity. The potential toxicity of high dose MP was a concern,but so were the complications of SRNS patients progressing to end stage renaldisease(ESRD).We did not observe in this study the deterioration of renal function during the follow up period.

Prior to this study there were few studies which used high dose IVMP for SRNS patients who don't respond to tacrolimus.Tune et al(6) first showed beneficial results of treatment in patients with SRNS using high dose IV MP given in a tapering schedule over 30 months.The results of our study show that treatment with high dose IV MP was effective in inducing remission in patients with SRNS in 37.5%cases.In the study by Tune and Mendoza et al(8) who treated 32 patients with SRNS children with FSGS,out of 32 patients(21 percent)achieved remission with IV MP and oral steroids alone and along with alkylating agents the remission rate is 65 percent.We have not used alkylating agents in fear of gonadal toxicity to children.Sa et al(11) had 40%complete remission with IV MP along with cyclophosphamide. Waldo et al(12) has complete remission in 38% and partial remission in 15%cases.Though we had complications in patients treated with IV methyl prednisolone,it is one of the treatment options available to treat SRNS patients who do not respond to tacrolimus.

We could not compare the efficacy of IVMP with different histopathologic variants as we have not done biopsy in all patients.

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DrP. Arun Prasath. "Role of High Dose Methylprednisolone in Children With Steroid Resistant Nephrotic Syndrome. " IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 11, 2018, pp 55-57.