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Efficacy Of Zinc Supplementation In Maintaining Sustained Remission In Children With Steroid- Sensitive Nephrotic Syndrome

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ABSTRACT

Background: Nephrotic syndrome (NS) is one of the most prevalent primary glomerular diseases affecting children, causing significant morbidity. This study was performed to determine the efficacy of zinc supplementation in maintaining sustained remission (SR) in children with steroid-sensitive nephrotic syndrome (SSNS).

Methods: This randomized controlled trial was conducted at the Pediatric Medicine Outpatient Department, Nishtar Hospital, Multan, from July 2024 to May 2025. A total of 192 children aged 2–12 years with frequently relapsing were enrolled through random sampling, and randomly assigned to receive either zinc supplementation plus standard therapy or standard therapy alone for six months. Zinc was given as 5 mg (<4 years) or 10 mg (>4 years) daily, and SR was assessed. Data were analysed using SPSS v26.0, with chi-square, and independent sample t-test applied, taking $p<0.05$ was considered significant.

Results: In a total of 192 children, 117 (60.9%) were male. The mean age, and duration of disease was 7.36 ± 2.02 years, and 2.03±0.61 years, respectively. The mean number of relapses was 2.15±0.41. Overall, the efficacy was noted in 74 (38.5%) children. The efficacy was seen in 46 (47.9%) children in Zinc group while no Zinc group showed efficacy in 28 (29.2%) children ($p = 0.011$). Efficacy was found to have significant association with socio-economic status in zinc treated group ($p=0.044$).

Conclusion: This study supports the use of Zinc supplementation in paediatric SSNS, exhibiting significant efficacy in imparting remission of relapses.

Keywords: Nephrotic Syndrome, Prednisolone, Proteinuria, Relapse, Zinc.

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INTRODUCTION

Nephrotic syndrome (NS) is one of the most prevalent primary glomerular diseases affecting children, causing significant morbidity[1]. The incidence of NS ranges between 1.2 to 16.9 per 100,000 children globally, while South Asia has one of the highest incidence rates of NS (7.1/100,000 children)[2,3] . In Pakistan, it is estimated that between 5 to 9% of all admissions among pediatric groups are due to renal diseases, and NS accounts for nearly 50% of these cases[4]. The NS frequently runs a relapsing course (among 80% cases) with extended periods of corticosteroids and other immunosuppressive therapy[5,6].

Hypovolemia, acute renal failure, edema, hypercoagulation, and infections are pathophysiological outcomes of NS that should be addressed symptomatically.[6] The early theory that an immune component might be contributing to the pathogenesis of the disease served as the foundation for treating NS with steroids[7]. Zinc supplements are considered to lower the risk of infection, which supports the use of zinc in NS along with standard treatment[8]. Regional data analyzing patients with steroid-sensitive nephrotic syndrome (SSNS) with frequent relapses receiving zinc supplements along with standard therapy showed sustained remission (SR) of 44.7%, compared to 27.5% receiving only the standard therapy group[9]. A local study evaluating children with NS reported that relapses occurred in 28.0% of patients receiving zinc supplements, compared to 34.5% with placebo[10].

There is a need to ascertain the efficacy of zinc supplementation in maintaining SR in children with SSNS, thereby lowering the number of relapses and disease morbidity. The findings of this study could pave the way for reasonable evidence about the role of zinc supplementation in children with SSNS. This study aimed to assess the efficacy of zinc supplementation in maintaining SR in children with SNSS.

METHODS

This randomized controlled trial (registered at clinicaltrials.gov) was performed at the outpatient department of pediatric medicine, Nishtar Hospital, Multan, Pakistan from July 2024 to May 2025. Approval from “Institutional Ethical Committee” was obtained (letter number: 7101, dated:03-06-24). Written and informed consents were obtained from parents/caregivers. A sample size of 192 was estimated (96 in each group) using 44.7% as the expected SR proportion in zinc supplementation plus standard treatment group versus 27.5% in standard treatment only group,[9] with a confidence level of 95%, and power of 80%. Sample selection was carried out through the probability random sampling method. The inclusion criteria were children of any gender, aged 2 to 12 years with SSNS who had

frequent relapses. The exclusion criteria were children with SSNS. Children with a history of chronic systemic illness other than nephrotic syndrome, or history of kidney disease like polycystic kidney disease were also excluded. SSNS was defined as proteinuria above 40 mng/m^2/hour, and serum albumin below 2.5 g/dl, along with edema, and patient responding to prednisolone treatment. Edema was assessed clinically as periorbital puffines, ascites or pit formation after pressing the skin for 5 seconds on dorsum of foot, shin or sacrum.

Among children fulfilling the eligibility criteria, demographic information like gender, age, and weight, along with duration of disease, and number of relapses were documented. Randomization was performed applying lottery method, and children were randomly allocated to either Zinc or no zinc supplementation group. In the zinc supplementation group, children were given 5 mg of elemental zinc sulfate as a single daily dose for children < 4 years of age, and 10 mg in > 4 years of age for a total duration of 6 months, along with standard therapy. The standard treatment protocol consisted of oral prednisolone 60 mg/m²/day, given as a single daily dose for an initial period of 4 to 8 weeks. If the patient achieved absence of proteinuria for 3 consecutive days before 8-week mark, the daily high-dose phase was concluded earlier. This induction phase was followed by a consolidation phase in which prednisolone was given at 40 mg/m² on alternate days for 2-week. Subsequently, the dose was gradually tapered over the next 1 to 2 months to reach a maintenance dose, usually ranging 0.5-1 mg/kg/day. The entire duration of corticosteroid therapy, including induction, consolidation, and tapering phases, was six months. In the no zinc supplementation group, children were given standard therapy without any zinc supplementation. A monthly follow-up was advised for a study duration of 6 months. Response to prednisolone treatment was absence of proteinuria within 8-weeks following treatment. Relapse of NS was defined as occurrence of +3 proteinuria by dipstick or lab test plus edema assessed clinically in previously diagnosed NS. Frequent relapse was named if 2 or more relapses in the previous six month. Data were collected for SR in both groups on a specially designed proforma. Data analysis was performed using IBM-SPSS Statistics, version 26.0. Qualitative variables were shown as frequencies and percentages. Quantitative variables were represented as mean and standard deviation (SD). Comparison of categorical data was made applying the chi-square test, while the independent sample t-test was applied for the comparison of numeric data, taking $p<0.05$ as significant.

RESULTS

Table 1: Comparison of Characteristics of Children in Both Study Groups (n=192)

Characteristics		Total (n=192)	Zinc (n=96)	No Zinc (n=96)	P-value
Age (years)	2-6	74 (38.5%)	40 (41.7%)	34 (35.4%)	0.374
	7-12	118 (61.5%)	56 (58.3%)	62 (64.6%)	
Gender	Male	117 (60.9%)	56 (58.3%)	61 (63.5%)	0.460
	Female	75 (39.1%)	40 (41.7%)	35 (36.5%)	
Residential status	Rural	84 (43.8%)	45 (46.9%)	39 (40.6%)	0.383
	Urban	108 (56.3%)	51 (53.1%)	57 (59.4%)	
Socioeconomic status	Poor	95 (49.5%)	50 (52%)	45 (46.9%)	0.440
	Middle-income	75 (39%)	35 (36.5%)	40 (41.6%)	
	Rich	22 (11.5%)	11 (11.5%)	11 (11.5%)	
Disease duration (years)		2.03±0.61	1.92±0.72	2.06±0.56	0.134
Number of relapses		2.15 ± 0.41	2.20±0.47	2.11±0.32	0.123

In a total of 192 children, 117 (60.9%) were male. The mean age was 7.36 ± 2.02 years. Residential status of 108 (56.3%) children was urban. Socio-economic status of 95 (49.5%) children was poor. The mean duration of disease was 2.03±0.61 years. The mean number of relapses was 2.15±0.41. **Table 1** compares characteristics of children with SSNS in both study groups.

Overall, the efficacy was noted in 74 (38.5%) children. The efficacy was seen in 46 (47.9%) children in Zinc group while no Zinc group showed efficacy in 28 (29.2%) children (p = 0.011), as shown in **Figure 1**.

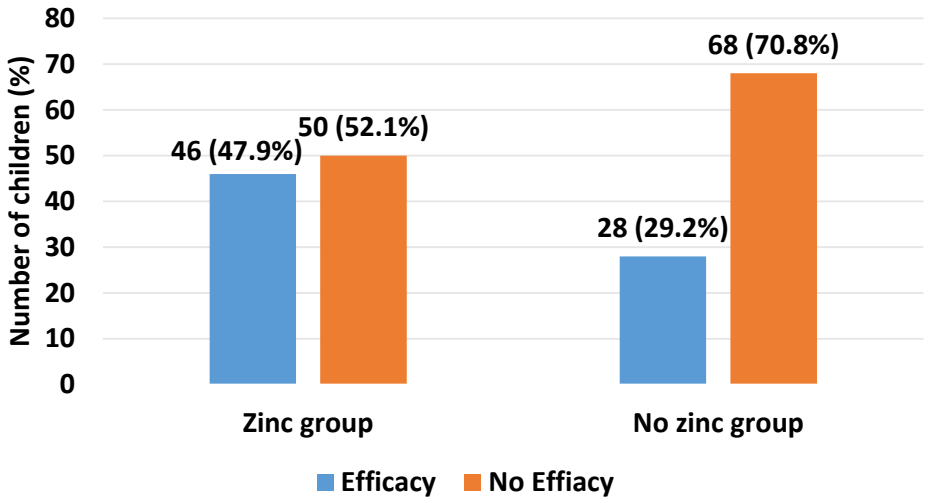

Figure-1: Efficacy (Sustained Remission) among children of both study groups (n=192)

Table-2: Stratification of effect modifiers with respect to efficacy (n=74)

Effect modifiers	Zinc (n=46)	No Zinc (n=28)	P-value
Age (years)			
2-6	23 (50%)	11 (39.3)	0.370
7-12	23 (50%)	17 (60.7%)	
Gender			
Male	22 (47.8%)	17 (60.7%)	0.281
Female	24 (52.2)	11 (39.3%)	
Residential status			
Rural	23 (50%)	11 (39.3%)	0.370
Urban	23 (50%)	17 (60.7%)	
Socioeconomic status			
Poor	17 (37%)	17 (60.7%)	0.044
Middle-income	23 (50%)	11 (39.3%)	
Rich	6 (13%)	-	

Weight (Mean±SD)	24.02±4.70	25.36±4.99	0.249
Disease duration (Mean±SD)	1.89±0.80	2.00±0.61	0.534
Number of relapses (Mean±SD)	2.04±0.21	2.00±0.36	0.547

It was found that efficacy was not having any significant association with age (p=0.370), gender (p=0.281), residential status (p=0.370), weight, (p=0.249), disease duration (p=0.534), or number of relapses (p=0.547). Efficacy was found to have a significant association with socio-economic status in zinc treated group (p=0.044). Children who reported efficacy were stratified with respect to various demographical and clinical characteristics in both study groups (**Table 2**).

DISCUSSION

Among children with SSNS, 60.9% were boys. A local study from Karachi reported that 67.1% children with SSNS were boys[11]. A high proportion of males (67.5%) was also observed by a study from India while treating children with SSNS. These results also favor the findings of the current study[10]. Male gender predominance was also revealed (74.1%) in a local study when examining children with SSNS[11]. The mean age of children with SSNS was 7.36±2.02 years in this research. A local study from Multan reported that the mean age of children with SSNS was 5.93±3.36 years.[12]

In terms of efficacy, it was 47.9% in zinc-treated children versus 29.2% among children without zinc treatment (p=0.011). A systematic review analyzing 8 full article about the role of zinc supplementation in reducing relapses in SSNS, involving 3 randomized controlled trials, suggested that zinc supplementation may aid SR or reduce relapse rates, while 3 observational studies indicated a significant link between low serum zinc levels and disease severity[13]. A study from Egypt documented that although, there was no major improvements in hospitalization rates or time to relapse, but zinc supplementation resulted in sustained remission in 80% children with frequently relapsing SSNS[14]. Regional data have shown that zinc supplementation significantly reduced the time to remission (11.8±3.96 vs. 18.3±5.14 days, p<0.001) and hospital stay duration (13.07±4.86 vs. 20.50±7.06 days, p<0.001) in children with NS[15]. A local study from Islamabad comparing the role of zinc supplementation versus B-complex in SSNS found that zinc supplementation resulted in better remission rates than B-complex supplementation[16]. The proposed mechanism could be that zinc deficiency may lead to downregulation of Th1 cytokines, a Th2 bias, and increased infection risk. Zinc supplementation enhances IL-2 and IFN-γ production, restoring the Th1 immune response. Since Th1-Th2 imbalance is linked to SSNS relapses, zinc's benefits may stem from its role in

correcting this immune defect[17,18]. A study from Iran described that NS children may benefit by correcting their serum zinc levels in NS[19]. The significant association among zinc levels and NS severity suggests that zinc deficiency may contribute to disease progression and relapse frequency[20]. Lower serum zinc levels have been associated with increased disease severity, possibly due to impaired immune function, increased susceptibility to infections, and a heightened inflammatory response. Given zinc's role in modulating the Th1-Th2 immune balance and reducing oxidative stress, supplementation may help in stabilizing remission and lowering relapse rates in children with nephrotic syndrome[17,18] .

The significant increase in SR rates observed among children receiving zinc, as compared to those on standard therapy alone, suggests that routine zinc supplementation could be considered as part of the therapeutic strategy for this patient population. Incorporating zinc into treatment protocols may help to reduce relapse frequency, limit cumulative steroid exposure, and potentially decrease steroid-associated adverse effects[21,22,23,24]. By promoting more stable disease control, zinc supplementation could reduce healthcare utilization, including hospitalizations and clinic visits, thereby improving overall quality of life. Given the low cost and favorable safety profile of zinc, its addition represents a pragmatic and accessible intervention where nephrotic syndrome burden is high and resources are limited[25]. However, these findings also underscore the need for regular assessment of zinc status in children with SSNS.

This study has certain limitations. The duration of follow-up was limited to six months, and longer-term studies are needed to assess whether the benefits of zinc supplementation persist over extended periods. Serum zinc levels were not routinely measured, which could have provided a more direct correlation between zinc deficiency and disease activity. Future studies should include serial zinc level assessments in SSNS.

CONCLUSION

The incidence of interstitial lung disease in rheumatoid arthritis patients was 43% with advanced age, smoking, duration of RA onset and positive rheumatoid factor as independent predictor of incidence of ILD. Given the significant association with elevated inflammatory markers and high mortality risk, early HRCT screening is essential for timely diagnosis and improved management.

LIST OFABBREVIATIONS

NS: Nephrotic syndrome

SR: Sustained Remission

SSNS: Steroid Sensitive Nephrotic Syndrome (SSNS).

FUNDING

None.

CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

Approval from the Institutional Ethical Review Board was obtained through letter number 7101, (Dated:03-06-24).

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE.

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