Comparison of Efficacy of Cyclophosphamide Versus Tacrolimus in Children With Steroid Dependent and Frequent Relapsing Nephrotic Syndrome

Khuram Rashid, Muhammed Imran, Hashim Raza, Shahid Ishaq, Muhammad Amir Misbah ul Qamar, Tahira Sumreen

Department of Paediatric Nephrology, Children Hospital Multan Pakistan

ABSTRACT

Objective: To compare the efficacy of Cyclophosphamide and Tacrolimus in the management of steroid dependent and frequent relapsing nephrotic syndrome in children.

Study Design: Quasi experimental study.

Place and Duration of Study: Department of Pediatric Nephrology, The Children's Hospital & The Institute of Child Health, Multan, from July 2020 to Dec 2020.

Methodology: A total of 120 patients presenting with steroid dependent and frequent relapsing nephrotic syndrome that need 2nd line drug were divided in two groups. Group A included patients using Cyclophosphamide in a dose of 2.5mg/kg and group B used Tacrolimus in a dose of 0.1mg/kg. All patients were monitored and compliance of drugs were noted. Efficacy was calculated as proportions of patients achieving maintained remission of disease for six months duration.

Results: Our study included 80(66.7%) boys versus 40 (33.3%) were girls having mean age 5.93±2.10 years (range 1-12 years). Mean weight was noted to be 17.1±3.84 kilograms. Majority 46 cases (76.6%) in Tacrolimus–group achieved complete remission compared to 22 cases (36.6%) in Cyclophosphamide-group, that results in usually exceedingly noteworthy $p<0.005$. Partial remission and drug resistance were 12cases (20%) and 2cases (3.33%) of Tacrolimus–group compared to 20 cases (33.3%) and 18 cases (30%) in Cyclophosphamide-group respectively. Sustained remission at 6months follow-up was 40 cases (66.7%) in Tacrolimus–group compared to 16 cases (26.6%) in Cyclophosphamide-group.

Conclusion: Tacrolimus was more effective in inducing remission (76.6%) as compared to cyclophosphamide (36.6%) in steroid dependent and frequent relapsing Nephrotic syndrome.

Keywords: Cyclophosphamide, Nephrotic syndrome, Tacrolimus.

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INTRODUCTION

Nephrotic disorder (NS) could be a condition in which leakage of proteins through the glomerular basement membrane happens.[1] The resultant proteinuria is ordinarily went with by edema, hypoproteinemia and hyperlipidemia.[2] Massive proteinuria in nephrotic syndrome (NS) occurs due to a disruption in the glomerular filtration barrier and subsequent impaired uptake of filtered protein as tubular resorptive capacity is overwhelmed.[3] It has been assessed that the yearly rate of NS is 1-3/100,000 children <16 a long time of age.[4] NS is classified as idiopathic when it is due to essential glomerulopathies or may be auxiliary to different disarranges.[3] Treatment objectives are reduction of proteinuria, to prevent disease complications such as infections, thrombo-embolism and renal insufficiency; and to avoid treatment related complications.[5]

Correspondence: Dr. Khuram Rashid, Department of Paediatric Nephrology, Children Hospital Multan Pakistan

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Cyclophosphamide(CP), an alkylating operator; when utilized in SDNS and FRNS for 8-12 weeks makes a difference to actuate reduction of proteinuria, to protect renal capacities and hence diminish the hazard of incessant kidney illness.[6] The component of activity of cyclophosphamide is thought to be due to immunosuppressive impacts on T-cells and it may straightforwardly anticipate cell division.[7] Tacrolimus is a macrolide immunosuppressant which hinders calcineurin and totally squares the translocation of the cytosolic component of the atomic calculate of actuated T cells.[5] TAC accomplished a prevalent antiproteinuric profile but by a organic component that remains obscure; agents have related this predominant control of proteinuria with TAC's more powerful impact on its concealment of vascular penetrability or its activity on intraglomerular hemodynamics.[8]

Previously limited work has been done on this subject in Pakistan, most of the studies have been conducted on adult population. Therefore present

comparative study is planned so that drug with higher efficacy can lead to good prognosis.

METHODOLOGY

This quasi experimental study was done at Department of pediatric Nephrology Children's Hospital & the Institute of Child Health, Multan Pakisan from July to December 2020 using non-probability purposive sampling technique. A total of 120 children with steroid dependent and frequent relapsing nephrotic syndrome that need 2nd line drug, aged 1-14 years of either gender were included in our study while patients who received prior Cyclophosphamide or Calcineurin inhibitor, patients with atypical features (Persistent HTN, hematuria, hypocomplementemia, renal insufficiency and patients whose parents do not give consent of participation were excluded.

Sample size was 120, which was calculated using WHO Sample size 2.0 software for single proportion sample size calculator, Level of significance(α)=5%, Power of Test(1-β)=90%, P1=0.825, P2=0.459, So the required total sample size is 120 i.e., Tac group 60, Cyclophosphamide group 60.9

Study was started after taking written permission from the institutional ethical committee(550/A). Those patients, who fulfill the inclusion criteria, were recruited for the study. After clarifying dangers and benefits of the study, written informed consent was taken from the parents/guardians. A total of 120 patients that need 2nd line drug were divided in two groups by blinded envelop system. Group A included patients using Cyclophosphamide in a dose of 2.5mg/kg for 8weeks and group B used Tacrolimus in a dose of 0.1mg/kg for 8weeks, in intensive care setting of nephrology department. After 8weeks if complete remission was achieved then Tacrolimus was continued up to 6months. All patients were monitored(CBC, RFTS monthly along with Blood pressure monitoring and physical examination for cyclophosphamide cosmetic side effects) and compliance of drugs were noted. All information were collected on specifically pre-designed performa. Outcome variable was maintained remission of disease in patients for at least 6months duration. Funds were arranged from Social welfare department for unaffordable patients.

Data was entered in SPSS version 23.0. Descriptive statistics was applied to analyze the data. The quantitative variables like age, weight, duration of disease was calculated by mean and standard deviation. Frequencies and percentages were calculated for qualitative variables i.e. gender, efficacy of cyclophosphamide and tacrolimus. Outcome variable was proportion of patients in whom sustained remission of disease for at least 6months duration after administration of drugs. Efficacy of both drugs was compared using T-test and *p*-value of ≤0.05 was taken as significant.

RESULTS

Our study included total of 120 children including 80(66.7%) boys versus 40(33.3%) were girls having mean age 5.93±2.10 years (range 3-12 years). Mean weight was noted to be 17.1±3.84 kilograms. Among 120, 64(53.3%) were SD and 56 (46.6%) were frequent relapsing nephrotic syndrome. Majority 46 cases (76.6%) in Tacrolimus–group achieved complete remission compared to 22cases (36.6%) in Cyclophosphamide-group, that results in usually exceedingly noteworthy $p<0.005$. Partial remission and drug resistance were 12cases (20%) and 2 cases (3.33%) of Tacrolimus–group compared to 20 cases (33.3%) and 18 cases (30%) in Cyclophosphamide-group respectively. Sustained remission at 6months follow-up was 40 cases (66.7%) in Tacrolimus–group compared to 16 cases (26.6%) in Cyclophosphamide-group. Hypertension (6.6%), nephrotoxicity (3.3%) were observed in Tacrolimus–group, while bone marrow suppression (6.6%) , alopecia and infections (3.3% each) were seen in Cyclophosphamide-group.

DISCUSSION

Treatment of SDNS, and FRNS in children can frequently demonstrate to be challenging.[1] Childhood nephrotic syndrome by and large incorporates a favorable guess, in any case administration of children with SDNS and SRNS have been challenging.[2] There are availability issues of cyclophosphamide(Oral form) in Pakistan and it need frequent monitoring to prevent drug associated side effects. Tacrolimus is easily available and need less monitoring. Therefore present study was planned, so that drug with better efficacy and lesser side effects can lead to better outcome.

Nephrotic disorder (NS) is among the foremost common pediatric kidney illnesses with a tall hazard of dreariness due to disease and thrombosis.[5] Steroids are recognized as first-line medications for nephrotic disorder. Most of the children (80-90%) respond to steroid treatment but approximately half of them are steroid dependent after treatment with steroids alone.[5] Different moment line drugs have been utilized in children to treat FR/SD nephrotic disorder.[5,6]

Table-I Association of efficacy of drugs with regards to study variables.

Study Variables	Efficacy of drugs		*p* value
	Cyclophosphamide Group (Group A)	Tacrolimus Group (Group B)	
Gender			
Male (n= 80)	42(52.5%)	38(47.5%)	0.584
Female (n=40)	18(45%)	22(55%)	
Age groups			
Up to 7 Years (n= 72)	30(41.6%)	42(58.4%)	0.022
More than 7 Years (n=48)	30(62.5%)	18(37.5%)	
Weight			
Up to 20 Kilograms (n=102)	50(49%)	52(51%)	0.025
More than 20 Kilograms (n=18)	10(55.6%)	08(44.4%)	
Duration of disease			
Up to 12 months (n=38)	24(63.1%)	14(36.9%)	0.063
More than 12 months (n=82)	36(43.9%)	46(56.1%)	

Table-II: Comparison of efficacy of Tacrolimus versus Cyclophosphamide group.

Efficacy of drugs	Cyclophosphamide Group (Group A)	Tacrolimus Group (Group B)	*p*-value
Complete remission	22(36.6%)	46(76.6%)	0.006
Partial remission	20(33.3%)	12(20%)	
Steroid resistant nephrotic syndrome	18(30%)	02(3.33%)	
Sustained reemission for 6months	16(26.6%)	40(66.7%)	

Table-III: Safety of Tacrolimus versus Cyclophosphamide group.

Safety of drugs	Cyclophosphamide Group (Group A)	Tacrolimus Group (Group B)	*p*-value
Hypertension	-	04(6.6%)	1.00
Nephrotoxicity	-	02(3.3%)	
Bone Marrow Suppression	04(6.6%)	-	
Alopecia	02(3.3%)	-	
Infections	02(3.3%)	-	

Table-IV: Definitions.22

Nephrotic Syndrome:	Presence of edema, nephrotic range proteinuria (>40mg/m²/hour or protein: Cr >2), hypoalbuminemia (albumin <2.5mg/dl) and hyperlipidemia (>200)
SDNS:	Two consecutive relapses on tapering steroids or within 2 weeks of stopping
FRNS:	Two relapses within 6 months of initial response to steroids or 4 relapses in 12 months
Complete remission (CR)	Disappearance of edema and proteinuria (Spot urine Protein creatinine ratio <0.2),
Partial remission (PR)	Disappearance of edema but non-nephritic range proteinuria persists.

Alkylating operators such as cyclophosphamide and chlorambucil are interchange specialists for children with regularly backsliding SDNS, FRNS and can initiate a maintained reduction in a few children.6 Cyclophosphamide straightforwardly anticipates cell division and diminishing DNA union. Its component of activity in NS is obscure but is apparently due to immunosuppressive impacts on T-cells.[7]

Calcineurin inhibitors (CNIs) hinder T-cell actuation and may be applying their impact in nephrotic disorder through this component.[8] Tacrolimus has as of late been examined as an elective to cyclosporine for its impacts and adequacy, in spite of the fact that it has been demonstrated not one or the other predominant nor second rate.[9] Beginning considers on tacrolimus reported results comparable to those seen in our ponder for the SRNS cohort, in spite of the fact that no considers have been distributed on its long-term side impacts.[10]

Additionally, the 3 RCTs and 1 comparative cohort study were used to prove the efficacy and safety of TAC comparing with other immuno-suppressive therapies in PRNS. TAC accomplished higher rates of complete remission, compared with mycophenolate mofetil and cyclophosphamide, indicating that TAC is a better agent in FRNS than mycophenolate mofetil and cyclophosphamide.[8] TAC showed no significant difference in complete remission rate, when compared to cyclosporine A.[7,8] Tac was to begin with utilized for treating SRNS in 1993, and it is right now broadly utilized, but restricted to short-term medications.[23]

In a arrangement of 92 children with FSGS (seven with asymptomatic proteinuria without NS) taken after on normal for a long time, Paik et al. watched a total abatement in 36 children (39%), fractional abatement in 14(15%) and determined NS in 13(14%); nine patients (10%) had renal inadequate and 20 had unremitting end-stage renal inadequate (21%). The normal time from beginning introduction to advancement of persistent end-stage renal infection was 67±43 months and renal survival at 5, 10 and 15 a long time was 84, 64 and 53%, individually.[18]

Tacrolimus serves as an elective to cyclosporine with a somewhat more appealing side effect profile as there's less hypertrichosis and gum hypertrophy. Be that as it may, other side impacts, counting tremor, hypertension, and diabetes, have been detailed. At a measurements of 0.1–0.2 mg/kg/d isolated in 2 dosages, a total reduction rate of 81% was accomplished in a think about of pediatric patients with SDNS by Jahan et al. A target trough level of 5–7 ng/mL is suggested.[13]

In spite of the fact that a consider by B Oemar detailed that a 12-week course of cyclophosphamide come about in a better extent of maintained reduction than the standard 8-week regimen, a consequent controlled ponder appeared no such contrast. Kemper *et al.* recommended that the 12-week regimen yields unfavorable comes about, with a larger part of children with SDNS backsliding early and requiring more elective treatments.[16]

Latta et al prescribe that the criteria for treating children with nephrotic disorder with cytotoxic treatment ought to incorporate a regularly backsliding nature of the nephrotic disorder, the improvement of steroid poisonous quality, such as cataract and development disappointment and Cushingoid status, and/or the improvement of mental complications from the utilize of steroid. Cyclophosphamide is favored over chlorambucil, with verbal cyclophosphamide at a measurements of 2-3mg/kg/day, keeping the white tally over 3000 cell/m3, and utilizing alternate day steroid concomitantly. Latta recommends pointing for less than 300mg/kg total measurements in guys.[24]

A study on "Therapies for steroid-sensitive nephrotic syndrome" conducted by RS Thalgahagoda, conclude that levamisole may be considered as the first choice of alternative therapy for patients with frequent relapses and mild steroid dependence as it has few adverse effects.16 Patients who are unresponsive to levamisole with EOD prednisolone warrant therapy with MMF or cyclophosphamide. The use of tacrolimus is reserved for patients with severe steroid dependence, often present from the onset of disease, and for those refractory to therapy with other second-line agents. Patients receiving prolonged therapy with tacrolimus and those with nephrotoxicity may be successfully managed with MMF or rituximab. Calcineurin inhibitors (CsA or tacrolimus) are the agents of choice in managing patients with steroid resistance.[17]

The limitations of a study were unavailability of resources.

CONCLUSION

Tacrolimus was superior to cyclophosphamide in induction of remission in SDNS and FRNS in children. Complete remission was essentially higher (76.6%) in Tacrolimus compared to cyclophosphamide (36.6%).

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

KR & MI: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

HR & SI: Data acquisition, data analysis, approval of the final version to be published.

MAMUQ: & TS: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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