Original Article

Cyclophosphamide versus cyclosporine in children with frequent-relapsing and steroid-dependent nephrotic syndrome in Khartoum State, Sudan

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Absteact:

Background: in children with frequent-relapsing and steroid-dependent (FR/SD) nephrotic syndrome (NS) remission can be achieved with either cyclophosphamide (CPM) or cyclosporine (CSA). Our objective was to compare the efficacy and safety of these agents.

Methodology: Records of all children with FR/SD NS who received CPM or CSA at the Pediatric Renal Unit, Soba Hospital, Khartoum, during the period 2005–2015 were retrospectively reviewed. Main outcomes were: remission rate, relapse rate, and renal outcome.

Results: We studied 82 children with FR/SD NS treated with CPM (59.8%) or CSA (40.2%). Males were 69.5% and females 30.5%. The mean admission age was 5 ± 3.10 years. At 6 months, 77.6% children on CPM and 60.3% on CSA were in complete remission (CR), (P=0.012) whereas 22.4% versus 39.4% relapsed respectively (P=0.012). At 12 months, 57.5% on CPM and 72.7% on CSA were in CR, (P=0.013) whereas 42.5% versus 27.3% relapsed respectively, (P=0.013). At 24 months, 16.6% on CPM and 29% on CSA were in CR, (P=0.030) whereas 83.4% versus 71% relapsed respectively, (P=0.030). The mean number of relapses per 24 months were 1.7± 0.86 in CPM group versus 2.2 ±0.85 in CSA group, (P=0.72). Mild complications were recorded in 12.4% of patients on CPM group versus 33.3% on CSA, (P=0.031). At the latest follow- up, there was no significant change from basal levels of TWBC, mean serum creatinine, GFR, or BMI, (P>0.05 for all parameters).

Conclusion: In children with FR/SD NS, both CPM and CSA were effective and safe in achieving remission with less risk of serious side- effects. However, long-term remission was less stable with both agents.

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Introduction:

About 70% of all children with steroid-sensitive NS (SSNS) will relapse; of whom 60% relapse frequently or become steroid-dependent[1-3]. Treatment of such children is difficult since prolonged steroid therapy may cause serious side-effects as well as increasing the risk of mortality [4]. A Cochrane meta-analysis showed that in children with SSNS, CPM and chlorambucil reduced the rate of relapse as compared to treatment with prednisone alone with no significant difference in relapse rate between the two drugs. No difference in efficacy (maintenance of remission) was found between intravenous CPM and oral CPM. CSA was found to be as effective as CPM and chlorambucil. The main concern about CPM is gonadal toxicity, but limitation of treatment to 8 weeks/course (2.5 mg/kg/day) minimizes this

side-effect without greatly increasing the rate of relapse [5]. Limitations of using CSA were the relapse rate and nephrotoxicity [6]. Therefore, it is uncertain which one of the two agents is better for children with FR/SD NS. The objective of this study was to compare the efficacy and safety of CPM and CSA in FR/SD NS.

Patients & Methods:

We retrospectively reviewed the records of all children (age >1-18 years) with FR/SD NS who were treated with oral CPM or CSA and followed-up at the Pediatrics Nephrology Unit, Soba University hospital, Khartoum, in the period between January 2005 to February 2015. We excluded all cases with incomplete records and those with follow- up period <6 months. NS, remission, relapse, FR, and SD were defined according to the International Study of Kidney Disease in Children (ISKDC) [7, 8]. NS: protienuria >40 mg/hr/m^2 or urine albumin/creatinine ratio (UACR) >0.2 gm/mmol and hypoalbuminemia <25 g/L ± edema. Steroid-responsive: complete remission (CR) with steroid treatment. CR: protienuria <4 mg/hr/m^2 or negative or trace (<30 mg) on Albustix for 3 consecutive days. Partial remission (PR): persistence of urine dipstick protienuria of 30-100 mg/dl with normalization of serum albumin. Sustained remission: no relapse for at least 6 months. Relapse is: protienuria ≥40 mg/hr/m^2 or Albustix +++ for 3 consecutive days after being in remission. Frequent relapse (FR) is 2 or more relapses within 6 months of initial response or 4 or more relapses within one year. Steroid-dependent (SD) is 2 consecutive relapses during steroid therapy or relapse within 14 days after stopping therapy.

Age, gender, height, weight and blood pressure, urine dipstick test for albumin, urine UPCR, hemoglobin, blood urea, serum creatinine, serum calcium and phosphorous and histological patterns were recorded. Treatment protocols and responses, complications, and outcome were also recorded. Renal impairment was defined as serum creatinine above the upper limit of normal for age. Estimated glomerular filtration rate (eGFR) was calculated from the Schwartz formula [9]. CKD was defined as GFR < 60 ml/min/1.73m^2 for ≥ 3 months and CKD5 requiring RRT as GFR <15 ml/min/1.73 m^2 [10, 11]. Hypertension was defined as blood pressure above 95th percentile for age [12]. Following induction of CR with prednisolone, CPM or CSA was started. Oral CPM was used in a dose of 2-2.5 mg/kg/day for 8-12 weeks in maximum cumulative dose of 168/mg/kg[13]. Steroid therapy was tapered and stopped over the next 8 weeks. CSA was given at a dose of 4-5 mg/kg daily for 12 months and gradually tapered and stopped [14]. Prednisone is then gradually reduced by 0.15-0.25 mg/kg every 4 weeks to a maintenance dose of 0.25-0.5 mg/kg continued for six or more months. Trough (12-hour) CSA levels were kept between 100-150 ng/ml. Indications for renal biopsy were: significant persistent hypertension, gross haematuria, and renal impairment. Main outcomes measures were: remission rate, relapses rate, complications and renal outcome.

Statistics:

Data was organized into master sheet using the Statistical Package for Social Sciences (SPSS) version 19. Data was presented using frequencies and percentages for categorical variables and means ± standard deviation (SD) for numerical continuous variables. Variables were compared using independent t-test for independent variables. For all statistical analysis P value less than 0.05 was as considered as statistically significant.

Ethical approval:

Ethical clearance was obtained from the Ethical Committee in Sudan Medical Specialization Board and Soba Hospital Research Committees.

Results:

We studied 82 children: 75 (91.4%) with SD NS and 7 (8.6%) with FR NS were included in the study. Males were 57 (69.5%) and females 25 (30.5%). Male to female ratio was 2.3:1. The mean age at admission was 5 ± 3.10 (range 1.2 -16) years. Oral CPM was used for 49 patients (59.8%) and CSA for 33 (40.2%).

Characteristics of CPM and CSA treated groups at initiation of treatment are shown in table 1. There was no statistically significant difference between the two groups except for the mean follow-up period which was significantly longer in CSA group (P=0.013). Renal biopsy findings were available in 36 patients (43.9%), showing no predominance of MCD, Table 2. CR, PR and relapse rates at 6, 12, and 24 months in CPM and CSA groups were compared and shown in Table 3. At 6 months: CR rate was significantly higher (P= 0.012) and the relapse rate was significantly lower in CPM group than CSA group (P= 0.012). Among the 11 cases who relapsed on CPM, eight had nephrotic protienuria and three had significant non-nephrotic protienuria. Among the 13 who relapsed on CSA, three had nephrotic protienuria and ten had significant non-nephrotic protienuria. At 12 months: 40 patients on CPM and 33 on CSA presented to follow-up. The CR rate was significantly higher (P= 0.013) and the relapse was significantly lower (P= 0.013) in CSA group than CPM group. At 24 months: 30 patients on CPM and 31 on CSA presented to follow-up. The CR rate was significantly lower (P= 0.030) and the relapse rate was significantly higher (P= 0.030) in CPM than in CSA-treated patients. Variables such as age, gender, initial levels of serum albumin, serum cholesterol and serum creatinine, pattern of relapses (FR versus SD) and renal histopathology were not significantly correlated with of rates of CR in CPM compared to CSA group (P=0.328, 0.286, 0.897, 0.112, 0.7.17, 0.834 and 0.336 respectively). The mean number of relapses per 24 months in CPM group was 1.7± 0.86 and in CSA 2.2 ±0.85 with no statistically significant difference (P=0.72). The renal outcome measures at latest follow-up, as measured by serum creatinine and GFR, did not change from the baseline levels (P>0.05 for all parameters) as shown in table 4. Mild complications of treatment were more observed in CSA-treated (33.3%) than CPM-treated (14.2%) patients (P=0.013), Table 5. The mean TWBC and BMI did not change significantly from basal levels with either CPM or CSA treatment (P>0.05 each).

Table 1: Characteristics (demographic, clinical and biochemical) of the study groups at the start of treatment

Patients characteristics	**CPM group (n =49)**	**CSA group (n =33)**	**P- value**
Male : Female ratio	3.5 : 1	1.4 :1	0.086
Mean age (years)	5 ± 3.05	5 ± 3.23	0.955
Mean Body Mass Index (BMI)	15.89±2.71	16.82±3.09	0.276
SDNS	46(93.9%)	29 (87.9%)	0.340
FRNS	3 (6.1%)	4 (12.1%)	0.340
Serum creatinine	0.58±0.46	0.73±0.39	0.797
Mean GFR (ml/min/1.73m^2)	99.70±40.31	130.01±118.34	0.581
Mean S. albumin (gm/L)	2.48 ± 0.878	2.31 ± 0.60	0.425
Mean S. cholesterol (mg/dl)	342.06±186.00	258.63±68.92	0.169
Hypertension	11(22.4%)	8 (24.2%)	0.850
Mean follow-up (months)	39.53±28.79(7-132)	56.72±31.51(15-132)	0.013*

* P value is statistically significant

Tabe 2. Renal biopsy findings in the study group, (n = 36)

Histopathology lesion	CPM Group	CSA group	Total
Minimal change disease (MCD)	7 (43.8%)	5 (25.0%)	12
Focal segmental glomeruloscelorosis (FSGS)	1 (6.20%)	9 (45.0%)	10
Mesangial proliferative glomerulonephritis (MesPGN)	8 (50.0%)	6 (30.0%)	14
Total	16	20	36

Table 3. Complete remission, partial remission and relapse rates at 6, 12 and 24 months (CMP versus CSA group)

Period of follow up	CPM group	CSA group	P value
At 6 months			
Complete remission	38/49 (77.6%)	20/33 (60.6%)	0.012
Relapse	11/49 (22.4%)	13/33 (39.4%)	
Nephrotic protienuria	8/49 (16.3%)	3/33 (9.1%)	0.012
Significant non-nephrotic protienuria	3/49 (6.1%)	10/33 (30.3%)	
At 12 months			
Complete remission	23/40 (57`5%)	24/33 (72.7%)	0.013
Relapse	17/40 (42.5%)	9/33 (27.3%)	0.013
At 24 months			
Complete remission	5/30 (16.6%)	9/31 (29%)	0.030*
Relapse	25/30 (83.4%)	22/33 (71%)	0`030

* P value is statistically significant

Table 4. The mean TWBC, serum creatinine, GFR and BMI of the study groups (basal versus latest follow up)

Treatment group	Parameter	Basal	Latest follow up	P value
Cyclophosphamide	Mean TWBC	9.93^3 ±4.15	11.08^3 ±4,31	0.060
	Mean serum creatinine (mg/dl)	0.58 ±0.46	0.61±0.32	0.782
	Mean GFR (ml/min/1.73m^2)	99.70 ±40.31	90.66±56.89	0.055
	BMI	15.89±2.71	17.10±1.14	0`657
Cyclosporine A	Mean TWBC	11.08^3 ±4.31	5.53^3 ±2.19	0.063
	Mean serum creatinine (mg/dl)	0.73±0.39	0.92±1.14	0.797
	GFR(ml/min/1.73m^2)	90.66±56.89	94.79±33.25	0.052
	Hypertension	8 (24.2%)	3 (9.4%)	0.001
	BMI	16.82±3.09	17.19±3.11	0.645

Table 5. Types and frequency of complications in CPM and CSA treated groups

Complications	CPM group n=49	CSA group n=33
Cushinoid appearance	1 (2.0%)	3 (9.0%)
Gingival hyperplasia	0 (0.0%)	2 (6.1%)
Hyperterichosis	0 (0.0%)	2 (6.1%)
Hemorrhagic cystitis	1(2.0%)	0 (0.0%)
Infection	2 (4.1%)	2 (0.0%)
Stunting of growth	3 (6.1%)	2 (6.1%)
Total	7 (14.3)	11 (33.3%)

P= 0.031

Discussion:

In children with frequent-relapsing (FR) and steroid-dependent (SD) nephrotic syndrome (NS) remission can be achieved, and relapse rate can be reduced, with steroid sparing-drugs. These agents are usually prescribed for children who develop adverse side effects from steroid treatment` They include Cyclophosphamide (CPM), Levamisole, and Cyclosporine (CSA). CPM and Levamisole have been commonly used as first line therapy and CSA as second line for those who continued to follow FR/SD course after the initial therapy. However, many studies showed different results regarding the efficacy and safety of CPM versus CSA [3, 14-19]. In Sudan published data comparing these agents in nephrotic children is lacking. We ,therefore, conducted this study to compare the efficacy and safety of CPM and CSA in treatment of a population of Sudanese children with SD/FR NS. The demographic, biochemical and clinical parameters of the two groups were well-matched at the initiation of treatment. Our data showed that both CPM and CSA were effective in achieving CR remission (77.6% and 60.3% respectively) in children with SD/FR NS up to 6 months of the start of treatment. At 12 months: the CR was still maintained in 57.5% of CPM group and 77.7% of CSA group. However, at 24 months both drugs had disappointing long-term efficacy as only 29% of CSA- and 16.6% of CPM-treated groups were in CR and the majority relapsed. Studies comparing CPM and CSA showed variable remission rates [17-19]. In this study, CPM-achieved CR rate of 77.6% at six months was similar to Rahman et al report (80%) [17]. Ponicelli et al reported a lower CR rate (64%) at nine months [18]. In our study, CPM-achieved CR dropped to 57.5% at 12

months and 16.6% at 24 months. These findings suggest failure of CPM to maintain stable long-term remission. Similar disappointing long-term efficacy with CPM had been reported in other studies [3, 15] despite the use of a higher cumulative dose of CPM (>170 mg/kg) [15]. In contrast, other studies showed better long-term efficacy of CPM treatment with 68-60% of treated children having stable remission at 24 months [18, 20]. These variations in response to CPM could be related to duration of treatment of CPM (8 versus 12 weeks). However, we used CPM in a dose of 2/kg for 8-12 weeks at a cumulative dose of 168 mg/kg as in these studies [18]. APN also suggested the benefit of treatment CPM for 12 weeks [21]. Different studies used CSA with different treatment durations: 9, 12 and 24 months [18, 19, 22] respectively. In general, long-term CSA therapy is recommended. In our study, we tapered CSA after 12 months and, therefore, we achieved a higher rate of remission up to 12 months (72.7%); but that dropped after tapering to 29% at 24 months. Similar higher short-term efficacy, but disappointing, long-term efficacy with CSA: 70% CR at 9 months and 20% at 24 months was reported in Ponticelli study [18]. In that study, CSA was tapered after 9 months. However, in studies using long-term CSA therapy, remissions at 12 and 24 months were achieved in 60% and 40% of the children, respectively [22]. Other similar studies reported stable remission rate (54%) at two years [23]. In this study, there was no significant change in the mean serum creatinine, GFR when basal and latest follow-up values were compared in both treatment groups (P>0.005 for both parameters). The prevalence of hypertension initially reported in CSA-treated group had significantly dropped (P=0.001) on latest follow-up. After two years 36.8% of CPM group and 51.5% of CSA group were shifted to other steroid-sparing agents.

In this study, tolerance to both drugs was generally good. Only mild complications were recorded which were more common in CSA than CPM group. Side effects, like hypertrichosis and gum hypertrophy seen in few patients on CSA, disappeared after drug tapering. Most of the previous studies revealed that these CSA-related complications can be reversed after completion of CSA therapy. However, Hino et al. reported CSA nephrotoxicity in 15% of their patients with SDNS [24]. Long- term toxicity of CPM was gonadal toxicity with subsequent risk of infertility mainly in boys. However, results of many reports varied markedly and were sometimes contradicting. Oligo/azospermia may occur with a cumulative CPM dose of 150- 250 mg/kg [25-27] but azospermia was reversible in some patients in some studies [28]. There was no definite sperm count that can predict fertile and infertile males [29] and no correlation was found between the cumulative dosage of CPM and the risk for sperm abnormalities in other reports [30]. Few studies in girls and women with FR childhood NS reported a risk for gonadal damage as some menstruating women developed transient amenorrhea with CPM treatment [31]. Other studies reported pregnancies after cumulative doses of 182–525 mg/kg CPM [32-34] In a meta-analysis of cytotoxic treatment (CPM versus Chlorampucil) for FR NS in children [35], it was concluded that cytotoxic therapy is effective in reducing the need for corticosteroids in many children with SSNS; but the long-term efficacy is still limited and, hence, firm guidelines could not be developed. Repeated courses of cytotoxic therapy should be avoided because of serious side effects. Gonadal toxicity and the risk of malignancies are inbuilt and only partly dose-dependent risks. CPM appears to be the drug of choice and is considered to be safer than Chlorampucil [35].

In conclusion: our study demonstrated that both CPM and CSA are effective in achieving remission up to 12 months in children with FR/SD NS. However, long-term remission was less stable with both drugs with the majority of patients being in relapse and needing other therapy. Both drugs were safe and well-tolerated, with no serious side-effects on short-term. Since CPM is safe, cheap, easy to administer and does not require blood level monitoring, we recommend its use as initial therapy for children with SD/FR NS. CSA is reserved for those who continue to relapse after CPM treatment.

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Disclosure:

The authors declare that the research protocol has been approved by Sudan Medical Specialization Board Research Committee and Soba Hospital Research Committees and an informed consent was then obtained. They also declare that the results of this study have not been published before except as abstracts.

Authors contribution:

The authors declare that they all had significant contribution to the study and they all agree with contents of the study.

Conflict of interest:

Authors declared no conflict of interest.

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