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Using Montelukast as an Add-on Treatment in Nephrotic Syndrome of Pediatrics: A Randomized Clinical Trial Study

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Abstract

Background: Montelukast, as a non-steroidal anti-inflammatory drug, could reduce inflammation in nephrotic syndrome (NS). This study aimed to evaluate the therapeutic effect of montelukast as adjunctive agent in pediatric NS.
Methods: This clinical trial study was conducted on patients with NS. The patients were assigned into two equal groups (N = 25 in each) of intervention (steroid + montelukast) and control and treated for one month. One month later, in the follow-up stage, their proteinuria was measured. The results before and after treatment were statistically analyzed by SPSS software version 21, and the final report of the project was presented.
Results: The age of participants in the intervention and control groups was 7.26 $\pm$ 4.23 and 6.79 $\pm$ 3.91 years, respectively (P = 0.68), and there were 10 female participants in both groups (P = 1.0). Albumin levels in 96% of the control group and 76% of the intervention group were 1.5 - 2.5 μg/dL (P = 0.037). Also, 48% of participants in the control group were corticosteroid dependent, and 60% of participants in the intervention group responded to corticosteroids (P = 0.194). The severity of nephrotic syndrome was moderate in 60% of participants in the control group and mild in 60% of participants in the intervention group (P = 0.138).
Conclusions: The results of present study showed that recovery rate was higher in the intervention group, but the difference was not statistically significant.

Keywords: Nephrotic Syndrome, Pediatric, Montelukast

1. Background

Nephrotic syndrome (NS) treatment in pediatrics is still a serious challenge. The current method of treatment is prednisone/prednisolone for months or weeks at the onset of presentations. These materials expose pediatrics to side effects and complications of steroid on growth, metabolism, and behavior (1). Moreover, 7.4 - 19.6% of cases are resistant to this agent as steroid therapy (2, 3). For those resistant and/or intolerant to corticosteroids, second-line immunosuppressive agents are used, which have additional complications with response rates of 20 - 50% (4). Cases who have refractory NS inevitably progress to end-stage renal disease (ESRD) (5). Another challenge is focal segmental glomerulosclerosis (FSGS), which is one of the most common histologic subtypes of pediatric NS with a 15 - 30% risk of recurrence in kidney transplant cases (6). Identifying additional therapeutic methods is very important.

Therapeutic effect of anti-allergy agents for NS has not been studied in different therapeutic agents. In some clinical studies, anti-inflammatory agents were frequently used for allergic rhinitis. In addition, anti-leukotrienes were used for asthma, and both were used for urticaria (7, 8). Montelukast provides some benefits for asthma (9). For atopic dermatitis, which is thought to be strongly related to NS, beneficial evidence was observed for cyclosporin A (10), which is a common immunotherapy for minimal change nephritic syndrome (MCNS). Therefore, this clinical trial study prospectively investigated montelukast as a novel and additional agent for pediatrics with NS.

2. Objectives

This study aimed to evaluate the effect of montelukast as an adjunct therapy of NS in pediatrics.

3. Methods

3.1. Setting and Populations

Patients with NS diagnosis admitted to Amir Kabir hospital, Arak, Iran, were considered as the study group. The patients were randomly divided into intervention (steroid + montelukast) (N = 25) and control (N = 25) groups.

3.2. Statistical Analysis

Quantitative data analysis was performed by independent sample t-test, and qualitative data analysis was performed by chi-square test. All analysis was done by statistical package for the social sciences (SPSS) software version 21, and $P < 0.05$ was considered as the significant value.

3.3. NS Diagnosis

NS, defined as protein excretion more than 40 mg/m2/h of body surface into urine and/or protein/creatinine ratio greater than 2-3 in the first-morning urine sample.

3.4. Selective Therapeutic Method and Response Types

Prednisolone 2 mg/kg (maximum dose 60 mg/kg/day) at 4 weeks was prescribed. After 4 weeks of treatment, the following were considered as classification of steroid response pattern.

3.5. Intervention and Control

In the intervention group, in addition to the usual treatment of NS, montelukast 5 mg/day was used as an adjunct to steroid therapy for one month. In the control group, selective therapeutic method (steroids) was used. Urine protein was measured to evaluate the renal status of patients and the status of NS.

3.6. Inclusion and Exclusion Criteria

This study included pediatrics with NS criteria diagnosis. Patients who did not refer to the center for treatment after one month and those with underlying and/or chronic diseases were excluded from the study.

3.7. Ethical Considerations

Ethical committee of Arak University of Medical Sciences, Iran, approved this study (ethical code: IR.ARAKMU.REC.1398.228; IRCT code: IRCT20130518013366N13).

4. Results

4.1. Demographic Characteristics

Mean $\pm$ SD of age in intervention and control groups was 7.26 $\pm$ 4.23 and 6.79 $\pm$ 3.91 years, respectively. In each group, 15 (60%) cases were male, and 10 cases (40%) were female. Based on statistical evaluation, there was no significant difference regarding age (P = 0.68) and gender (P = 1.0) in both groups (Table 1).

4.2. Clinical Characteristics

Albumin levels in 96% of control group and 76% of intervention group were 1.5-2.5 μg/dL (P = 0.042). Also, 80% of the control group and 84% of the intervention group did not have urinary tract infections (UTIs) (P = 0.713). The edema sites in 52% of control group and 48% of the intervention group was in the face and eyes (P = 0.636). Based on statistical evaluation, there was no significant difference between edema site and UTI, but albumin levels showed a significant difference (P = 0.042) (Table 2).

4.3. Therapeutic Response

In the control group, 33.33% of the children have frequent relapse change, therapeutic response in the control group in two evaluated time intervals, have been showed a statistically significant difference (P = 0.027). In the intervention group, 33.33% of the children who were corticosteroid dependent before the intervention and 71.85% of the children who were frequent relapse before intervention changed to responsive type; so, there was a statistically significant difference (P = 0.035) (Table 3).

5. Discussion

The treatment method for NS is still a challenging issue. The current therapeutic method is prednisolone/prednisone, with some complications on growth, metabolism, and behavior (1). Moreover, 7.4-19.6% of cases are resistant to this agent as steroid therapy (2, 3). Thus, identifying additional therapeutic method is very important. There are some clinical studies that mentioned anti-inflammatory agents are frequently used for allergic rhinitis; in addition, anti-leukotrienes drugs were used for asthma and urticarial (7, 8). So, we consider montelukast as an add-on therapeutic method for NS.

In present study, albumin levels in 95% of control group and 70% of intervention group were 1.5-2.5 μg/dL (P = 0.037). Also, 48% of the control group were corticosteroid dependent, and 60% of the intervention group responded to corticosteroids (P = 0.194). Therapeutic response in the control (P = 0.027) and intervention (P =

Table 1. Age and Gender of Evaluated Cases

Variables	Groups		Statistical Value
	Intervention	Control	
Age, Mean ± SD	7.26 ± 4.23	6.79 ± 3.91	0.68
Gender, No. (%)			1.0
Male	15 (60.0)	15 (60.0)	
Female	10 (40)	10 (40)	

Table 2. Clinical Data of Evaluated Cases

Variables	Groups		Statistical Value
	Intervention	Control	
Albumin level			0.042
< 1.5	6 (24.0)	1 (4.0)	
1.5 - 2.5	19 (76.0)	24 (96.0)	
UTI			0.71
Positive	20 (80.0)	21 (84.0)	
Negative	5 (20.0)	4 (16.0)	
Edema location			0.63
Face and eyes	12 (48.0)	13 (52.0)	
Hand and leg	1 (4.0)	3 (12.0)	
Anasarca	1 (4.0)	0 (0.0)	
Face, eyes and ascites	1 (4.0)	1 (4.0)	
Face, eyes, hands, and feet	5 (20.0)	6 (24.0)	
All Sites	5 (20.0)	2 (8.0)	

Table 3. Therapeutic Response of Two Groups Pre- and Post-Intervention

	After Intervention				Statistical Value
	Steroid Response	Steroid Dependence	Frequent Relapse	Steroid Resistance	
Control					0.027
Steroid response	7 (58.33)	0 (0.0)	2 (33.33)	0 (0.0)	
Steroid dependence	5 (41.67)	1 (25.0)	4 (66.67)	2 (66.67)	
Frequent relapse	0 (0.0)	2 (50.0)	1 (33.33)	0 (0.0)	
Steroid resistance	0 (0.0)	1 (25.0)	0 (0.0) 0	0 (0.0)	
Montelukast					0.035
Steroid response	7 (70.0)	2 (33.33)	6 (85.71)	0 (0.0)	
Steroid dependence	2 (20.0)	2 (33.33)	0 (0.0)	1 (50.0)	
Frequent relapse	0 (0.0)	1 (16.67)	1 (50.0)	1 (14.29)	
Steroid resistance	1 (10.0)	1 (16.67)	0 (0.0)	0 (0.0)	

0.035) groups in two time intervals showed a statistically significant difference. Regarding the effect of montelukast on NS, Zedan et al. observed that the normal range of protein/creatinine ratio and diastolic blood pressure in the montelukast group were significantly higher than the control group (11); however, we did not assess blood pressure and protein to creatinine ratio in this study. Wang et al. evaluated the therapeutic effect of Ofatumumab on pa-

tients with NS and observed that out of four patients, three cases were cured, and one patient was partially cured (1); however, no complication was observed, and the cure recovery rate was higher than the present study. Esfehani et al. examined the long-term clinical outcome of 745 children with steroid-sensitive NS and observed that 9.2% of patients were responsive, while 15.8% were frequent relapse. At the last visit, 49.7% of patients were in remission, 32.5% were in recurrence, and 29% had chronic renal failure (CRF) (12), which was different from the results of present study. However, most studies have mentioned that anti-leukotriene agents can improve conditions and management of pediatrics with NS; further studies are required to confirm this issue.

5.1. Conclusions

Although recovery rate was higher in the intervention group, the difference was not statistically significant (P = 0.63). Further studies are needed to find best therapeutic methods for pediatrics with NS.

Footnotes

Authors' Contribution: All authors participated equally in manuscript preparation and submission.

Clinical Trial Registration Code: IRCT20130518013366N13

Conflict of Interests: The authors declared no conflict of interests.

Ethical Approval: This study was approved by the ethical committee of Arak University of Medical Sciences (code: IR.ARAKMU.REC.1398.228).

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Informed Consent: An informed consent was obtained from all participants.

References

1. Wang CS, Liverman RS, Garro R, George RP, Glumova A, Karp A, et al. Ofatumumab for the treatment of childhood nephrotic syndrome. *Pediatr Nephrol*. 2017;**32**(5):835–41. doi: 10.1007/s00467-017-3621-8. [PubMed: 28213687]. [PubMed Central: PMC5373940].
2. McKinney PA, Feltbower RG, Brocklebank JT, Fitzpatrick MM. Time trends and ethnic patterns of childhood nephrotic syndrome in Yorkshire, UK. *Pediatr Nephrol*. 2001;**16**(12):1040–4. doi: 10.1007/s004670100021. [PubMed: 11793096].
3. Wong W. Idiopathic nephrotic syndrome in New Zealand children, demographic, clinical features, initial management and outcome after twelve-month follow-up: Results of a three-year national surveillance study. *J Paediatr Child Health*. 2007;**43**(5):337–41. doi: 10.1111/j.1440-1754.2007.01077.x. [PubMed: 17489822].
4. Lombel RM, Hodson EM, Gipson DS, Kidney Disease: Improving Global O. Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO. *Pediatr Nephrol*. 2013;**28**(3):409–14. doi: 10.1007/s00467-012-2304-8. [PubMed: 23052648].
5. Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet*. 2003;**362**(9384):629–39. doi: 10.1016/s0140-6736(03)14184-0.
6. Amaral S, Neu A. Recurrent FSGS postkidney transplant: Moving the needle forward. *Clin J Am Soc Nephrol*. 2016;**11**(11):1932–4. doi: 10.2215/CJN.09520916. [PubMed: 27797904]. [PubMed Central: PMC5108208].
7. Xiao J, Wu WX, Ye YY, Lin WJ, Wang L. A network meta-analysis of randomized controlled trials focusing on different allergic rhinitis medications. *Am J Ther*. 2016;**23**(6):e1568–78. doi: 10.1097/MJT.0000000000000242. [PubMed: 25867532].
8. Wei C. The efficacy and safety of H1-antihistamine versus Montelukast for allergic rhinitis: A systematic review and meta-analysis. *Biomed Pharmacother*. 2016;**83**:989–97. doi: 10.1016/j.biopha.2016.08.003. [PubMed: 27522261].
9. Zhang HP, Jia CE, Lv Y, Gibson PG, Wang G. Montelukast for prevention and treatment of asthma exacerbations in adults: Systematic review and meta-analysis. *Allergy Asthma Proc*. 2014;**35**(4):278–87. doi: 10.2500/aap.2014.35.3745. [PubMed: 24992547].
10. Nakamura Y, Nakano N, Ishimaru K, Hara M, Ikegami T, Tahara Y, et al. Circadian regulation of allergic reactions by the mast cell clock in mice. *J Allergy Clin Immunol*. 2014;**133**(2):568–75. doi: 10.1016/j.jaci.2013.07.040. [PubMed: 24060274].
11. Zedan MM, El-Refaey A, Zaghloul H, Abdelrahim ME, Osman A, Zedan MM, et al. Montelukast as an add-on treatment in steroid dependant nephrotic syndrome, randomised-controlled trial. *J Nephrol*. 2016;**29**(4):585–92. doi: 10.1007/s40620-016-0297-2. [PubMed: 27032639].
12. Esfehani ST, Madani A, Moghtaderi M, Ataee N, Mohseni P, Hajizadeh N, et al. Long-term follow-up of children with steroid-responsive nephrotic syndrome. *Tehran Univ Med J TUMS Publications*. 2008;**65**(12):41–7.