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The Effect of Oral Cyclophosphamide in the Treatment of Children with Refractory Idiopathic Nephrotic Syndrome

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Original Paper

Introduction. Nephrotic syndrome (NS) is the most common chronic kidney disease in children. Patients who do not respond to steroids are steroid resistance nephrotic syndrome (SRNS). Cyclophosphamide (CP) has been used in the treatment of SRNS, but its effectiveness has been questioned. The aim of this study was to evaluate the drug response and side effects of CP in the treatment of SRNS.

Methods. This study performed as a historical cohort (1997 to 2017) in idiopathic SRNS patients over one year of age who did not enter remission and used oral. All patients were followed up with CBC and regular visits to control drug side effects.

Results. In this study, 52 SRNS patients with a mean age of 5.3 ± 5.3 years were studied, of whom 24 (46%) were male and 22 (54%) were female. The follow-up period of patients was 1 to 264 months. In this study, 38.5% of patients were sensitive to CP and 61.5% of patients were resistant to CP. The response to CP was not significantly different between the ages of higher 6 years and under ($P > .05$). There was no significant relationship between remission rate and type of pathology and CP addition to treatment. But there was a significant difference between ESRD and CP resistance.

Conclusion. It can be concluded that CP has no significant effect on the remission of SRNS patients, but has made a significant difference in the development of ESRD in patients.

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INTRODUCTION

Nephrotic syndrome (NS) is one of the most common glomerular kidney diseases in children. The disease has a clinical description including severe proteinuria, hypoalbuminemia, and edema. NS is idiopathic in 90% of patients.[1,2] In patients who do not reduce proteinuria with steroid use, it is called steroid resistance nephrotic syndrome (SRNS). Unfortunately, there is currently no ideal treatment for these patients, and unfortunately 50% of idiopathic SRNS patients progress to End Stage Renal Disease (ESRD).[3,4]

Cyclophosphamide (CP) has been used in the past to treat SRNS. Recent studies have reported different results regarding the effect of CP. A number of studies have reported acceptable results in the use of CP in SRNS patients. In a retrospective study of 51 SRNS children treated with CP, Complete remission was observed in 43% of patients.[5] While other studies have shown opposite results. Only 20% of SRNS patients had partial or complete remission following a course of CP treatment, which was no different from the untreated group.[6] In another study in children

with SRNS whose pathology was focal segmental Glomerulosclerosis (FSGS), the rate of remission treatment with CP and prednisolone (PDN) was similar to that of PDN alone.[7] Therefore, the recommendation to take CP is currently in doubt. Because there are limited studies on the results of SRNS treatment with CP in Iran.[8] The aim of this study was to evaluate the response and side effects of CP in the treatment of SRNS in the Children's Medical Center Hospital.

MATERIALS AND METHODS

This study was performed as a historical cohort of patients referred to the hospital of the Children's Medical Center during the years 1997 to 2017. This study was conducted under the supervision of the ethics committee of Tehran University of Medical Sciences (TUMS) and the patients' information was used in anonymous manner. Inclusion criteria was patients with nephrotic syndrome over one year of age who did not enter remission after 4 weeks of 2 mg/kg PDN daily and in the later stages of their treatment was used oral CP. In this study, only idiopathic SRNS patients were included and secondary SRNS cases were excluded. Also, patients with minimal change nephrotic syndrome (MCNS) or DMP or FSGS pathology biopsy were included in the study and patients with sclerosis or severe glomerular fibrosis biopsy were excluded. In this study, 2.5 mg/kg oral CP daily was administered for 3 months and all patients received concomitant PDN. All patients were followed up with CBC and regular visits to control drug side effects. Patients whose information was distorted or incomplete were excluded. For statistical analysis, we used SPSS 24 software. Quantitative data were reported as mean and standard deviation (SD) and qualitative data as ratio. Independent t-test was used to compare the means in the variables with normal distribution, Mann-Whitney test was used in the non-parametric variables and Chi-square test was used to compare the qualitative variables. Significance level was considered less than 0.05.

RESULTS

In this study, out of 52 SRNS patients, 24 (46%) were male and 22 (54%) were female. The mean age of patients was 5.3 ± 3.2 (1 to 13) years. The follow-up period of patients was 1 to 264 months (Table 1). In this study, 38.5% of patients were sensitive to cyclophosphamide and 61.5% of patients were resistant to cyclophosphamide. The response to cyclophosphamide was not significantly different between the ages of higher and under 6 years ($P > .05$). Of the 50 reported kidney biopsies, 4 (8%) had MCNS, 27 (54%) had DMP, and 19 (38%) had FSGS. There was no significant relationship between remission rate and type of pathology. In this study, 4 cases (7.7%) of peritonitis, 3 cases (5.8%) of leukopenia, 1 case (1.9%) of alopecia, and 1 case (1.9%) of cystitis were observed. Thirteen cases (25%) were ESRD patients, all of whom were resistant to CP. Of the 39 patients who did not ESRD, 19 were resistant to CP. There was a significant difference between ESRD and CP resistance. In 38 cases (73.1%) CP was the first immunosuppressive drug with PDN, while in 14 cases (26.9%) CP was added to PDN after not responding to cyclosporine. There was no significant difference between the two groups in terms of remission (Table 2).

Table 1. Demographic Information

Age, y*	5.3 ± 3.2
Gender, %	
Male	24 (46.2)
Female	28 (54.8)
Complication, %	
Peritonitis	4 (7.7)
Leukopenia	3 (5.8)
Alopecia	1 (1.9)
Cystitis	1 (1.9)
Follow-up, mo**	7 (0.5 to 60)

*Mean ± SD
**Median (Min to Max)

DISCUSSION

SRNS is a rare kidney disease in children, that included 20% of patients with nephrotic syndrome in children.[9] In report of International Study of Kidney Disease in Children (ISKDC) in treatment of 55 SRNS patients, the pathology was 45.5% MCD, 47.5% FSGS, and 7% MPGN.[10,11] In the study of Otukesh *et al.* MCD was observed in 27%, FSGS in 37%, MPGN in 32%, and global sclerosis in 5.7% of patients.[12] In our study, the prevalence of various pathologies in SRNS patients was different from other studies. In our study most common histopathology was DMP. The best treatment for SRNS patients is still unclear. Previous studies have shown that children with MCD or late steroid-resistant respond better

Table 2. Comparison Sensitive and Resistance to CP

	Response to CP			*P*
	Sensitive		Resistance n (%)	
	Complete Remission n (%)	Partial Remission n (%)		
Age				
< 6	10 (27.77)	4 (11.11)	22 (61.12)	> .05
> 6	3 (18.75)	3 (18.75)	10 (62.5)	
Treatment				
PDN + Cyclophosphamide	11 (28.94)	3 (7.89)	24 (63.17)	> .05
PDN + Cyclosporine + Cyclophosphamide	2 (14.28)	4 (28.57)	8 (57.15)	
Pathology				
MCNS	2 (50)	0	2 (50)	
DMP	5 (18.51)	5 (18.51)	17 (62.98)	> .05
FSGS	4 (21.05)	2 (10.52)	13 (68.43)	
ESRD				
Yes	0	0	13 (100)	< .05
No	13 (33.33)	7 (17.94)	19 (48.73)	

to immunosuppressive therapy than patients with FSGS or Early resistant.[13,14] In our study, there was no relationship between the type of pathology and the response to cyclophosphamide. Most researchers believe that alkylating drugs have little therapeutic effect in SRNS patients.[15] In ISKDC study on 62 SRNS patients with FSGS pathology showed that CP has no effect on remission in these patients but shortens the time to remission.[7] In another study of 125 patients treated with oral CP, 20.15% of CP-sensitive patients had remission for more than 2 years.[9] In the study of Hasan Otukesh *et al.* 80% of patients were resistant to oral cyclophosphamide and complete or partial remission was seen in 20.7% of patients.[12] In our study, 38.5% of patients were sensitive to CP and 61.5% were resistant, and in the group sensitive to CP, 25% had complete remission, and 13.5% had partial remission. But another study CP showed higher rate of remission, including a study in Canada found that CP caused complete or partial remission in 46% of patients.[16] In another study in Brazil, 51 patients treated with CP reported a success rate of 43.1%. In this study, no association was found between patients' pathology and response to CP.[5] While, we seen any association between pathology and response to CP. Patients with partial response to steroids have been shown to be more likely to respond to CP or cyclosporine and less likely to progress to CKD.[17] In the study by Otukesh *et al.* 46.1% of patients who were resistant to oral CP progressed to ESRD. It has also been shown that the risk of ESRD is lower in patients who are sensitive to CP.[16] In our study, ESRD was observed in 25% of patients and ESRD did not occur in patients who were sensitive to CP which it is in line with pervious results. Complications of CP were observed in 51 treated patients including 1 case of leukopenia, 1 case of alopecia, 1 case of TB serositis, and 1 case of primary peritonitis.[5] In a study in India, no case of cystitis was seen in patients treated with CP. Intravenous treatment of CP showed 4 cases of bacterial peritonitis, 3 cases of alopecia, 1 case of cellulite, and 1 case of vomiting. In orally treated patients 2 cases of alopecia, 1 case of peritonitis, 1 case of cellulite, and 1 case of vomiting were observed.[18] We also observed bacterial peritonitis the most complication and contrary to this study 1 case of cystitis was observed.

This study had some limitations, including lack of access to a number of patient records and follow-up, and shortcomings in recording patient follow-up.

CONCLUSION

We suggested in future studies, investigate the effect of cyclophosphamide with a larger sample size. It can be concluded form the results that CP has no significant effect on the remission of SRNS patients.

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