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Original Article

Comparison of Efficacy of Levamisole Versus Mycophenolate Mofetilin Children with Frequently Relapsing Steroid Sensitive Nephrotic Syndrome

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Abstract

Background: Steroid sensitive nephrotic syndrome patients usually develop relapses in 40-50% of cases and exert significant burden on healthcare system and different treatment modalities are being used for sustained remission of relapses.
Objective: To compare the efficacy of levamisole versus mycophenolate mofetilin children with frequently relapsing steroid sensitive nephrotic syndrome.
Study type, settings & duration: This study was conducted at Department of Pediatric Nephrology, The Children's Hospital and Institute of the Child Health, Multan from July 2020 to June 2021.
Methodology: ; Children (n = 80) with Steroid-sensitive Nephrotic syndrome frequent Relapsers were randomized in 2 groups; Group A received Levamisole 2-2.5 mg/kg on alternate days for 6 months while group B received MMF (750-1000 mg/m^2 daily) along with standard therapy i. e prednisolone at a dose of 60 mg/m^2 per day for 4-8 weeks or less if reached absence of proteinuria for 3 consecutive days, followed by 40 mg/m^2 on alternate days for 2 weeks followed by gradual tapering over 1-2 months to the minimum dose of 0.5 to 1 mg/kg/day for a total duration of 6 months.
Results: Our study included 80 children presenting with frequently relapsing steroid sensitive nephrotic syndrome. Of these 80 study cases, 63.8% (n=51) were boys while 36.2% (n=29) were girls. Mean age of our study cases was 7.45±2.08 years (ranging from 3 to 12 years (boys 6.78±1.50 years versus girls 8.62±2.44 years, *p*=0.001) and 61.3% (n=49) were aged more than 6 years. Mean weight of our study cases was 24.98±8.12 kilograms (minimum weight 17 Kg to maximum 37 Kg). Mean duration of nephrotic syndrome was noted to be 2.11±1.02 years (1 year to 3 years) and most of these children i.e. 43 (53.7%) belonged to urban areas and 37 (46.3%) were from poor family background. Overall efficacy was noted to be 70.0% (n=56). Efficacy in group A was 90% (n=36) while that in group B it was 50.0% (n=20) (*p*=0.001).
Conclusion: Our study results support the use of Levamisole in children with frequently relapsing steroid sensitive nephrotic syndrome as it was significantly more efficacious in remission of relapses in these children as compared with mycophenolatemofetil. Levamisole was found to be quite safe, reliable and without any side effects which should be given to these children for desired outcomes.
Key words: Steroid sensitive nephrotic syndrome, levamisole, mycofenolate mofetil.

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Authors Contribution

SI & MI conceptualized the project. SI also did the data collection. SI & HR did the literature search. KR & MSZ performed the statistical analysis. Drafting, revision & writing of manuscript were done by KR, MSZ & MA.

Introduction

Nephrotic syndrome contributes towards major workload in pediatric nephrology departments all over the world and majority of these children present with steroid sensitive nephrotic syndrome (SSNS) while estimated 20% children have steroid resistant nephrotic syndrome.[1] Nephrotic syndrome is one of the major primary glomerular illnesses encountered in children and is associated with substantial morbidity pattern as it generally follows a relapsing course along with prolonged use of corticosteroid therapy and other immune suppressive treatment therapies.[2]

Nephrotic syndrome is a disease that involves leakage of proteins in urine, that may result in life threatening situations due to hypovolemia, hyper coagulation, and infection.[3,4] European data have revealed that annual incidence of nephrotic syndrome is 1–7 per 100, 000 children, 2 per 100,000 children in north America and higher proportions in Indian Sub - continent while cumulative prevalence in Europe is estimated to be around 16 children out of 100,000 children.[5] Majority of these children are steroid sensitive minimal change disease (MCD), however 80% of these children experience relapses followed by initial response to routine corticosteroid therapy and more than half of these children experience frequent relapses and 30–50% become steroid dependent.[6,7]

Treatment strategies for pathophysiological outcomes of nephrotic syndrome that involve hypovolemia, acute kidney injury, edema, hypercoagulation and infections are based upon symptomatic management.[8] The basis of management of nephrotic syndrome using steroid therapy was based upon classical hypothesis of the association of immunological factors involved in the pathophysiology of the illness to use immunosuppressive drugs to prevent relapses.[9]

Both levamisole as well as mycophenolatemofetil are used to control relapses in children with frequently relapsing nephrotic syndrome; however, There are no studies comparing efficacy of these in these children while descriptive studies have reported varying proportions for efficacy of both drugs.

On literature search, local studies on this topic are scarce. No such study has been conducted before in our country, so this study was planned to compare effectiveness of levamisole with mycophenolatemofetil to sustain remission in children with steroid sensitive nephrotic syndrome frequent relapsers, thus reducing number of relapses and morbidity of the disease of our local population.

Methodology

Children (n=80) with Steroid-sensitive Nephrotic syndrome frequent relapsers for at least 6 months or more duration aged 2–12 years of either sex were included in this randomized controlled trial. This study was conducted at department of pediatric Nephrology, The Children's Hospital and Institute of the Child Health, Multan from July 2020 to June 2021. Proper approval of hospital Ethics committee was taken. Steroid Sensitive Nephrotic syndrome was defined by proteinuria >40 mg/m^2 per hour, and serum albumin <2.5 g/dl by laboratory test along with edema assessed clinically and patient respond to prednisolone treatment. Edema is said to be positive with anyone or more of the following present i.e. periorbital puffiness, ascites or pit formation after pressing the skin for 5 sec on dorsum of foot, shin or sacrum. Treatment response is defined as absence of proteinuria within 8 weeks of starting standard therapy. Frequent Relapse was defined as two or more relapses in six months, Sustained Remission was defined as if the patient doesn't relapse in 6 months after start of study. Relapse of Nephrotic syndrome was defined as occurrence of +3 proteinuria by dipstick or lab test plus edema assessed clinically in a patient previously diagnosed with nephrotic syndrome.

Patients with steroid resistant nephrotic syndrome and infrequent relapsers i.e having less than 2 relapses in 6 months duration, H/o chronic systemic illness other than nephrotic syndrome (cardiac, metabolic, malignancy, pulmonary, neurologic, rheumatologic), H/o kidney disease like polycystic kidney disease (PKD) and those who were lost to follow up were excluded from our study. Sample size was calculated with confidence level= 95% and alpha= 5% (one-sided) with power = 80%, with using expected (efficacy) proportion p1= 90%[10] and expected (efficacy)proportion p2=40.8%.[11] Estimated sample size was n=80. Total sample size was divided into two groups. n_1=40 sample size for Levamisole group while n_2=40 sample size for Mycofenolate Mofetil group. Demographic information of patients (name, age, gender, weight, duration of disease, number of prelapses) was taken. These children were then randomized in 2 groups; Group A received Levamisole 2-2.5 mg/kg on alternate days for 6 months while group B received MMF (750-1000 mg/m^2 daily) along with standard therapy i. e prednisolone at a dose of 60 mg/m^2 per day for 4-8 weeks or less if reached absence of proteinuria for 3 consecutive days, followed by 40 mg/m^2 to on alternate days for 2 weeks followed by gradual tapering over 1-2 months to the minimum dose of 0.5 to 1 mg/kg/day for a total duration of 6 months. Children were called for follow up after every one month for 6 months for evaluation. Efficacy was defined as if the patient sustained remission for 6 months in study patients.

Data was entered and analyzed using SPSS version 24. Analysis was done to compare proportion of Levamisole group versus Mycofenolatemofetil group by applying chi – square test at 95% CI. Frequencies and percentages were calculated for categorical study variables such as; age groups, gender, family history, socioeconomic status and efficacy. Mean ±SD was presented for numerical variables like weight, age and duration of disease

The ethical approval was obtained from Ethical Committee (EC) of The Children's Hospital and Institute of the Child Health, Multan

Results

Of these 80 study cases, 63.8% (n=51) were boys while 36.2% (n=29) were girls. Mean age of our study cases was 7.45±2.08 years (ranging from 3 to 12 years (boys 6.78±1.50 years versus girls 8.62±2.44 years, *p*=0.001) and 61.3% (n=49) were aged more than 6 years. Mean weight of our study cases was 24.98±8.12 kilograms (minimum weight 17kg to maximum 37kg). Mean duration of nephrotic syndrome was noted to be 2.11±1.02 years (1 year to 3 years) and most of these children i.e. belonged to urban areas 43 (53.7%) and 37 (46.3%) were from poor family background. Baseline characteristics were comparable in both groups (Table-1).

Table 1: Baseline characteristics in levamisole and mycophenolate mofetil groups. (n=80)

Characteristics	*Groups*		
	Group A (n = 40)	*Group B (n = 40)*	*p value*
Gender			
Male (n= 51)	25 (62.5%)	26 (65.0%)	0.999
Female (n=29)	15 (37.5%)	14 (35.0%)	
Age groups			
Up to 6 Years (n= 31)	17 (42.5%)	14 (35.0%)	0.647
More than 6 years (n=49)	23 (57.5%)	06 (65.0%)	
Residential status			
Rural (n= 37)	19 (47.5%)	18 (45.0%)	0.998
Urban (n=43)	21 (52.5%)	22 (55.0%)	
Disease duration (In Years)			
Mean (SD)	2.08±0.65	1.98±0.57	0.471
Weight (In Kg)			
Mean (SD)	19.28±3.58	19.90±3.54	0.435
Mean weight 24.98±8.12			

Table 2: Distribution of efficacy of levamisole and mycofenolate mofetil among study cases.

*Efficacy * (n=80)*	*Group A*		*Group B*	
	F	*%*	*F*	*%*
Yes (n=56) (70%)	36	47.9	20	50
No (n=24) (30%)	04	52.1	20	50
Total	40	100	40	100

* *p*= 0.001

Efficacy (the patients who sustained remission for 6 months after start of therapy) was noted to be 70% (n=56). Efficacy was noted in 90% (n=36) in group A whereas it was 50% (n=20) in group B (*p*=0.001) (Table-2).

Discussion

Management of pediatrics frequently relapsing steroid sensitive nephrotic syndrome involves extended use of oral prednisolone on alternate days, use of levamisole along with oral prednisolone, cyclophosphamide for 3 months, mycophenolate mofetil, Rituximab and calcineurin inhibitors.[12-14]

Our study included 80 children presenting with frequently relapsing steroid sensitive nephrotic syndrome. Of these 80 study cases, 63.8% (n=51) were boys while 36.2% (n=29) were girls. Different studies done in children presenting with frequently while relapsing steroid sensitive nephrotic syndrome have documented male gender predominance as has been reported in our study. Arun et al[15] reported 63.4% children with frequently relapsing steroid sensitive nephrotic syndrome. Sherali et al[16] has also reported male gender predominance with 72% children with steroid sensitive nephrotic syndrome. Abeyagunawardena et al[17] also reported similar results showing male gender predominance. Another study by Hoseini et al[18] has also reported 55% male children predominance with nephrotic syndrome. A study conducted in Karachi by Bajeer et al[19] has reported 63.5% male gender preponderance in pediatric frequently relapsing steroid sensitive nephrotic syndrome, similar to our results.

Mean age of our study cases was 7.45±2.08 years (ranging from 3 to 12 years (boys 6.78±1.50 years versus girls 8.62±2.44 years, *p*=0.001) and 61.3% (n=49) were aged more than 6 years. Arun et al[15] also reported similar results with 88.4±38.3 months mean age in children with nephrotic syndrome. Sherali[16] reported 7.65±3.20 years mean age of the children with nephrotic syndrome. Another study by Hoseini et al[18] has also reported 8.35±4.48 years mean age of nephrotic syndrome. A study conducted in Karachi by Bajeer et al[19] has reported similar results.

Mean weight of our study cases was 24.98±8.12 kilograms (minimum weight 17kg to maximum 37kg). Mean duration of nephrotic syndrome was noted to be 2.11±1.02 years (1 year to 3 years). Majority of our study cases i.e. 108 (56.3%) belonged to urban areas, 43 (53.7%) were from urban areas and 38 (47.5%) were from poor family background. A study conducted in Karachi by Bajeer et al [19] has also documented mean weight was 20 kilograms.

Efficacy was noted in 70% (n=56) while efficacy was noted in 90% (n=36) while it was 50% (n=20) in group B (p=0.001). Moorani et al [10] has documented 90% efficacy of levamisole, close to our findings while Sinha et al[11] has reported 40% efficacy of mycophenolate mofetil in frequently relapsing steroid sensitive nephrotic syndrome. A study from Poland has also documented significant reduction in relapses (p=0.02) following Levamisole treatment in these children.[20]

Our study results support the use of Levamisole in children with frequently relapsing steroid sensitive nephrotic syndrome asit was significantly more efficacious in remission of relapses in these children as compared with mycophenolate mofetil. Levamisole was found to be quite safe, reliable and without any side effects which should be given to these children for desired outcomes.

Conflict of interest: None declared.

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