Original Article

Cyclosporine versus Cyclophosphamide in Childhood Nephrotic Syndrome

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ABSTRACT

OBJECTIVE: To determine the response of Cyclosporine versus Cyclophosphamide in childhood nephrotic syndrome.

PLACE AND DURATION: Nephrology Unit, National Institute of Child Health, Karachi, from April - September 2012.

STUDY DESIGN: Prospective Comparative study.

METHODS: 158 patients aged 6 months to 15 years with either steroid resistant (SR) or steroid dependent nephrotic syndrome (SDNS) were randomly assigned to receive either cyclosporine (CS –arm) or cyclophosphamide (CP-arm) for 3 months along with alternate day prednisolone. Treatment response and side effects were monitored clinically and by laboratory tests (spot urine protein–creatinine ratio in both arms, serum creatinine in CS-arm and complete blood counts in CP-arm). Outcome was defined after 12 weeks as complete remission (CR), partial remission and resistance. Data including demographics, type of NS, treatment response and adverse effects were collected and analyzed on SPSS-16.

RESULTS: There were 79 patients in each arm. Mean age in both arms was almost identical (6.8±3.9 and 6.9±3.7 years). Among 158, 87(55%) were SD and 71(45%) were SRNS. Majority (78.5%) in CS-arm achieved CR compared to 34.2% in CP- arm. This is highly significant (p value <0.001). Partial remission was observed in 19% of CS –arm compared to 48% in CP-arm and 2.5% were resistant in CS – arm compared to 17.7% in CP –arm. Hypertrichosis (5%), hypertension (3.7 %), gum hyperplasia(3.7%), nephrotoxicity(2.5%) were observed in CS -arm, whereas bone marrow suppression (7.5%) , alopecia and infections (2.5% each) were noted in CP- arm .

CONCLUSIONS: Cyclosporine was more effective in inducing remission (78.5%) as compared to cyclophosphamide (34.2%) in childhood NS.

KEY WORDS: Nephrotic syndrome, Cyclosporine, Cyclophosphamide, Steroid resistance Nephrotic syndrome.

This article may be cited as: Khemani S, Moorani KN. Cyclosporine versus Cyclophosphamide in Childhood Nephrotic Syndrome. J Liaquat Uni Med Health Sci. 2016;15(02):57-62.

INTRODUCTION

Management of childhood Nephrotic syndrome (NS) is challenging one. Treatment goals are to induce remission of proteinuria, to avoid complications of disease such as infections, thrombo-embolism and progressive renal dysfunction; and to limit the drug related toxicity[1-3]. Kidney Disease Improving Global Outcomes (KDIGO), for children having first episode of NS recommend standard course of oral prednisolone 60 mg/m^2/ day as single morning dose for 4-6 weeks followed by 40 mg/m^2 on alternate day with slow tapering over 3-6 months[4].

Majority of patients (85-95%) will respond within first few weeks and are called steroid sensitive nephrotic syndrome (SSNS)[2,4]. However 40-60% patients may behave as either steroid dependent (SD) or frequently relapsing (FR) cases and require repeated courses of corticosteroids, which is associated with high risk of steroid toxicity[1-3].

A small group of patients (<10%) may not respond to daily steroid therapy for 4 weeks either from very beginning or during the course of disease and are known as steroid resistant (SRNS)[1,3,4]. Thus children with steroid sensitive (SDNS and FRNS) and steroid resistant may require alternative therapy to avoid long term steroid toxicity in SD /FR and proteinuria associated progressive renal dysfunction in SR[3-5].

Therefore, alternative immunosuppressive (IS) therapies to treat difficult nephrotic syndrome (SRNS and SDNS/FRNS) includes alkylating agents (cyclophosphamide, chlorambucil), immune-modulator (levamisole), calcineurin inhibitors (CNI) like cyclosporine and tacrolimus, antimetabolites (mycophenolate mofitil) and more recently rituximab have been used with varying success and adverse effects[5-9]. CNIs are recommended as first-line therapy

for children with steroid-resistant NS and as steroid-sparing agents for children with frequently relapsing or steroid-dependent NS.[4, 5] Cyclosporine acts by inhibiting interleukin-2-driven T-cell activation and directly targeting the podocyte and stabilization of actin cytoskeleton. CS has been recognized as effective in treating children with SD and SR with success rate of 50-100% [10-12].

Cyclophosphamide (CP), an alkylating agent; when used in SDNS and FRNS for 8-12 weeks helps to induce remission of proteinuria, to preserve renal functions and thus reduce the risk of chronic kidney disease (CKD)[4,10,11]. The mechanism of action of cyclophosphamide is thought to be due to immunosuppressive effects on T-cells and it may directly prevent cell division by cross-linking DNA strands and decreasing DNA synthesis[10,11]. Cyclophosphamide and Cyclosporine (CS) have been used as second line therapies after initial steroid in SDNS and SRNS[4-5]. In comparing short term safety profile of CS and CP, CS has been found to be superior to CP in inducing remission in SRNS [5,8,9]. So in SRNS, cyclosporine is considered as first line treatment and when used in combination with low dose of prednisolone it is more effective than used alone[10-13]. However, lower rates of relapse, long relapse free period and permanent remission has been found in CP responsive SDNS, FRNS and in some cases of SRNS[13-15].

In Pakistan, use of both CS and CP for induction of remission in difficult to treat nephrotic syndrome (SD/FR and SRNS) have been reported with variable response [16,17].

In this randomized study we compared the short term effects of two drugs in similar group of patients to assess the response in terms of remission and their adverse affects in steroid resistant and FR/SDNS. So that appropriate recommendation may be made about their use in such group of patients.

Objective: The objective of this study was to determine the response of cyclosporine versus cyclophosphamide in childhood nephrotic syndrome.

PATIENT AND METHODS

This prospective comparative study was conducted in the Nephrology department of National Institute of Child Health (NICH), Karachi from April to September 2012 after approval from NICH ethical review Committee. A purposive sampling technique was used and a total of 158 patients with childhood nephrotic syndrome, 79 in each group were studied. Sample size was calculated on the basis of 0.016% prevalence, at 95% confidence interval with 0.3% precision using EPI software version 6[3].

Children with steroid resistant and steroid dependent nephrotic syndrome (as per operational definition) of either gender, aged 6 months to 16 years were enrolled after informed consent from parents. Parents were explained about the treatment protocols, its compliance, and regular follow up and expected side effects of the drugs.

Irrespective of underlying histopathology and steroid response, patients were randomized to receive either oral cyclophosphamide (CP–arm) in a dose of 2-3 mg/kg/day for 12 weeks (total cumulative dose <168mg/kg) or cyclosporine in a dose of 5mg / kg / day in two divided doses for 12 weeks (CS-arm). Patients were followed weekly in outpatient department to monitor clinical response like disappearance of edema, side effects of CS like hypertension, hypertrichosis; for cyclophosphamide such as anemia, petechiae, hematuria, alopecia and infection like acute respiratory infection /diarrhea. Spot urine protein creatinine ratio (SUPCR), complete blood counts (CBC) for bone marrow suppression (in cases of CP) and serum creatinine (Cr) for nephrotoxicity (in cases of CS) were done as baseline and at week 1 and thereafter 2 weekly. Outcome was defined after 12 weeks of therapy as complete remission (SUPCR <0.2), partial remission (SUPCR 0.2-2.0) and resistance to prescribed drug (persistent edema and proteinuria with SUPCR >2) [2-5]. Cyclophosphamide was withdrawn for one week if patient develop either bone marrow suppression or infection and resumed to complete the calculated cumulative dose once patient recovered from infection and bone marrow depression.

The dose of CS was reduced by 25%-30% if serum Cr of patient raised by more than 25-50% above the baseline or above normal level and drug was continued at lower dose till subsequent serum Cr become normal or stopped if remains persistently high.

Data including demographics, type of NS according to steroid response (SD or SR), response to treatment and adverse effects were collected and analyzed on SPSS-16. Qualitative variables like gender, type of NS were represented by frequencies and percentages. Mean ±SD was calculated for quantitative variables like age. The response to treatment in two arms was compared using Chi-square test at 5% level of significance.

***Definitions*:**

Complete remission (CR) was defined as disappearance of edema and proteinuria (SUPCR <0.2), Partial remission (PR) as disappearance of edema but persistence of non-nephritic range proteinuria (SUPCR

0.2-2). SDNS was defined as two consecutive relapses occurring on switching to alternate prednisolone and SRNS if edema and proteinuria (SUPCR > 2) persists after 4 weeks of 60mg /m^2 / day of prednisolone.
CS and CP resistant NS were defined if nephrotic range proteinuria and edema persisted after 12 weeks of therapy with either CS or CP) [4,11].

RESULTS

Among 158 patients studied, 83 (53%) were male and 75 (47%) female with male to female ratio of 1.10:1. Table I shows the age group distribution in two groups and the mean age in CS-arm was 6.8±3.9 and in CP-arm 6.9±3.7 years. There was no difference of mean age in two groups (p=0.436). Majority of patients (58. 22%) were above 5 years of age in both arms. Mean weight and height in CS-arm was 21.3 ±9.4 kg and 110.03 ±23.7 cm, and in CP arm it was 21.16 ±9.08 kg and 110.06 ±23.8 cm respectively. Status of patients according to primary response to corticosteroid treatment at the time of enrolment and before starting CS or CP treatment in each arm is given in Table II. This table shows that 87 children (55%) were steroid dependent (SD) and 71(45%) were steroid resistant (SRNS). This table also shows that there was no difference in number of patients with SDNS in two arms (CS= 44 versus CP=43, p= 0.50). Similarly there was no difference in number of patients in SRNS (CS 35 versus CP 36). Table 3 shows outcome of treatment at 12 weeks of therapy. Overall response to therapy shows that 89 patients (56.3%) with nephrotic syndrome achieved complete remission, 53(33.5%) partial remission and whereas 16(10.1%) were resistant to either cyclophosphamide or cyclosporine. However when comparison of response to each treatment regimen, it is evident that majority of patients (78.5%) in CS-arm achieved complete remission compared to 34.2% in CP-arm. This is highly significant (p value <0.001). Partial remission was observed in 19% of CS –arm compared to 48% in CP-arm. Drug resistance was found in only 2.5% in CS –arm compared to 17.7% in CP –arm.
Side effects of treatment groups are shown in Table 4. This shows that in CS –arm, 4 children (5%) developed hypertrichosis, each 3 developed hypertension (3.7%), gum hyperplasia (3.7%) and whereas nephrotoxicity was observed in two cases(2.5%).
In CP-arm, 6 patients (7.5%) showed bone marrow suppression and each two developed alopecia and infections (2.5%). Nephrotoxicity was resolved on reduction of cyclosporine. Bone marrow recovered after withdrawal of cyclophosphamide for one week and drug was not discontinued permanently in a single patient.

TABLE I: AGE GROUPS OF CHILDHOOD NEPHROTIC SYNDROME IN CYCLOSPORINE AND CYCLOPHOSPHAMIDE ARMS (n=158)

Age groups	Cyc-losporine	Cyclophos-phamide	Total n (%)
Mean age ±SD	6.8 ±3.9	6.9 ±3.7	
≤ 5 Years	34 (43.03%)	32 (40.50 %)	66 (41.77%)
>5 years	45 (56.96%)	47 (59.49%)	92 (58.22%)
Total	79(100%)	79(100%)	158(100%)

TABLE II: STATUS OF PATIENTS ACCORDING TO STEROID RESPONSE IN CHILDHOOD NEPHROTIC SYNDROME (n=158)

Steroid response	Cyc-losporine	Cyclophos-phamide	Total
*SDNS	44 (56%)	43 (54%)	87 (55%)
†SRNS	35 (44%)	36 (46%)	71 (45%)
Total	79(100%)	79(100%)	158(100%)

P-value: 0.50
**Steroid dependent nephrotic syndrome, †Steroid resistant nephrotic syndrome.*

TABLE III: RESPONSE TO CYCLOSPORINE VERSUS CYCLOPHOSPHAMIDE IN CHILDHOD NEPHROTIC SYNDROME (n=158)

Outcome	Cyc-losporine N (%)	Cyclophos-phamide N (%)	Total
Complete remission	62 (78.5%)	27 (34.2%)	89 (56.3%)
Partial remission	15 (19.0%)	38 (48.1%)	53 (33.5%)
Resistant	2 (2.5%)	14 (17.7%)	16 (10.1%)
Total	79(100%)	79(100%)	158(100%)

P-value: <0.001

DISCUSSION

Childhood nephrotic syndrome generally has a favorable prognosis, however management of children with SDNS and SRNS have been challenging[1-3]. Though various protocols for such difficult to treat cases are available but there is variation in disease severity,

TABLE IV: SIDE EFFECTS OF CYCLOSPORINE VERSUS CYCLOPHOSPHAMIDE IN CHILDHOOD NEPHROTIC SYNDROME (n=22)

Side Effects	Cyclosporine	Cyclophos-phamide
Bone Marrow Suppression	-	6(7.5%)
Alopecia	-	2(2.5%)
Infections	-	2(2.5%)
Hematuria	-	1(1.25%)
Hypertension	3(3.7%)	-
Hypertrichosis	4(5%)	-
Nephrotoxicity	2(2.5%)	-
Gum hyperplasia	2(2.5%)	-

response to treatment and availability of resources for provision and monitoring of drug protocols in different countries[1-4].

In this study we compared the efficacy of CS with CP in difficult NS and found that CS was effective in inducing complete remission of proteinuria in 78.5% compared to cyclophosphamide, which was effective in only 34% of cases. (p value <0.001). Many studies have shown that CS is effective in 60-85 % of difficult cases of NS (both SD and SRNS)[5,10-12,18]. In a multicenter controlled trial of CS testing the efficacy and safety of CS versus CP, Plank C et al showed that CS can induce remission in 60% of SRNS compared to 17% after cyclophosphamide[13]. In a study on SRNS from Lahore it has been reported that CS induced complete remission in 75%, partial remission in 25% whereas CP induced complete remission in 50%, partial remission in 10% and 40% were resistant[16]. In an earlier study when CS used for 12 weeks' duration in steroid resistant "Focal Segmental Glomerulosclerosis", the overall response was 86.6% with CR in 56.6% and partial response in 30%[18]. This was similar to overall response to CS (78.5%) in current study[19]. However a higher resistance to CS (40%) has been reported recently from Multan by Imran M et al compared to ours (2.5%)[20].

We observed a high resistance to cyclophosphamide (66%) in this study. Similar percentages of resistance to cyclophosphamide have been reported in earlier studies[14,21]. In a study from Iran, Otukesh H et al also reported 80% of resistance to CP in SRNS[22]. Local study from Pakistan has also showed that CP was ineffective in 50% of children with SRNS[16].

Another important finding in our study was that the partial remission to CS was less(19%) compared to CP which was 48% suggesting that CS is more effective than CP in inducing short term remission. Similar findings have been reported in other studies[17-21]. These partial responders to cyclophosphamide will ultimately need either CS or mycophenolate for induction and maintenance of remission to avoid steroid toxicity, risk of relapses and serious infections[21-24]. Although aggressive therapy with alkylating agents like cyclophosphamide has been common in past, but due to lack of efficacy, risk of severe infection, bone marrow suppression, long term risk of sterility and secondary malignancies, it has been replaced by other immunosuppressive therapies [5-7,19 ,24-26]. But due to high cost of cyclosporine, cyclophosphamide is still used as first line immunosuppressive alternative drug for difficult to treat nephrotic syndrome in many developing countries including Pakistan[16,17,19,20].

We observed bone marrow suppression (leucopenia) in 7.5% of cases in CP arm compared to reported figure of 32% in meta-analysis by Latta K et al[23]. Bone marrow suppression has not been reported with CS, a finding endorsed by the current study. Alopecia was noted in 2.5% of children received CP which is significantly less than 18% as reported by others[10, 22]. Though, nephrotoxicity (raised serum creatinine) is the main side effect of CS but was observed in only 2.5% of cases which is less than 6% reported in the literature[10, 18]. Gingival hyperplasia and hypertrichosis were observed in 2.5% and 5% of cases which is much less than reported in literature of 32% and up to 70 % of cases respectively[10,18, 25].

CONCLUSION

The response to cyclosporine was superior to cyclophosphamide in induction of remission in nephrotic syndrome. Complete remission was significantly higher (78.5%) in CS arm compared to cyclophosphamide (34.2%). A high resistance to cyclophosphamide compared to cyclosporine is comparable to literature.

RECOMMENDATION AND LIMITATION

We recommend CS as first line alternative immunosuppressive therapy in difficult cases of nephrotic syndrome. However, randomized controlled trials comparing the CS with mycophenolate mofitil should be undertaken.

An important limitation of the study was selection of cases without considering underlying histopathological

findings which is against the standard practice.

Conflict of interest: None

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