Role of Montelukast in Reducing the Rate of Relapse of Childhood Idiopathic Nephrotic Syndrome

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Abstract

Background: Relapse of idiopathic nephrotic syndrome is caused by overexpression of IL-13. Montelukast a leukotriene receptor antagonist that may reduce relapse by inhibiting IL-13.

Objective: To assess the effect of montelukast in reducing the rate of relapse of childhood idiopathic nephrotic syndrome.

Methods: A randomized controlled trial was conducted in the Department of Paediatrics, Sylhet MAG Osmani Medical College Hospital, Sylhet from January 2023 to October 2024. A total of 104 children with 1st attack of nephrotic syndrome aged 2 to 10 years were included. Every case was allocated to either Group-A or group-B by block randomization. Thus, each group consisted of 52 children. Prednisolone was started in both groups in a dose of 60mg/m2 daily for 6 weeks. Then, prednisolone was given in a dose of 40 mg/m2 every alternate day for another 6 weeks. Group A (cases) also received montelukast (4mg for children up to5 years of age and 5 mg for children aged 6 years and above) for 12 months. In group B (control) montelukast was not given. Patients in both groups were followed up 3 monthly for one year to monitor the number of relapse and adverse effect of montelukast. Thirteen patients were excluded from final analysis due to lost to follow up (n = 6; 3 in group A and 3 in group B) or steroid resistance (n = 7; 4 in group -A and 3 in group -B).

Results: Out of 91 children (45 in group –A and 46 in group –B), 49(53.8%) patients had relapse. Relapse rate was significantly higher in group -B than group A (71.7% vs 35.6%). In group A, majority 7 (43.8%) had relapse at 9 months whereas in group B, 16 (48.5%) had relapse at 6 months, that was significant between two groups. In group A, 13 (81.3%) patients had IFRNS (Infrequent relapse nephrotic syndrome) whereas in group B, 15 (45.5%) had FRNS (Frequent relapse nephrotic syndrome), the difference between two groups were statistically significant (p=.001). Few adverse effects of montelukast were found.

Conclusion: The result of this study showed that montelukast is effective in reducing the rate of relapse of childhood idiopathic nephrotic syndrome.

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Introduction

Nephrotic syndrome is one of the commonest renal diseases in children. It is usually a chronic disease associated with repeated relapse and remission. Children with nephrotic syndrome need frequent hospitalization for management of initial attack, relapse and complications. Relapse of nephrotic syndrome is usually related to various complications. Repeated use of prednisolone to treat relapse creates significant adverse effects. So, prevention of relapse is very important.

About 90% cases of nephrotic syndrome are primary or idiopathic (Shanta et al., 2023).[1] Further more certain underlying conditions like IgA nephropathy, systemic lupus erythematosus, henoch-schonlein purpura, amyloidosis, hepatitis B and C, malaria, syphilis, have been identified as secondary causes of nephrotic syndrome.

Leukotriene receptor antagonist montelukast exerts its anti-inflammatory effect through suppression of T-helper type 2 cytokines,IL-4, IL- 10 and IL-13(Wu et al., 2003).[2] In podocyte level upregulation of cysteinyl leukotriene-1 receptor by IL-13blocked by montelukast (Park et al. ,2015).[3]

Montelukast is safe and well-tolerated, less-toxic, suitable for long-term administration and relatively low adverse effects (Marques et al., 2022).[4] Rarely few adverse effects may be observed, such as sleep disturbance, increased liver enzymes, hyper activity, abdominal pain, vomiting (Al-Shamrani et al., 2022).[5]

Objectives

General objective:

To assess the effect of montelukast in reducing the rate of relapse of childhood idiopathic nephrotic syndrome.

Specific objectives:

1. To estimate the number of relapses in montelukast treated group.
2. To estimate the number of relapses in standard treatment group.
3. To compare the relapse rate between two groups.
4. To record the adverse effects of montelukast.

Methods

This was an open labelled randomized controlled trial, carried out in the Department of Paediatrics, Sylhet MAG Osmani Medical College Hospital, Sylhet from January, 2023 to October, 2024.Study population were all children with initial attack of idiopathic nephrotic syndrome admitted in Department of Paediatrics. This study included 104 children, 52 in each group. A total of 104 patients, aged 2 – 10 years with first episode of idiopathic nephrotic syndrome satisfying the selection criteria were included in this study. Children below 2 years and above 10years, secondary cause of nephrotic syndrome (Lupus nephritis, HSP nephritis, IgA nephropathy etc), steroid resistant nephrotic syndrome, congenital nephrotic syndrome, nephrotic syndrome with hematuria and hypertension, were excluded from the study.

Sample was collected by consecutive sampling. Informed written consent was taken from legal guardian. Patients were divided into two groups; Group A (experimental group) and B (control group). Group A received prednisolone and montelukast on the other hand only prednisolone was given in group B. A total 52 patients were included in group A and 52 patients in group B. Every case was allocated to either group A or group B by block randomization . Block size was 4 (2×2).

Assessment of response of treatment was done by protein free urine for consecutive 3 days, absence of edema and ascites, adequate diuresis and doing spot protein creatinine ratio.

Data were processed manually and analyzed with the help of statistical package for social science (SPSS) version 26.0. Mean and standard deviation was calculated for quantitative data, percentages were calculated for analysis of qualitative data. Unpaired t-test was used for quantitative variables and Chi square test was used for qualitative variables. A p value <0.05 was considered as significant.

Results

A total of 104 patients, aged 2 – 10 years with first episode of idiopathic nephrotic syndrome satisfying the selection criteria were included in this study. Children below 2 years and above 10years, secondary cause of nephrotic syndrome (Lupus nephritis, HSP nephritis, IgA nephropathy etc), steroid resistant nephrotic syndrome, congenital nephrotic syndrome, nephrotic syndrome with hematuria and hypertension, were excluded from the study. Thirteen patients were excluded from final analysis due to lost to follow up and steroid resistance.

Table I: Baseline characteristics of study patients (n=91)

Baseline characteristics	Group A (Experimental) (n=45*)		Group B (Control) (n=46#)		P value
	n	%	n	%	
Age (years)					
2-6	36	80.0	33	71.7	
>6-8	6	13.3	8	17.4	
>8-10	3	6.7	5	10.9	
Mean±SD	4.5	±2.2	4.9	±2.4	[a]0.424[ns]
Range (min-max)	2.0-	10.0	2.0	-10.0	
Sex					
Male	26	57.8	22	47.8	[b]0.342[ns]
Female	19	42.2	24	52.2	

Group A (experimental group) received prednisolone and montelukast
Group B (control group) received only prednisolone
ns= not significant
[a]p value reached from student t-test; [b]p value reached from chi square test

Majority of the patients belonged to age group 2-6 years in both groups. The mean age was found 4.5±2.2 years in group A and 4.9±2.4 years in group B. In group A 26(57.8%) were male and 19(42.2%) were female. In group B male and female were 22(47.8%) and 24(52.2%) respectively. There were no significant difference regarding age and sex between two groups.

Table II: Distribution of the study patients according to relapse rate (n=91)

Relapse	Group A (Experimental) (n=45*)		Group B (Control) (n=46#)		P value
	n	%	n	%	
Relapse occur	16	35.6	33	71.7	0.001[s]
No relapse	29	64.4	13	28.3	

s= significant; p value reached from chi square test

After 1 year of follow up, among 45 patients of group A, 16 (35.6%) patients had relapse and among the 46 patients in group B, 33 (71.7%) patients had relapse. The difference between group A and group B regarding relapse was statistically significant (p=.001).

Table III: Relapse time of study patients (n=49)

Relapse time	Group A (Experimental) (n=16)		Group B (Control) (n=33)		P value
	n	%	n	%	
At 3 months	4	25.0	14	42.4	
At 6 months	3	18.8	16	48.5	0.004[s]
At 9 months	7	43.8	2	6.1	
At 12 months	2	12.5	1	3.0	

s= significant; p value reached from chi square test

In group A, majority 7(43.8%) patients had relapse at 9 months and in group B, 16(48.5%) had relapse at 6 months. The difference between group A and group B regarding duration of relapse time was statistically significant (p=.001).

Table IV: Types of relapse in study subjects (n=49)

	Group A (Experimental) (n=16)		Group B (Control) (n=33)		P value
	n	%	n	%	
IFRNS	13	81.3	11	33.3	
FRNS	3	18.8	15	45.5	0.005[s]
SDNS	0	0.0	7	21.2	

s= significant; p value reached from chi square test

Majority 13(81.3%) patients had IFRNS in group A and 15(45.5%) had FRNS in group B, that was statistically significant between two groups (p=0.001).

Table V: Adverse effects of montelukast (n=45)

Adverse effects	Frequency	Percentage
Sleep disturbance	2	4.4
Hyperactivity	1	2.2
Abdominal pain	1	2.2

Regarding adverse effects, 2 (4.4%) patients had sleep disturbance, 1 (2.2%) had hyperactivity and 1 (2.2%) had abdominal pain.

Discussion

This open labelled randomized controlled trial was performed to observe the effect of montelukast in reducing the rate of relapse of childhood idiopathic nephrotic syndrome. A total of 104 patients with nephrotic syndrome 1st attack were included in this study,13 patients were excluded from final analysis due to lost to follow up and steroid resistance. After 1 year of follow up, relapse rate was significantly lower in prednisolone and montelukast group compared to prednisolone only group. In prednisolone and montelukast group, majority had infrequent relapse nephrotic syndrome and none had steroid dependent nephrotic syndrome while in prednisolone only group, near about half of the patients had frequent relapsing nephrotic syndrome and one fifth had steroid dependent nephrotic syndrome.

In this study, after one year of follow up, among the 91 patients, 49 (53.8%) patients had relapse where more than one third of the patients (35.6%) in experimental group and majority of the patients (71.7%) in control group had relapse. Relapse rate was significantly lower in experimental group.

In Pakistan, Raza et al. (2021) [6] found overall 35.4% patients had relapse where experimental group had lower relapse rate (18.8%) that was treated with montelukast than control group (52.1%) not received montelukast. The difference was statistically significant ($p<0.001$).

In Sri Lanka, Abeyagunawardena et al. (2021) [7] reported significant reduction in relapse rate in experimental group while comparing with control group. In control group, 71.7% patients had relapse. A prospective longitudinal study was conducted in a tertiary center of Bangladesh among children with idiopathic nephrotic syndrome, where 70.1% had relapse (Akter et al., 2022). [8]

The use of montelukast as an adjunctive therapy in nephrotic syndrome has shown promising result across several studies. In this study,25% of patients treated with montelukast experience relapse at 3 months, compared to 42.4% in the non -montelukast group. In experimental group majority(43.8%) had relapse at 9 month and in control group majority (48.5%) patients had relapse at 6 months. The duration of relapse time between two groups were statistically significant($p=.001$).

Ghosh et al. (2023) [9] emphasized that, alternative therapies including montelukast,are being increasingly explored for their role in long term management of nephrotic syndrome.

The study by Park et al.(2015) [3]showed potential mechanisms through which montelukast might exert its effects. They found that higher level of IL13 disrupted the glomerular filtration barrier and led to effacement of foot process of podocyte. Treatment with montelukast restore the integrity of ZO-1 protein in experimental model of human podocyte. This finding suggest that, montelukast reverse the dysfunction of human podocytes caused by IL-13.

In this study, the main adverse effect of Montelukast was sleep disturbance (4.4%) followed by abdominal pain (2.2%) and hyperactivity (2.2%). In accordance to this study, Al-Shamrani et al. (2022) [5] found that sleep disturbance, agitation, abdominal pain and hyperactivity were the common adverse effect of montelukast.

Conclusion

It can be concluded that montelukast is effective in reducing the rate of relapse of childhood idiopathic nephrotic syndrome.

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