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Revisiting the Role of Steroid-Sparing Agents in Frequently Relapsing, Steroid-Dependent, and Steroid-Resistant Nephrotic Syndrome in Children: A Multicentric Prospective Observational Outcomes Study

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ABSTRACT

Background: Frequently relapsing nephrotic syndrome (FRNS), steroid-dependent nephrotic syndrome (SDNS), and steroid-resistant nephrotic syndrome (SRNS) in children are associated with recurrent relapses, cumulative corticosteroid toxicity, and significant impairment of growth and quality of life. Steroid-sparing agents (SSAs) are therefore essential for long-term disease control. However, real-world data on their effectiveness, safety, and quality-of-life outcomes remain limited, particularly from resource-constrained settings.
Objectives: To evaluate real-world prescribing patterns of steroid-sparing agents in children with FRNS, SDNS, and SRNS, assess their effectiveness and safety, and determine their impact on health-related quality of life.
Methods: This multicentric prospective observational study was conducted between 01 May 2016 and 30 April 2017 across two tertiary-care hospitals in eastern India. Children aged 2–12 years with FRNS, SDNS, or SRNS initiated on a steroid-sparing agent for the first time were enrolled and followed for a minimum of six months, with extended follow-up up to twelve months in a subset. Although data collection was completed in 2017, analysis and manuscript preparation were delayed due to academic and administrative processes. Clinical outcomes, adverse events, and quality of life were assessed using validated PedsQL Family Impact and ESRD modules.
Results: A total of 104 children were enrolled. Levamisole was the most frequently prescribed steroid-sparing agent (93.3%). At six months, complete remission was achieved in 84.5% of patients, with steroid discontinuation in 36%. At twelve months, sustained remission was observed in 79.1%, and more than 70% achieved steroid withdrawal. Adverse events were predominantly mild and reversible. Quality-of-life scores showed significant improvement at both six and twelve months ($p < 0.05$).
Conclusion: Levamisole remains an effective, safe, and well-tolerated first-line steroid-sparing agent in children with FRNS and SDNS, providing sustained remission, meaningful steroid reduction, and significant improvement in quality of life.

Keywords*: Nephrotic syndrome, Steroid-sparing agents, Levamisole,* Frequently relapsing nephrotic syndrome, Steroid-dependent nephrotic syndrome.

INTRODUCTION

Nephrotic syndrome is one of the most common chronic glomerular disorders in childhood and is characterised by heavy proteinuria, hypoalbuminaemia, oedema, and hyperlipidaemia. Although the majority of children achieve initial remission with corticosteroid therapy, a substantial proportion develop complicated disease phenotypes such as FRNS, SDNS, or SRNS, which are associated with increased morbidity and long-term complications.[1–3]

Prolonged corticosteroid exposure in these children leads to significant adverse effects, including growth suppression, obesity, hypertension, behavioural disturbances, and increased infection risk.[4,5] Steroid-sparing agents have therefore become essential to maintain remission while reducing steroid-related toxicity. In SRNS, immunosuppressive agents are often required due to poor steroid responsiveness.[6]

Levamisole continues to be widely used in FRNS and SDNS owing to its immunomodulatory effects, favourable safety profile, oral administration, and affordability, especially in low- and middle-income countries.[10–12] Despite guideline recommendations, variability in real-world treatment practices persists, and patient-centred outcomes such as quality of life are often under-reported.[13–16] This study aimed to address these gaps.

METHODS

This prospective observational study was conducted at two tertiary-care centres after institutional ethics approval. Children aged 2–12 years with FRNS, SDNS, or SRNS initiated on a steroid-sparing agent for the first time were enrolled after informed consent. Baseline demographic, clinical, and laboratory data were recorded.

Patients were followed monthly for six months, with a subset followed up to twelve months. Outcomes included remission status, relapse frequency, steroid discontinuation, adverse events, renal function, and quality of life assessed using PedsQL Family Impact and ESRD modules. Data were analysed using descriptive statistics, with $p < 0.05$ considered statistically significant.

RESULTS

Of the 104 enrolled children, 56 had FRNS, 44 had SDNS, and 4 had SRNS. Baseline demographic and clinical characteristics are summarised in **Table 1**. Levamisole was the predominant first-line steroid-sparing agent, while cyclophosphamide and mycophenolate mofetil were used selectively, mainly in SRNS or after levamisole failure (**Figure 1**).

At six months, levamisole achieved high rates of complete remission with low relapse frequency. Sustained remission remained predominant at twelve months, although relapse and treatment failure increased modestly, necessitating escalation in some cases **(Figure 2)**. Steroid discontinuation increased substantially over time. Quality-of-life scores improved significantly at both six and twelve months (**Table 2**). Adverse events were mostly mild and reversible, with no new safety signals identified.

Table 1. Demographic and Baseline Characteristics of Study Participants (N = 104)

Variable	FRNS (n=56)	SDNS (n=44)	SRNS (n=4)	Total (N=104)
Mean age at presentation (years, Mean ± SD)	6.58 ± 2.12	6.80 ± 2.49	8.2 ± 1.9	6.68 ± 2.29
Mean age at onset of nephrotic syndrome (years)	3.57 ± 1.37	5.19 ± 2.18	6.4 ± 1.6	4.30 ± 1.94
Male, n (%)	40 (75.5)	30 (68.2)	0	70 (67.3)
Female, n (%)	13 (24.5)	14 (31.8)	4	32 (30.8)
Male : Female ratio	3.1 : 1	2.1 : 1	–	2.6 : 1
Interval between NS onset and steroid dependence/relapse (years)	3.0 ± 1.61	1.73 ± 1.53	–	2.43 ± 1.69

Table 2. Quality of Life Scores with Levamisole Therapy at Baseline, Six Months, and Twelve Months

Parameter	Baseline (Mean ± SD)	6 Months (Mean ± SD)	12 Months (Mean ± SD)	Statistical Significance
ESRD Total Score	69.81 ± 4.88	80.07 ± 6.30	77.32 ± 7.32	**$p < 0.01$ (6 mo); $p < 0.05$ (12 mo)**
PedsQL Family Impact Score	35.19 ± 4.32	60.32 ± 6.98	56.04 ± 10.84	**$p < 0.01$ (6 mo); $p < 0.05$ (12 mo)**

Figure 1. Distribution of Steroid-Sparing Agents Used in the Study Population

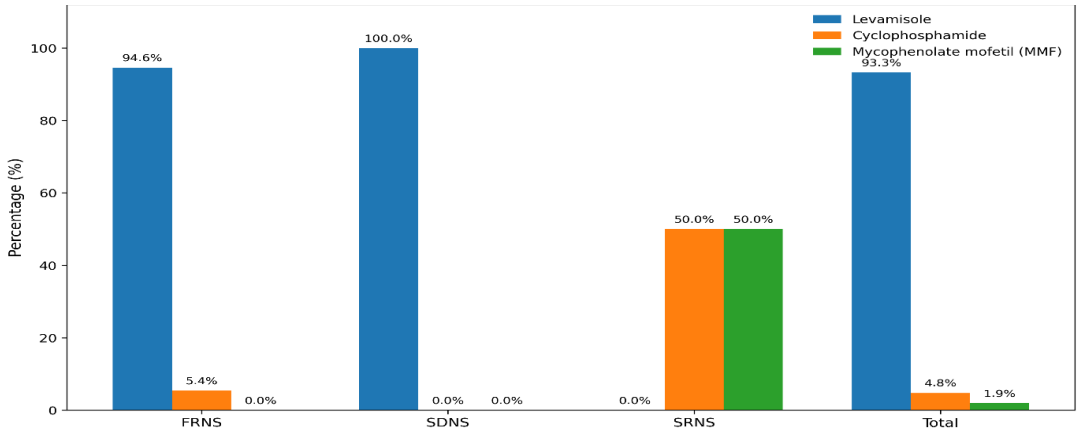
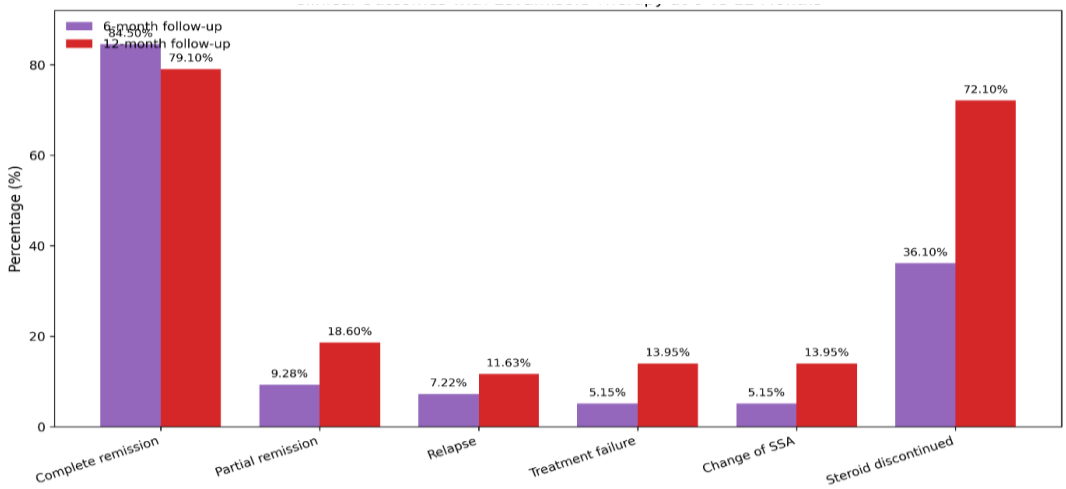


Figure 2. Comparison of Clinical Outcomes with Levamisole Therapy at Six-Month and Twelve-Month Follow-Up



DISCUSSION

This multicentric observational study provides robust real-world evidence supporting the continued role of levamisole as an effective and safe first-line steroid-sparing agent in children with FRNS and SDNS. The remission rates and steroid-sparing benefits observed are consistent with previous observational studies and randomised trials.[10–12,17–19]

Comparative studies have demonstrated that levamisole is not inferior to mycophenolate mofetil for relapse prevention, supporting its use before escalation to more intensive immunosuppression.[11,18–21] Current KDIGO and IPNA recommendations continue to endorse levamisole in relapse-prone steroid-sensitive nephrotic syndrome.[1,2,20]

Importantly, this study highlights significant improvement in health-related quality of life, reflecting reduced disease burden and improved psychosocial well-being of children and caregivers. These findings align with contemporary evidence indicating persistent quality-of-life impairment in nephrotic syndrome, particularly in SRNS.[14,16,21]

CONCLUSION

Levamisole remains an effective, safe, and feasible first-line steroid-sparing agent in children with FRNS and SDNS. Its use is associated with sustained remission, significant steroid reduction, and meaningful improvement in quality of life. Outcomes in SRNS remain less favourable, underscoring the need for further research in this subgroup.

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