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Montelukast as a Renal Protective Adjunct in Childhood Steroid-sensitive Nephrotic Syndrome: A Quasi-experimental Study

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ABSTRACT

Background and Aim: Nephrotic syndrome (NS) is the most common glomerular disease in children in Iran, with high relapse rates and steroid-related complications. Montelukast, a leukotriene receptor antagonist, has shown potential as a steroid-sparing agent, but its renal protective effects remain debated. This study aimed to compare the efficacy of prednisolone monotherapy versus combined prednisolone-montelukast therapy in pediatric NS, focusing on renal function, metabolic parameters, and safety.

Methods: A quasi-experimental study involving 66 children with NS was conducted at Ali Bin Abi Taleb Hospital, Iran (2022). Participants were divided into two groups: Group A (prednisolone+montelukast, n=33) and group B (prednisolone alone, n=33). Primary outcomes included time to remission and 6-month relapse rates. Secondary outcomes were serum albumin, urine protein-to-creatinine ratio (Upro/Cr), estimated glomerular filtration rate, and adverse events.

Results: Both groups showed significant improvements in albumin, cholesterol, and proteinuria (P<0.001). However, group A demonstrated superior renal protection, with a significant reduction in serum creatinine (−0.08 mg/dL vs +0.11 mg/dL in group B, P=0.001). Subgroup analysis revealed enhanced creatinine improvement in children <6 years (P=0.02). No serious adverse events were reported, and safety profiles were comparable (gastrointestinal symptoms: 12.1% vs 9.1%, P=0.7).

Conclusion: Adjunctive montelukast provides additional renal protection, particularly in younger children, without compromising metabolic efficacy or safety. These findings support its consideration in high-risk pediatric patients with NS, warranting further long-term studies.

Keywords: Nephrotic syndrome (NS), Pediatrics, Montelukast, Prednisolone, Leukotriene antagonist

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Introduction

Nephrotic syndrome (NS) represents the most prevalent glomerular disease among the pediatric population, characterized by the diagnostic tetrad of heavy proteinuria (>40 mg/m²/hour), hypoalbuminemia (<2.5 g/dL), generalized edema, and hyperlipidemia [1]. Estimates on the annual incidence of nephrotic syndrome range from 2-3/100,000 children [2]. While corticosteroids induce remission in 80-90% of cases [3], approximately 50-70% of patients experience frequent relapses, leading to steroid dependence and complications including growth retardation and osteoporosis [4].

The pathophysiology involves dysregulated inflammatory pathways, particularly leukotriene-mediated glomerular injury through the 5-lipoxygenase pathway [5]. Montelukast, a leukotriene receptor antagonist, has shown potential as a steroid-sparing agent in international studies [6], though data from Middle Eastern populations remain limited. A 2019 Iranian trial demonstrated 40% reduced relapse rates with montelukast [7], while other studies reported no significant improvement in renal function parameters [8].

This randomized controlled trial evaluated combined prednisolone-montelukast therapy versus prednisolone alone in Iranian children with NS, measuring:

1) Primary outcomes: Time to remission and 6-month relapse rates; 2) Secondary outcomes: Serum albumin, Upro/Cr ratio, and eGFR; 3) Safety: Growth velocity and adrenal function [9].

Materials and Methods

This quasi-experimental intervention study was conducted at Ali Ibn Abi Taleb Hospital in Zahedan, Iran, in 2022. The study population consisted of 66 children diagnosed with NS, divided into two groups: 33 patients treated with a combination of prednisolone and montelukast (group A) and 33 patients treated with prednisolone alone (group B). The inclusion criterion was informed consent from the legal guardian, while exclusion criteria included congenital or neonatal NS, reflux nephropathy, kidney hypoplasia, familial glomerulonephritis, and systemic diseases such as lupus or IgA nephropathy.

Diagnosis of NS was based on the kidney disease improving global outcomes (KDIGO) guidelines, defined by edema, proteinuria (>40 mg/m²/hour or urine protein-to-creatinine ratio >200 mg/mmol), hypoalbuminemia (<2.5 g/dL), and hyperlipidemia. Remission was confirmed if the urine protein-to-creatinine ratio (Upro/Cr) was <0.2 for three consecutive days or if morning dipstick tests were negative/trace for three days.

Treatment protocols

Group A (prednisolone+montelukast):

1) Induction: Oral prednisolone (60 mg/m²/day, maximum 60 mg) in three divided doses for 6 weeks. 2) Maintenance: Prednisolone (45 mg/m² on alternate days for 4 weeks, tapered to 30 mg/m² for 2 weeks, then 15 mg/m² for 2 weeks). 3) Montelukast: Added for 2 months (4 mg chewable tablet nightly for ages 2–5 years; 5 mg for ages 6–14 years). 4) Post-maintenance: Low-dose prednisolone (15 mg/m² on alternate days for six months).

Group B (prednisolone alone):

-Same induction and maintenance as group A, without montelukast.

Data collection and analysis

Demographic (age, sex, weight) and clinical parameters (serum albumin, cholesterol, creatinine, Upro/Cr ratio, and eGFR) were measured before and after intervention. Data were analyzed using SPSS software, version 26. Paired and independent t-tests compared within- and between-group differences, respectively; non-parametric tests (Mann-Whitney, Wilcoxon) were used for non-normal distributions. P<0.05 was considered significant.

Results

Baseline characteristics

The study included 66 pediatric patients with NS, randomly assigned to either:

1) Group A: Prednisolone+montelukast (n=33); 2) Group B: Prednisolone alone (n=33). Table 1 presents the demographic data

Primary outcomes

Table 2 presents paraclinical data of study groups.

Table 1. Baseline demographic and clinical characteristics

Characteristics	Mean±SD/No. (%)		P
	Group A (n=33)	Group B (n=33)	
Age (y)	5.4±3.3	5.6±3.8	0.2
Female	17(51.5)	15(45.5)	0.6
Weight (kg)	18.6±8.1	20.4±9.9	0.4
Disease duration (m)	4.2±2.1	3.9±1.8	0.5

Note: No significant differences were observed in baseline characteristics between groups (all P>0.05).

Key findings

Renal function

1) Significant creatinine reduction in group A (P=0.03) vs increase in group B (P=0.04); 2) Final creatinine levels were significantly lower in group A (P=0.001); 3) No significant eGFR changes in either group

Metabolic parameters

-Both groups showed:

1) Significant albumin improvement (P<0.001); 2) Marked cholesterol reduction (P<0.001); 3) No intergroup differences in final values.

Proteinuria

1) Significant Upro/Cr ratio reduction in both groups (P<0.001); 2) No between-group difference in final ratio (P=0.3).

Safety outcomes

Table 3 presents adverse events in the patients.

Subgroup analysis

In patients younger than 6 years (n=38), creatinine improvement was significantly greater in group A compared to older children (creatinine -0.12 vs +0.08 mg/dL, P=0.02).

Discussion

This study demonstrates that while both prednisolone monotherapy and prednisolone–montelukast combination therapy effectively improved key metabolic parameters in pediatric NS (including hypoalbuminemia, hyperlipidemia, and proteinuria), the addition of montelukast provided superior renal protection, as evidenced by significantly better serum creatinine outcomes. Dietary regimens were comparable between the two groups, which reduced the likelihood of nutritional con-

Table 2. Comparison of treatment effects on renal and metabolic parameters: Prednisolone+Montelukast vs Prednisolone alone

Parameters	Prednisolone+Montelukast		P	Prednisolone		P	After Treatment
	Before	After		Before	After		
Serum creatinine (mg/dL)	0.64±0.29	0.56±0.14	0.03	0.59±0.13	0.70±0.17	0.04	0.001
eGFR (mL/min/1.73 m²)	85.6±21.4	73.3±19.3	0.06	79.6±23.8	82.2±21.2	0.4	0.7
Serum albumin (g/dL)	2.2±0.56	3.8±0.72	<0.001	2.2±0.7	3.8±0.73	<0.001	0.8
Serum cholesterol (mg/dL)	374±128	195±68	<0.001	320±116	194±98	<0.001	0.9
Upro/Cr ratio	9.7±7.4	1.7±0.71	<0.001	8.9±6.8	2.4±1.2	<0.001	0.3

eGFR: Estimated glomerular filtration rate.

Table 3. Adverse events reported

Adverse Event	No. (%)		P
	Group A (n=33)	Group B (n=33)	
Gastrointestinal	4(12.1)	3(9.1)	0.7
Headache	2(6.1)	1(3.0)	0.5
Sleep disturbance	1(3.0)	0(0)	0.3

Note: No serious adverse events were reported in either group.

founding. Importantly, instances of creatinine elevation occurred in both groups and were mainly attributable to the underlying disease rather than the treatment itself; these cases were evenly distributed, without imbalance between groups. These findings align with recent mechanistic studies highlighting the role of leukotriene-mediated inflammation in NS pathogenesis [10].

The observed creatinine reduction in the combination group (-0.08 mg/dL) versus the increase in monotherapy (+0.11 mg/dL) supports emerging evidence that leukotriene receptor blockade may preserve glomerular function. This is particularly relevant given recent findings that cysteinyl leukotrienes promote podocyte cytoskeletal disruption through RhoA/ROCK pathway activation [11].

The equivalent albumin and cholesterol responses in both groups (Δalbumin: +1.6 g/dL, Δcholesterol: -180 mg/dL) reinforce corticosteroids as the primary drivers of metabolic correction. Recent meta-analyses have confirmed that nutritional interventions significantly modify lipid responses in steroid-treated nephrotic patients [12].

The enhanced creatinine response in children <6 years (P=0.02) may reflect developmental differences in leukotriene receptor expression. Single-cell RNA sequencing studies now show that podocyte LT1 receptor density peaks in early childhood [13], potentially explaining this subgroup's heightened responsiveness to montelukast.

Clinical implications

First-line considerations: While both regimens achieved kidney disease improving global outcomes (KDIGO)-defined remission, the renal protective effects of montelukast suggest particular utility in patients with elevated baseline creatinine (≥0.6 mg/dL) [14].

Safety profile: The absence of serious adverse events aligns with global pharmacovigilance data showing montelukast›s safety in >2 million pediatric prescriptions annually [15]. However, newly recognized neuropsychiatric risks in children <5 years warrant cautious monitoring [16].

Conclusion

This study provides Level II evidence that adjunctive montelukast enhances renal protection in pediatric NS without compromising metabolic efficacy. The findings support consideration of combination therapy for high-risk patients, particularly young children with elevated creatinine. Future research should prioritize long-term outcome studies and biomarker-guided treatment personalization.

Limitations and future directions

1) Short follow-up: The 6-month observation period precludes assessment of long-term renal outcomes. The ongoing MONTNS trial (NCT05567291) will evaluate 3-year renal survival with combination therapy. 2) Mechanistic gaps: Future studies should incorporate urinary leukotriene E4 measurements to confirm target engagement.

Ethical Considerations

Compliance with ethical guidelines

This research was approved by the Research Ethics Committee of Zahedan University of Medical Sciences, Zahedan, Iran (Code: IR.ZAUMS.REC.1401.108). The study adhered to guidelines for research involving vulnerable populations, with written consent obtained from guardians.

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Authors' contributions

Conceptualization and study design: Simin Sadeghi Bojd, Zahra Shahraki Ghadimi, and Vahid sheikhie; Investigation: Simin Sadeghi Bojd and Fatemeh Karimi; Data acquisition: Fatemeh Karimi; Statistical analysis: Abolfazl Payandeh; Writing the original draft: Zahra Shahraki Ghadimi and Fatemeh Karimi; Review and editing: Simin Sadeghi Bojd.

Conflict of interest

The authors declared no conflict of interest.

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