ORIGINAL ARTICLE

Comparison of Efficacy of Tacrolimus Versus Cyclosporine in Childhood Steroid-Resistant Nephrotic Syndrome

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Abstract

Objective: To compare the efficacy of tacrolimus versus cyclosporine (Calcineurin Inhibitors) in the management of childhood steroid-resistant nephritic syndrome (SRNS).

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Paediatric Nephrology at The Children's Hospital and Institute of Child Health, Lahore, from August 2014 to September 2015.

Methodology: Patients of either gender aged 1 - 12 years, with the diagnosis of mesangioproliferative glomerulonephritis (MesangioPGN), focal segmental glomerulosclerosis (FSGS) or minimal-change disease (MCD) were included. Patients were assigned into two groups, one given tacrolimus in dose of 0.1 - 0.2 mg/kg/day in two divided doses, and other given cyclosporine in dose of 150 - 200 mg/m^2/day in two divided doses along with oral steroids 30 mg/m^2/day in divided doses, followed by alternate day with tapering dosage. Trough drug levels were done with dose adjustment accordingly. Patients were monitored and followed for the response to treatment and adverse effects of these two calcineurin inhibitors.

Results: A total of 84 patients, 58% males and 42% females, were included in the study. The age ranged from 1.25 to 12 years. The most common histopathological diagnosis was MesangioPGN (69.04%), FSGS (21.4%), and MCD (9.52%). Complete response was seen in 80.95% and 97.6% patients treated with cyclosporine and tacrolimus, respectively. Partial response was in 19.05% patients treated with cyclosporine and 2.4% in patients with tacrolimus. The most common adverse effect with cyclosporine and tacrolimus was hypertrichosis in 80.95% and 2.38%, hypertension 16.66% and 11.9% respectively while gum hypertrophy with cyclosporine was seen in 26.19% patients.

Conclusion: Tacrolimus was more efficacious than cyclosporine in achieving remission in childhood SRNS with insignificant adverse effects.

Key Words: *Childhood steroid-resistant nephrotic syndrome. Remission. Partial response. Adverse effects. Tacrolimus. Cyclosporine. Calcineurin inhibitors.*

INTRODUCTION

Nephrotic syndrome is the most common chronic renal disease which effects paediatric population world over. Its prevalence has been reported more in subcontinent paediatric population.[1] Steroid-resistant nephrotic syndrome (SRNS) patients are those who have persistent proteinuria even after taking 60 mg/m^2/day in divided doses of prednisone for a period of 4 weeks.[2] Though nephrotic syndrome is a disease with good prognosis, yet 10 - 20% patients show SRNS course and in our country it has been reported in 30% of patients.[3] The patients with SDNS are prone to steroid toxicity while SRNS patients show complicated disease course with involvement of glomerular filtration barrier and can progress to end-stage renal disease (ESRD) specifically with NPHS2 mutation.[4,5] The patients with SRNS are more at risk of disease complications, drug adverse effects and renal injury and even more difficult to manage when they fail to show response to calcineurin inhibitors.[6] If the patient is not responding to treatment and there is still proteinuria, then the prognosis is not good.[7] In the management of SRNS, the goal of treatment is either to achieve complete remission or at least partial remission as it is the most important predictor of disease outcome.[8] Focal segmental glomerulosclerosis (FSGS) or mesangioproliferative glomerulonephritis (MesangioPGN) and minimal change disease (MCD) are the histological diagnosis in idiopathic SRNS in paediatric population.[9]

A marked increase in incidence of FSGS has been noted over the last few decades. It remains the most important cause of ESRD in children as about 50% of paediatric patients with FSGS progress to ESRD over a time period of 5-10-years.[10] The agents used for treatment of SRNS include calcineurin inhibitors (tacrolimus, cyclosporine), angiotensin converting enzyme inhibitors (ACEI), chlorambucil, mycophenolate mofetil, and intravenous methylprednisolone as remission is reported to be achieved in 50 - 60% of patients with SRNS.[11] Another treatment option for SRNS management is Rituximab.[12] The optimal treatment option for management of SRNS

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and most effective combination of various drugs to be used, is not known as various studies showed variable response and adverse effects of different agent.[13]

The objective of this study was to compare the treatment response and adverse effects of either tacrolimus or cyclosporine in combination with oral steroids.

METHODOLOGY

This quasi-experimental study was conducted in the Department of Paediatric Nephrology, The Children's Hospital and Institute of Child Health, Lahore, from August 2014 to September 2015. After approval of the Hospital Ethical Committee and consent from parents, patients of either gender between the age of 1 and 12 years, diagnosed with nephrotic syndrome, were included in the study. Patients were taken as SRNS when no response to medication was observed in terms of clearance of urine protein despite getting 4 weeks' treatment of oral prednisolone in dose of 60 mg/m^2/day. Percutaneous renal biopsy was performed and only patients with idiopathic nephrotic syndrome as MCD, FSGS, and MesangioPGN were included. Patients having atypical nephrotic syndrome features as hypertension, deranged renal function tests, gross hematuria, and low complement levels were excluded from the study.

Patients were inducted consecutively with idiopathic SRNS having blood pressure less than 95th centile for age and height and normal renal functions. They were assigned to treatment either with tacrolimus or cyclosporine by labelling even and odd serial numbers, in the two groups, respectively. Tacrolimus was given in dose of 0.1 - 0.2 mg/kg/day and cyclosporine was given in dose of 150 - 200 mg/m^2/day, both in two divided doses (daily). Oral steroids were also prescribed in daily dose of 30 mg/m^2/day for one month and thereafter, every other day in gradually tapering dosage daily. Patients were called for regular follow-up in terms of compliance, response to treatment and for monitoring of drug adverse effects.

Parents/patients were educated for urine protein monitoring, the subsidence of edema and maintain record in written form. Urinary protein excretion was monitored either with urine dipstick or boiling method on the first morning voided urine sample. Complete remission was taken in patients who showed urine protein nil by urine dipstick or proteinuria < 4 mg/m^2/hour. Partial remission was taken when proteinuria with urine dipstick was + to ++ by dipstick (or proteinuria > 4 mg to < 40 mg/m^2/hour. No response was taken to drug when patient had proteinuria +3 on urine dipstick or > 40 mg/m^2/hour despite 3 months of appropriate therapy; and drug was stopped if no remission achieved within 3 months period.

Blood pressure was regularly monitored on each visit and antihypertensives were added if BP was more than 95th percentile for age and sex. If there was increase in blood pressure from base line then patients were started on captopril as antihypertensive. Angiotensin receptor blockers and calcium channel blockers were also added if blood pressure was not being controlled with single drug. There was also regular monitoring of renal function tests, liver function tests, blood sugar, electrolytes, magnesium and uric acid for different adverse effects of both drugs. Acute kidney injury was taken when there was fifty percent increase in serum creatinine level or an increase of 0.5 mg/dl from baseline. The drug-trough levels were done for both cyclosporine and tacrolimus. Initial trough levels for cyclosporine were aimed at 120 - 140 ng/ml and tacrolimus were aimed at 5.0 - 10.0 ng/ml and dose adjusted accordingly. Data regarding the age, sex, weight, blood pressure, urea, creatinine, histopathology, cholesterol, albumin, follow-up duration, drug used for treatment and response to treatment, drug adverse effects were recorded on specified proforma. Results were shown in the form of frequencies and percentages along with mean ± SD. Data was analyzed on SPSS version 20.0 and comparison was statistically analyzed by chi-square test. Results were taken significant at p-value < 0.05.

RESULTS

A total of 88 patients were included; 45 received tacrolimus and 43 patients received cyclosporine. Two patients from tacrolimus group expired due to septicemia after 2 months of therapy, whereas in cyclosporine group out of 43 patients, one patient was lost to follow-up. Out of 84 patients who were studied, 49 (58%) patients were males and 35 (42%) females. One patient from both groups were lost follow-up. Patient distribution in both groups is shown in Table I.

The patients included in the study were having age range of 1.25 - 12 years, with mean age of 5.95 ±3.20 years. Most of the patients were in between 3 to 8 years of age. The weight ranged from 9.20 kg to 47 kg with mean weight of 20.55 ±7.89 kg. Blood pressures along with other parameters as urea, creatinine, albumin, cholesterol level are given in Table II. The trough level of drugs, tacrolimus and cyclosporine were also done in study patients. The mean drug level of tacrolimus was 4.68 ±2.89 ng/ml and cyclosporine was 183.41 ±63.38 ng/ml.

The most common histopathological diagnosis was MesangioPGN which was present in 58 (69.04%) patients followed by FSGS which was present in 18 (21.42%) patients. MCD was present in only 8 (9.52%) patients. The patients diagnosed at presentation with SRNS were 42 (50%) and patients who showed course of disease as late non-responders were 42 (50%). The

Table I: Patient distribution.

Drug group	Gender	Frequency	Percent	Lost follow-up	Expiry	Total patients
Cyclosporine	Male	22	26.1	00	00	22
	Female	20	23.8	01	00	21
Tacrolimus	Male	27	32.1	01	02	30
	Female	15	17.8	00	00	15
	Total	84	100.0	02	02	88

Table II: Descriptive statistics.

Variables	Minimum	Maximum	Mean	Std. Deviation
Age (years)	1.25	12.00	5.9547	3.20920
Weight (kg)	9.20	47.00	20.5535	7.89181
Systolic blood pressure (mm Hg)	90.00	130.00	103.8140	9.13495
Diastolic blood pressure (mm Hg)	50.00	90.00	69.7674	7.41648
Urea (mg/dl)	12	90	29.33	15.284
S. Creatinine (mg/dl)	0.20	1.10	0.6214	0.21569
S. Cholesterol (mg/dl)	232.00	786.00	399.2262	126..38108
S. Albumin (mg/dl)	1.40	3.80	2.2915	0.58049
Cyclosporine drug level (ng/ml)	85.20	319.30	183.41	63.38
Tacrolimus drug level (ng/ml)	00.50	15.20	4.68	2.89

Table III: Response to treatment depending upon histology.

Drug	Histopathology	Response					
		Complete		Partial		No response	
		Frequency (n)	Percentage%	Frequency (n)	Percentage%	Frequency	Percentage %
Cyclosporine	FSGS	8/9	88.88%	1/9	11.12%	0/9	00%
	MCD	5/6	83.33%	1/6	16.67%	0/6	00%
	MesangioPGN	21/31	67.74%	6/31	19.35%	0/31	00%
	Total	34/42	80.95%	8/42	19.04%	0/42	00%
Tacrolimus	FSGS	9/9	100%	0/9	00%	0/9	00%
	MCD	2/2	100%	0/2	00%	0/2	00%
	MesangioPGN	30/31	96.7%	1/31	3.3%	0/31	00%
	Total	41/42	97.6%	1/42	2.4%	0/42	00%

overall complete response in 84 patients to both drugs was seen in 75 (89.28%) patients and partial response was seen in 9 (10.71%) patients. Complete response was achieved by 34 (80.95%) in the cyclosporine-group and partial response was seen in 8 (19.05%) patients, while in the tacrolimus group, response was seen in 41 (97.6%) patients and partial response was observed in just one (2.4%) patient. Comparison of response to treatment between the two groups showed p-value of 0.014, which is quite significant, as tacrolimus was more effective in achieving response to treatment as compared to cyclosporine. Response to treatment depending upon histology is shown in Table III.

The adverse effects like hyperglycemia, hyperkalemia, hypomagnesemia and hepatotoxicity were not observed in any patients in both groups. Hyperuricemia was seen in only one patient treated with cyclosporine. The most common adverse effect seen with treatment of cyclosporine was hypertrichosis which was seen in 34 (80.95%) patients while in tacrolimus group hypertrichosis was seen in just one (2.38%) patient. Gum hypertrophy was seen in 11 (26.19%) patients treated with cyclosporine. The group treated with cyclosporine had hypertension in 7 (16.66%) patients which was seen in 5 (11.9%) patients treated with tacrolimus, but the difference was not statistically significant (p=0.532). There was mild derangement of renal function tests seen in 2 (4.7%) patients treated with cyclosporine.

DISCUSSION

Steroid-resistant nephrotic syndrome accounts for 10 - 15% of patients and in paediatric nephrology practice its management is arduous. Calcineurin inhibitors are currently recommended as first line medications in management of childhood SRNS.

Choudhry *et al*. in their randomized controlled trial, non-blinded study, compared the efficacy and safety of tacrolimus and cyclosporine in paediatric patients with SRNS.[14] The study group included histopathological diagnosis as minimal change disease, FSGS or mesangioproliferative glomerulonephritis as our study inclusion criteria was also the same. In this study, patients were followed for only 6 months while in their study follow-up was done up to one year. Though rate of remission at 12 months of follow-up was the same in

both groups of their study, yet patients with relapse was more with cyclosporine. Their study showed hypertrichosis and gum hypertrophy as most significant adverse effect in patients treated with cyclosporine and the same were the findings in this study. Their study result in terms of efficacy showed that both drugs were of same efficacy when used with steroids while in the present study, tacrolimus efficacy was greater in achieving response.

A study done by Butani *et al*. showed that tacrolimus is effective and safe for treatment of SRNS in children.[15] Another study done by Wang *et al*. showed comparison of tacrolimus and cyclosporine in treatment of childhood nephrotic syndrome.[16] In their study, it was concluded that tacrolimus is more effective in short-term for achievement of remission in SRNS with less adverse effects as renal toxicity, as in the present study. Hamasaki *et al*. found that for cyclosporine response in a total of 35 patients, (23 patients with MCD, 7 with FSGS, and 5 with MesangioPGN),[17] complete remission was achieved in 88.6% patients while partial remission was in 2.8% patients and patients with no remission were 8.5%. In this study, majority of patients had MesangioPGN. In cyclosporine group out of 42 patients, 80.9% had complete remission and partial remission was seen in 19.1% patients. Roberti *et al*. reported outcome of SRNS paediatric patients treated with tacrolimus at single center with complete remission in 58% patients, partial response in 32% patients and no response in 9% patients.[18] There was remarkable difference in this study results as patients treated with tacrolimus showed complete response in 97.6% patients and partial response was observed in 2.4% patients.

Though one study done by Gulati *et al*. compared tacrolimus and cyclophosphamide and their study showed that tacrolimus along with alternate day steroids led to complete remission in 52.4% patients; and that combination therapy of tacrolimus and steroids was a safe initial treatment option in management of paediatric SRNS.[19]

Jahan *et al*. showed that SRNS paediatric patients, treated with tacrolimus, had a response of up to 80% with complete remission achieved in 64% patients and least adverse effects.[20] While in comparison, this study showed response rate of 97.4% in patients treated with tacrolimus. One retrospective study by Klaassen *et al*. concluded that cyclosporine in management of SRNS is an effective choice and it can be discontinued in many patients who have achieved remission.[21] Another recent study by Inaba *et al*. concluded that cyclosporine has got considerable remission rate in children with SRNS.[22]

The Canadian Society of Nephrology recommended in the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines that in children with SRNS, calcineurin inhibitor (CNI) be used as initial therapy along with low dose steroid therapy.[23] Lanewala *et al*. studied the effect of both cyclosporine and tacrolimus in primary FSGS. Their study showed complete remission in 52.6% patients and partial response in 35% patients treated with cyclosporine.[24] While tacrolimus showed complete remission in 28.5% patients and partial remission was seen in 71.4% patients, but their study results included both SDNS and SRNS patients. The prevalence of IgM nephropathy in one part of our country is in 13.6% patients presenting as SRNS as reported by Shakeel *et al*.[25]

As immunofluorescence was not available in the study centre, therefore, the authors could not differentiate patients with histopathology showing MesangioPGN from IgM nephropathy versus idiopathic MesangioPGN. The patients were followed for 6 months and results cannot be generalized for this duration of follow-up. Also patients in FSGS and MCD groups were small as compare to patients in MesangioPGN group and this should be taken into account when comparison to other centres is done.

CONCLUSION

The results of this study showed that tacrolimus is more effective in achieving complete remission as compared to cyclosporine with significantly less cosmetic side effects. However, these results cannot be generalized due to patient number in different histopathologic groups and absence of well designed RCT along with short duration of follow-up. So further multicentre randomized control trials are required.

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