Original article

A Randomized Controlled Trial of Intravenous Vs Oral Cyclophosphamide in Steroid Resistant Nephrotic Syndrome

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Abstract:

This is a randomized, parallel group, active controlled trial to compare the efficacy of intravenouswith oral cyclophosphamide in patients with steroid-resistant nephrotic syndrome (SRNS). Fifty consecutive children with SRNS were biopsied and then randomized to receive either oral cyclophosphamide (OCP) at a dose of 2mg/kg per day for 12 weeks or intravenous cyclophosphamide (IVCP) at a dose of 500 mg/m² per month for 6 months. Both groups received tapering doses of oral steroids. The response was evaluated in terms of induction of complete remission (CR) or partial remission (PR), time to remit and side effects. The groups were followed up to determine the duration of remission, percentage of patients who remain in sustained remission for more than one year after completion of therapy, change in steroid response status, progression to Chronic Kidney Disease stage 3 or more. Of the 50 patients, OCP was given to 25 children and IVCP to 25 children. The demographic data, histopathology, biochemical profile, and duration of follow-up in the two groups were comparable. The rates of induction of complete remission were 52% vs 44% and partial remission was 8% vs 8%in the intravenous and oral group respectively. Time to remit was shorter with OCP than IVCP (53days vs 84.4 days).Incidence of side effects (both major and minor) was 36% in IVCP vs 20% in OCP group. The actuarial cumulative sustained remission in our study was 12% in IVCP compared with 16% in OCP at 1 year after completion of therapy. 12% children in oral group and 12% in IV group exhibited restoration of steroid sensitivity. Thus in our study overall more than half of SRNS patients showed initial response to CP, but only one fourth patients had sustained remission on follow up. Oral and IV CP were equally efficacious and safe in idiopathic SRNS in children.

Keywords: cyclophosphamide, steroid-resistant nephrotic syndrome

Introduction:

Steroid resistant nephrotic syndrome (SRNS) is a heterogeneous disease characterized by persistence of proteinuria after 4-8 weeks of corticosteroid therapy [1, 2] Calcineurin inhibitors have a favorable response in SRNS. However calcineurin inhibitors are expensive, potentially nephrotoxic and need to be continued for a long period of time leading to issues of cost, compliance and complications. Although generic formulations have decreased the cost of therapy with calcineurin inhibitors the need for prolonged indefinite course, therapeutic drug monitoring, repeat renal biopsies makes these drugs beyond the reach of many patients from resource poor settings. Re-examining the role of less expensive drugs is therefore important. Cyclophosphamide is cheap,easily available,has a finite course leading to better compliance and hence remains an attractive option especially in developing countries.Although a report from the International Study of Kidney Disease in Children showed no benefit with oral cyclophosphamide[3], results from case series[4,5] and

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small trials[6,7] suggest it may be an effective therapy especially in Indian children.A few studies[6,9] on the subject seem to favour the intravenous route of administration over oral. This study was undertaken to define the utility of cyclophosphamide in the management of SRNS as well as to assess the efficacy of the oral versus the intravenous route of administration in these patients

Materials and Methods:

We prospectively studied consecutive patients of steroid-resistant nephrotic syndrome aged between 1 and 15 years, who presented to our nephrology division between January 2008 and June 2011. Informed parental consent and where applicable patient's assent was obtained before starting treatment. Nephrotic syndrome was defined as presence of hypoalbuminemia (<2.5 g/dl), proteinuria (>40 mg/m² per hour), and edema.Steroid resistance was defined as failure to achieve remission at the end of 4 weeks of treatment with daily prednisolone at the dose of 60mg/m². Exclusion criteria included age less than 1 year, pretreatment with immunosuppressive drugs other than prednisolone in the preceding 6 months, eGFR less than 60 ml/min calculated from height and serum creatinine using the Schwartz equation. It was also decided that patients who developed serious infections such as peritonitis, septicemia, meningitis, septic arthritis, or osteomyelitis more than once during cyclophosphamide therapy, would not be continued on cyclophosphamide therapy but would remain part of the study.

All the study patients underwent a renal biopsy. Theywere randomized according to random table to receive either IVCP (Group 1) or OCP (Group 2). Oral CP was given in the dose of 2mg/kg for duration of 12 weeks and IVCPwas administered as monthly pulses of 500 mg/m² per month for 6 doses. Both groups received alternate day steroids in tapering doses. Patients in IV group received hydration and premedication with ondansetron prior to cyclophosphamide administration. The drug was dissolved in 250 ml of normal saline and infused intravenously over 4 h in a supervised day-care setting. Patients were not given Mesna.

The children were followed fortnightly during the treatment period. At each visit, the child was evaluated clinically for evidence of disease activity and complications.Complete blood count and urine routine was done fortnightly during the therapy period. Serum albumin, cholesterol, creatinine, urine for spot albumin creatinine ratio, 24 hours urine albumin was done monthly during the study period. The children were monitored for infections, leukopenia (less than 4000/μL), and alopecia. When infections or leukopenia were present, the next dose of IVCP was delayed and OCP were withheld until complete normalization of counts or recovery from the infection. After completion of therapy, children were followed up monthly with clinical and urine examination and 2 monthly with biochemistry and quantification of proteinuria.

Response to therapy -

Short-term outcome was assessed at the end of cyclophosphamide therapy in terms of induction of complete remission (CR), partial remission (PR) or no response (NR). CR was defined as urinary protein being nil or trace on at least 3 consecutive days or urine protein to creatinine ratio <0.5. Partial remission was defined as urine protein excretion <2+, or urine protein to creatinine ratio between 0.5 and 2 and serum albumin >2.5 g/dl. No response was defined as persistence of 3+ or 4+ proteinuria, or urine protein to creatinine ratio>2 (nephroticrange

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proteinuria). Frequency and severity of side effects were compared in both the groups.Major side effects were defined as those that required hospitalization.

Follow-up post treatment -

The mean duration of remission after cessation of treatment was noted in each group. Sustained remission lasting for >1 year or acquisition of steroid-responsive status were considered as favorable outcomes. Persistence of proteinuria, development of low GFR (less than 60 ml/min), ESRD or deathwere considered as unfavorable outcomes.

Statistical Analysis -

Around 15 patients per year fulfilling the case definition could be enrolled, hence a period of three and a half year for enrolling patients.A constraint of sample size due to overall low incidence of SRNS was considered. Randomization was done by random number table. Concealment was done by sequentially numbered, sealed, opaque envelopes. The two groups were compared with respect to intention-to-treat principle. Comparison of variables in both groups is done by Mann-Whitney test and unpaired t-test and response in both groups analyzed by Fisher's exact test.

Results:

55 patients with idiopathic SRNS were identified. Two patients were excluded in view of increased serum creatinine at presentation and another three for not giving consent to cyclophosphamide therapy. Data of the remaining 50 patients was used for the purpose of the study. 25 patients were enrolled in each group. Group 1 (IV CP) had 17 males, 8 females whereas group 2 (OCP) had 14 males and 11 females. Baseline variables such as the age of onset of nephrotic syndrome, serum albumin and cholesterol, severity of proteinuria and histopathology were comparable between the two groups (Table 1).

Response to cyclophosphamide

In Group 1(IV CP), 15 of 25(60%) patients achieved remission. 13 achieved CR, 2 achieved PR. In Group 2(Oral CP), 13/ 25 (52%) achieved remission. 11 had CR and 2 PR. The results are comparable (p.076). Time to achieve remission was significantly longer in the Group 1(86.07+29.10days) as compared to Group 2 (47.45+26.06 days) (p=0.002).

Major side effects were seen in 7 patients (14%), 5 in the Group 1 and 2 in Group 2. The difference was not significant p 0.417. Minor side effects were seen in 7 patients; 4 in Group 1, 3 in Group 2; which were comparable (p=1.00). None of the patients required discontinuation of treatment in view of more than two major side effects in the study period. No patient died during the treatment period.None had hemorrhagic cystitis (Table 2). There was no significant change in hemoglobin or creatinine after cyclophosphamide therapy in either of the two groups (p=0.587and 0.936 respectively) (Table 3).

Follow up post treatment

The entire cohort was followed up for a mean duration of 17.8 months, 17.72 months in the Group 1, 17.92 in Group 2 which was similar (p=0.892).Mean duration of remission was similar in both groups 8.13+8.85 months vs 9.15+8.28 months (p=0.963).Number of patients who had sustained remission for upto 1 year post cessation of treatment was similar (3 patients in Group 1 vs 4 patients in Group 2). Restoration of steroid responsiveness was seen in 3 patients in both Group1 and Group 2.4 patients progressed to renal insufficiency during the study group (3 in Group 2, 1 in Group 1) and 1 patient from Group 2 died of progressive renal failure. One of the patients in renal insufficiency had

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a familial SRNS. One patient from Group 1 who had a rapid progression to ESRD was transplanted.

Discussion:

Studies on the use of cyclophosphamide in SRNS have reported variable response rates ranging from 0% to 70%.[6,7,8] Two randomized controlled trials concluded that children with SRNS respond poorly to cyclophosphamide with only 17-25% of patients achieving remission[3,8]. The study performed by Tarshish*et al* reported that there was no significant difference in the outcome of patients with FSGS treated with cyclophosphamide (p=1.00; RR, 1.050; 95% CI, 0.75-1.470) compared to oral prednisolone alone[3]. The ISKDC study,which included children with MCNS and FSGS reported a somewhat higher complete remission rate with cyclophosphamide and intermittent prednisolone (56%) than with intermittent prednisolone alone (40%), but there was no significant difference in the long term outcome between these treatments (p=0.13; RR,1.59; 95% CI,0.58-3.231)[8.]

An observational study by Gulati *et al* in patients with FSGS treated with IVCP and oral steroids reported CR in 65% and PR in 15% cases[9]. Favorable response to cyclophosphamide has been previously reported from India irrespective of the underlying histopathology. In a study to consider racial factors on cyclophosphamide sensitivity, 80% of Indian children with SRNS responded to oral cyclophosphamide and prednisone (including CR and PR both)[10]. High remission rates of 65% were noted with cyclophosphamide in Indian children with FSGS[11]. Histopathological heterogeneity, ethnic differences and genetic diversity may be responsible for these varied observations. Three published studies are available comparing the efficacy of oral versus IV cyclophosphamide (Table 4).

Earlier studies with small number of patients one with 13 MCNS patients and another with 12 FSGS patients found a superior response with IV cyclophosphamide 100% vs 17% in the MCNS study; 40% vs 0% in the FSGS study[6,12]. A more recent RCT by Mantan *et al* included both MCNS and Non MCNS which compared IV with oral cyclophosphamide found a comparable response with either route of administration. However their oral arm also had pulses of high dose IV dexamethasone at periodic intervals.

Our study included patients with both MCNS (58%) and Non-MCNS pathology (42%); 26% of our patients had FSGS and 16% mesangio-proliferative GN. Overall remission rate with cyclophosphamide was 56% with the majority (48%) achieving complete remission. The response rates were comparable in both the IV (60%) as well as the oral group (52%).This is similar to the findings reported by Mantan*et al* although we did not use any steroid pulses in the oral arm. The time to achieve remission in our study was significantly shorter in the oral (47.45+26.06 days) as compared to the IV group (86.07+29.10 days). The cumulative dosage of cyclophosphamide was significantly lower in the intravenous group. Major infectious complications requiring hospitalization was seen in a total of 14% of the children and was comparable in the two groups. Follow-up revealed that 25% of the children who achieved remission had sustained remission lasting > 1 year and 21 % showed a return of steroid sensitivity. They were equally divided in the oral and IV group. One child developed pulmonary tuberculosis 6 months after omission of cyclophosphamide therapy. 4 unresponsive patients 3 from the oral group and 1 from the IV group

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progressed to ESRD. 1 in the oral group had a familial NS.

Limitations:

A limitation in our study was that genetic evaluation was not done hence the contribution of genetically mediated resistance to therapy could not be assessed.

Conclusion:

Our study concluded that cyclophosphamide is a moderately effective drug in the management of SRNS in Indian children and induces remission in half the patients one fourth of whom maintain remission for more than a year. The efficacy as well as the safety was comparable in the oral as well as the intravenous group. Considering the cost and compliance issues cyclophosphamide remains an important drug in the setting of SRNS in Indian children in a resource poor set up.

Table 1: Baseline variables

Patient characteristics at enrollment	Group 1 (Intravenous cyclophosphamide)	Group 2 (oral cyclophosphamide)	p-value
No of patients	(n=25)	(n=25)	-
Age of onset	4.33 +3.32	4.68+3.02	0.566 not significant
Age at enrollment	4.54+3.46	5.34+2.96	0.229 not significant
Serum albumin(g/L)	1.69+0.66	1.92+0.57	0.089 not significant
Serum cholesterol	412.8	448.8	0.327 not significant
Serum Creatinine	0.53+.13	0.69+0.64	1.304 not significant
Urine albumin/Cr	5.88+4.49	6.87+7.68	0.078 not significant
Histopathology			-
MCNS	15	14	
FSGS	5	8	
Mesangio-proliferative	5	3	

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Table 2: Complications seen during therapy with cyclophosphamide

Side Effects	Group1	Group 2	p value	Total
Major			0.417	
Spontaneous bacterial peritonitis	4	1		5
Cellulitis	1	1		2
Minor			1.00	
Alopecia	3	2		5
Emesis	1	1		2

Table 3: Comparison of pretreatment and post treatment parameters

Parameters	Group 1	Group 2	p value	Total
Hb at the start of therapy	10.65+1.96	11.36+1.55	0.159	11.36
Hb at the end of therapy	9.76+1.19	9.99+1.71	0.587	9.99
Serum albumin at the start of therapy	1.69+0.66	1.92+0.57	0.089	1.2
Serum albumin at the end of therapy	2.73+1.06	2.76+1.15	0.831	2.76
Serum cholesterol at the start of therapy	412.80+84.7	448.80+129.50	0.327	430.8
Serum cholesterol at the end of therapy	266.20+137.55	257.12+139.82	0.793	261.16
Urine albumin/Cr at the start of therapy	5.88+4.49	6.87+7.68	0.938	6.87
Serum Cr at the start of therapy	0.53+0.13	0.69+0.64	0.192	0.69
Serum Cr at the end of therapy	0.52+0.12	0.52+0.13	0.936	0.52

Table 4: Comparative Studies of Oral versus Intravenous Cyclophosphamide

	Study ID	No. of Pts	Histology	Primary intervention	CR/PR
1	Elhence *et al* Ped Nephrol 1994	13 RCT	MCNS	A-IV CP 500mg/m^2 monthly for 6 month B-Oral CP 2.5 mg/kg for 8 weeks	A-CR 100% B-CR 17%
2	Adhikari *et al* Ped Nephrol 1997	12 Not a RCT	FSGS	A-IV CP monthly for 6 months plus IV methylpred for 3 consecutive days +oral steroids B-Oral CP 2.5 mg/kg for 18 months plus IV methyl pred for 3 consecutive days + oral steroids	A- CR 40% PR 20% B- CR 0 PR 86%
3	Mantan *et al* Ped Nephrol 2008	52 RCT	MCNS24, FSGS 14, Mesan PGN	A-IV CP monthly for 6 months plus AD steroids B-Oral CP 2.5 mg/kg for 18 months plus IV Dexamethasone	A-CR 53.8% B-CR47.8%

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