ORIGINAL ARTICLE

MANAGEMENT OF CHILDHOOD STEROID DEPENDENT NEPHROTIC SYNDROME WITH CYCLOPHOSPHAMIDE – AN EXPERIENCE AT AYUB TEACHING HOSPITAL, ABBOTTABAD

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Background: This study has been done in children with Steroid dependent nephrotic syndrome (SDNS) to check for the response to cyclophosphamide and relapse on follow up for one year after completion of treatment. **Methods:** This study was conducted over two years and nine months. Patients were taken as steroid dependent when there were two consecutive relapses occur on steroids tapering or within two weeks of stopping treatment. Children of either sex between ages of 1–14 years, diagnosed case of SDNS were included in this study. Renal biopsy was not done in any patient. After achieving remission with oral steroids, cyclophosphamide was given after calculation of maximum cumulative dose 168 mg/kg for 8 – 12 weeks along with oral steroids. Follow up done every two weeks till completion of treatment for response and adverse effects and thereafter for one year. **Results:** There were 31 patients, 23 (74.2%) male and 8 (25.8%) females. Age ranged from 1.5 years to 11 years with mean age 5.44±2.39 years. There was full response to cyclophosphamide as none of patient had proteinuria on cyclophosphamide therapy. After completion of cyclophosphamide course, four patients (12.9%) relapsed on follow up while 87.9% remain in complete remission. Only one female patient (3.23%) had adverse effect in form of hair fall and she recovered after completion of treatment. None of patient showed any other adverse effect including haematuria. **Conclusion:** Cyclophosphamide is an effective therapy in management of childhood SDNS with minimum adverse effects in medium term.

Keywords: Cyclophosphamide; Steroid dependent nephrotic syndrome; Remission; Children

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INTRODUCTION

In children nephrotic syndrome is not very common with incidence of 7 cases/100000 per year.[1]This disease is presumed to be due to lymphocytes dysfunction.[2] Most of children with idiopathic nephrotic syndrome are steroid sensitive yet about majority relapse.[3] Many complications are associated with relapses as hypovolemia, hypertension, thromboembolism and infections.[4]

Patient who relapse and take steroids for long period of time are at risk for adverse effects of steroids like stunted growth, hypertension, infections and decrease bone minerlization.[5] As about half of children who relapse are either frequent relapse or steroid dependent.[6] According to Kidney Disease Improving Global Outcomes (KDIGO) Steroid Dependent Nephrotic Syndrome (SDNS) is define as when there are two consecutive relapses either on steroid dose tapering or within two weeks of stopping of drug.[7] There are second line drugs as levamisole, chlorambucil, cyclosporine and cyclophosphamide which are used as steroid sparing drugs in children who relapse frequently or who are steroid dependent.[8]

Cyclophosphamide is an alkylating agent, recommended by KIDGO for management of SDNS in children.[7] Duration of treatment is for 8 to 12 weeks along with steroids. This is immunosuppressive drug which effect T cells and inhibits cell division by inhibition of DNA synthesis. Studies have shown that use of cyclophosphamide in management of childhood SDNS has led to low relapse rate and longer period of remission.[9] This study will help in making protocol for management of SDNS in children in our part of world.

This study has been done in paediatric patients with Steroid dependent nephrotic syndrome (SDNS) to check for the response of local population to cyclophosphamide and relapse on follow up after one year after completion of treatment.

MATERIAL AND METHODS

This cross-sectional study was conducted in OPD of the Paediatrics department of Ayub Teaching hospital, Abbottabad from July, 2017 till March, 2019. Institutional review board approval was taken. Parents and patients were counselled about the study aim by treating doctor and then were included in the study after taking informed consent. Children of either sex between ages of 1–14 years who were diagnosed as case of steroid dependent nephrotic syndrome (SDNS) either in our hospital or referred from other health centres were included in this study.

Children less than one year and more than 14 years were not included due to atypical nephrotic syndrome. Paediatric patients were taken as SDNS when there was relapse during the tapering of corticosteroid or within 2 weeks after discontinuation of corticosteroids. Patient was taken as case of relapse when child presented with oedema and +2 or +3 protein on urine dipstick for three consecutive days. Renal biopsy was not done in any patient. Patients with secondary nephrotic syndrome were excluded. Patients were initially treated with oral prednisolone in dose of 2mg/kg/day till remission was achieved for three consecutive days. When remission was achieved then cyclophosphamide was started. Cyclophosphamide was given after calculation of maximum cumulative dose 168 mg/kg and tablet of 50 mg with dose of 2–3 mg/kg adjusted between 8–12 weeks duration. Oral prednisolone then given in dose of 1 mg/kg on alternate day regimen, tapering done and stopped with last dose of cyclophosphamide.

Initial follow up of patients was done after one week and then every two weeks till completion of treatment in paediatric nephrology OPD by assigned paediatric nephrologist Afterwards patients were followed up monthly for one year. At initial follow up visit and subsequent follow up, patient complete blood count and urine detail report was done to observe for the adverse effects of drug. Patient with total leukocyte count (TLC) less than 4000/cmm and haematuria, drug was stopped till TLC rises above 4000/cmm and haematuria resolved. Patients were also advised for home urine protein monitoring with early morning sample either with urine dipstick or boiling method. Complete remission was taken when urine protein was nil or trace. Urine protein +2 was taken as partial response and proteinuria ≥3+ was taken as no response. Patients were monitored for 12 weeks for response to treatment after initiation of therapy. Patient's data was collected and recorded on specific proforma. Variables recorded include were age, sex, weight and blood pressure. Laboratory investigations serum albumin, cholesterol, serum creatinine and urea were recorded. Data was analysed by SPSS 20.0 and the results were considered significant with *p*-value <0.05.

RESULTS

There were total of 31 patients included in this study, 23 (74.2%) were male and 8 (25.8%) were female. Age ranged from 1.5 years to 11 years with mean age 5.44±2.39 years. Weight of patients ranged from 10–40 kg with mean weight of 20.03±6.89. Descriptive statistics given in table-1. All patients initially responded to steroid induction therapy and afterwards given cyclophosphamide. There was full response to cyclophosphamide as none of patient had proteinuria on cyclophosphamide therapy.

After completion of cyclophosphamide course, four patients (12.9%) relapsed on follow up while 87.9% remain in complete remission. One patient relapsed as parents stop the medication on their own as patient was symptom free. One patient relapsed within one month of stopping treatment with cyclophosphamide. Two patients relapsed on follow up of one year. Only one female patient (3.23%) had adverse effect in form of hair fall and she recovered after completion of treatment. None of patient showed any other adverse effect including haematuria.

Table-1: Weight, Blood pressure, Cholesterol, Urea, Creatinine table

	N	Minimum	Maximum	Mean	Std. Deviation
Weight (kg)	31	10.00	40.00	20.0258	6.89130
Systolic BP (mm Hg)	31	90.00	170.00	111.2258	14.27050
Diastolic BP (mm Hg)	31	60.00	120.00	74.1935	11.48164
S. Cholesterol (mg/dl)	31	250.00	587.00	357.0323	77.46289
S. Albumin (gm/l)	31	1.20	3.0	2.05	0.49
Urea (mg/dl)	31	17.00	48.00	29.2581	6.41856
Creatinine (mg/dl)	31	0.10	0.9	0.52	0.25

DISCUSSION

Management of steroid dependent nephrotic syndrome in children is not only an issue for the parents and children but also the paediatric nephrologists as it is one of the causes of end stage renal disease in children.[10] This condition is cause of poor quality of life as not only affect children health but also families.[11] We have conducted this study in children with Steroid dependent nephrotic syndrome to check for the response of local population to cyclophosphamide and relapse on follow up after one year after completion of treatment. In our part of world adherence to treatment for long time and affordability of treatment are the main issues in management of chronic diseases. Cyclophosphamide is not only short-term use medication but also an affordable option. In Pakistan only two centres in Karachi have published the data but data on wide use of cyclophosphamide is lacking.

Ali EMA *et al*[12] in their retrospective study did comparison of cyclophosphamide with cyclosporine in management of SDNS. Their study included 69.5% male and 30.5% females whereas in our study 74.2% were male and 25.8% were females. Children were followed at 6, 12 and 24 months for observation of response. In children who were given cyclophosphamide at 6 and 12 months, 77.6% and 57.5% were in complete remission respectively. In comparison, we followed the study population and checks for remission at one year and in our study 87.1% patients were in complete remission while only 12.9% patients relapsed. Abeyagunawardena S *et al*[13] did study by reviewing the data by and compared intravenous cyclophosphamide with oral. In children who got oral cyclophosphamide, 40% patients relapse at one year while 60% were still in remission. In our study the 87.1% patients remained in complete remission at follow up on one year. Though in Abeyagunawardena S *et al* study various adverse effects were observed but, in our study, only one female patient got alopecia which recover after treatment was over.

Bajeer IA *et al*[14] did one study in one of the main paediatric nephrology centres of Pakistan and used cyclophosphamide along with steroids in children with relapsing steroid sensitive nephrotic syndrome. In their study males were 63.5% while females were 63.5%, while in ours study males were 74.2% and females were 25.8%. The range of treatment duration was 9 to 13 weeks while in our study it was 8 to 12 weeks. They did renal biopsy in all the patients while we did not perform biopsy in any of patient and the duration of complete remission ranged from 7 to 23 months. While in our study one patient relapsed within one month of post cyclophosphamide and three patients relapsed in 8 to 9 months. Rest of the patients remain protein free for one year of follow up.

Another study done in Karachi, Pakistan by Moorani KN *et al*[15] used cyclophosphamide in difficult nephrotic syndrome which included frequent relapse, SDNS and steroid resistant patients. Complete response was seen in 57.77% patients and partial response was seen in 22.22% patients. Moorani KN *et al* study included multiple adverse effects of cyclophosphamide while in our study only one patient had alopecia.

Azib S *et al*[16] retrospectively studied the single course of cyclophosphamide in children with SDNS and concluded that short course of cyclophosphamide one of the effective therapies in management of SDNS. In their study the patients were having sustained remission of 57% at one year of follow up while in our study it was 87.9%. Thalgahagoda RS *et al*[17] in their review article have recommended the use of cyclophosphamide and even IV cyclophosphamide can be repeated if required but repeat course should best be avoided due to risk of malignancy. In one of educational review by Deschênes G *et al*[18] it was concluded that about one third of patients treated with cyclophosphamide remain in remission for long.

Gajjar R *et al*[19] have described cyclophosphamide as the one the most effective therapy as second line in management of SDNS in their educational review. As there is also less risk of relapse at one and even two years when comparison done to prednisolone. Liping Tan *et al*[20] in their Systematic Review and Meta-Analysis concluded that cyclophosphamide is to be preferred for initial management of SDNS in children. As cyclophosphamide is used for SDNS in adults. Mehta S *et al*[21] reported one rare case of cyclophosphamide-induced melanonychia in one adult female patient as this condition is not frequent. In our patients only one patient had alopecia.

There are limitations in the study as we did not follow the patient for long term, significant no of patients with SDNS can present with steroid resistant and may also persist in adulthood as studied by Korsgaard T *et al*[22] as our hospital is not a referral centre so the patients with SDNS are not in great number.

CONCLUSION

Cyclophosphamide in one of the effective therapies in management of childhood SDNS with minimum adverse effects and maintain protein free duration for medium term. As these results are based on a single center study experience with limited no of patients and that without controls, multicenter randomized control trial is required to further validate the findings of our study.

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AUTHORS' CONTRIBUTION

SSHS: Theme, data collection, data analysis, data interpretation, write-up. BA: Data collection, writing, literature search. AR, SN: literature search. AR: Supervision.

REFERENCES

1. Gruppen MP, Bouts AH, Weide MCJ, Merkus MP, Zurowska A, Maternik M, *et al*. A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome. Kidney Int 2018;93:510–18.
2. Davin JC. The glomerular permeability factors in idiopathic nephrotic syndrome. Pediatr Nephrol 2016;31:207–15.
3. Karunamoorthy S, Thanigachalam D, Jeyachandran D, Ramanathan S, Natarajan G, Thoppalan B. The safety and

efficacy of mycophenolate mofetil in children and adolescents with steroid-dependent nephrotic syndrome: a single-centre study. Clin Kidney J 2020;13(2):179–83.
4. Park Shin J. Complications of nephrotic syndrome. Korean J Pediatr 2011;54(8):322.
5. A study of efficacy of levamisole in children with frequently relapsing and steroid-dependent nephrotic syndrome. Indian J Res 2019;8(3):26–7.
6. Hettiarachchi HNS, Raja M, Karunadasa UI, Thalgahagoda RS. Efficacy and side effects of mycophenolate mofetil therapy in children with steroid dependent nephrotic syndrome in a tertiary paediatric nephrology centre in Sri Lanka. Sri Lanka J Child Health 2018;48(1):53–8.
7. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal change disease. Clin J Am Soc Nephrol 2017;12:332–45.
8. Pravitsitthikul N, Willis N, Hodson E, Craig J. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. Cochrane Database Syst Rev 2013;(10):CD002290.
9. Khemani S, Moorani KN. Cyclosporine versus Cyclophosphamide in Childhood Nephrotic Syndrome. J Liaquat Univ Med Health Sci 2016;15(2):57–62.
10. Wang C, Travers C, McCracken C, Leong T, Gbadegesin R, Quiroga A, *et al*. Adrenocorticotropic Hormone for Childhood Nephrotic Syndrome. The ATLANTIS Randomized Trial. Clin J Am Soc Nephrol 2018;13:1859–65.
11. Teeninga N, Kist-van Holthe JE, Nauta J. Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome. J Am Soc Nephrol 2012;24:149–59.
12. Ali EMA, Elhaj NAO, Abdelraheem MB, Ellidir RA, Osman R. Cyclophosphamide versus cyclosporine in children with frequent-relapsing and steroid-dependent nephrotic syndrome in Khartoum State, Sudan. Khartoum Med J 2017;10(3):1402–10.
13. Abeyagunawardena S, Jayaweera AHHM, Thalgahagoda RS, Karunadasa UI, Abeyagunawardena AS. Intravenous pulsed vs oral cyclophosphamide therapy in steroid dependent nephrotic syndrome. Sri Lanka J Child Health 2017;46(4):317–21.
14. Bajeer IA, Khatri S, Tresa V, Hashmi S, Mubarak M, Lanewala AA. Histopathological Spectrum and short-term outcome of treatment with cyclophosphamide in relapsing steroid-sensitive nephrotic Syndrome. J Coll Physicians Surg Pak 2018;28(6):436–9.
15. Moorani KN, Hotchandani HM, Zubair AM, Lohana NC, Veerwani NR. Immunosuppressive therapy in children with primary nephrotic syndrome: single center experience, Karachi, Pakistan. BMC Nephrol 2019;20:239.
16. Azib S, Macher MA, Kwon T, Dechartres A, Alberti C, Loirat C. Cyclophosphamide in steroid-dependent nephrotic syndrome. Pediatr Nephrol 2011;26:927–32.
17. Thalgahagoda RS, Jayaweera AH, Karunadasa UI, Abeyagunawardena AS. Therapies for steroid-sensitive nephrotic syndrome. Asian J Pediatr Nephrol 2018;1:56–61.
18. Deschênes G, Dossier C, Hogan J. Treating the idiopathic nephrotic syndrome: are steroids the answer? Pediatr Nephrol 2019;34:777–85.
19. Gajjar R, Miller SD, Meyers KE, Ginsberg JP. Fertility preservation in patients receiving cyclophosphamide therapy for renal disease. Pediatr Nephrol 2015;30:1099–1106.
20. Tan L, Li S, Yang H, Zou Q, Wan J, Li Q. Efficacy and acceptability of immunosuppressive agents for pediatric frequently-relapsing and steroid-dependent nephrotic syndrome. Medicine 2019;98(22):e15927.
21. Mehta S, Makkar V, Soha PM, Sethi S, Kaur S. Cyclophosphamide-Induced Melanonychia in a Patient with Steroid Dependent Nephrotic Syndrome: A Rare Presentation. Saudi J Kidney Dis Transpl 2019;30(4):978–81.
22. Korsgaard T, Andersen RF, Joshi S, Hagstrøm S, Rittig S. Childhood onset steroid-sensitive nephrotic syndrome continues into adulthood. Pediatr Nephrol 2019;34(4):641–8.

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