Original Article

OPEN ACCESS

Role of Zinc Supplementation in Comparison to B Complex for Reducing the Frequency of Sustained Remission in Steroid-Sensitive Nephrotic Syndrome Among Pediatric Age Group

Fatima Hashmi[1], Shahzadi Sumbal Ghazi[2], Hassan Mumtaz[3], Maryam Amjad[4], Nahdia Zaman[5], Shahzaib Ahmad[6]

[1]Neonatology Department, PIMS Islamabad, [2]Pediatrics Department, PIMS Islamabad, [3]Surgery Department, KRL Hospital Islamabad, [4]Pediatrics Department, Holy Family Hospital Islamabad,
[5]Pediatrics Department, Holy Family Hospital Islamabad, [6]King Edward Medical University, Lahore

Author`s Contribution

[1]Conception or design of the work [2]Critical Analysis, [3]Drafting and reviewing the manuscript [4]Data Acquisition, [5]Data Analysis, [6] Active Participation in active methodology

Funding Source: None
Conflict of Interest: None

Received: Dec 23, 2020
Accepted: Aug 17, 2021

Address of Correspondent
Dr. Hassan Mumtaz
House Surgeon KRL Hospital Islamabad
hassanmumtaz.dr@gmail.com

ABSTRACT

Objective: To evaluate and compare the effectiveness of zinc and B-Complex supplementation to prevent the recurrence of nephrotic syndrome in the cases priory responsive to corticosteroid therapy.

Methodology It is a randomized controlled trial conducted at OPD Pediatric medicine, Shaheed Zulfiqar Ali Bhutto University, PIMS Children Hospital Islamabad from October 3, 2016 to April 2, 2017. 192 patients (96 in each group) were included in the study after obtaining informed consent from parents or guardians taken before determining the population. Patients were randomly assigned to two groups (Group 1: Zinc and Group 2: B-Complex) to receive oral zinc sulphate (10 mg / day) or B-Complex using a random number table. The patients were followed up after 4 months. All data were collected by the researchers themselves in a structured form.

Results: The age of 192 participants of the trial averaged 6.38±3.42 years of age ranging from 1-12 years. There were 88 (45.8%) men and 104 (54.2%) women cases. In group 1, there were 22 (22.9%) and in group 2, there were 47 (49%) cases that had been pardoned. The recurrence of nephrotic syndrome was significantly higher in group 1 than group 2 (p = <0.001).

Conclusion: The findings of this study suggest that Zinc supplementation is more preferrable to B-Complex supplementation as the rate of continuous remission was higher in the zinc group, so in the future may be added to the treatment regimen to treat steroid-sensitive nephrotic syndrome.

Keywords: Zinc supplementation, Nephrotic syndrome, Relapse, Remission

Cite this article as: *Hashmi F, Ghazi SS, Mumtaz H, Amjad M, Zaman N, Ahmad S. Role of Zinc Supplementation in Comparison to B Complex for Reducing the Frequency of Sustained Remission in Steroid-Sensitive Nephrotic Syndrome Among Pediatric Age Group. Ann Pak Inst Med Sci. 2021; 17(3):236-240. doi. 10.48036/apims.v17i3.408.*

Introduction

Among the glomerular pathologies, nephrotic syndrome is one of commonest glomerular diseases in pediatric age group. Several treatment regimens are usually employed for the treatment of nephrotic syndrome. The use of corticosteroids is common due to the responsiveness of the nephrotic syndrome, but relapses are frequent in many cases. Efforts in drug development for steroid-sensitive nephrotic syndrome led to the use of Zinc supplementation in those cases. Nephrotic syndrome is characterized by 'nephrotic- range' proteinuria, hypoalbuminemia, hyperlipidemia, and edema. In the pediatric age group, nephrotic- range proteinuria implies the protein excretion of equal to or more than 40 mg/mL/hour. The usual practice in adult population is to collect 24 hour-urine sample. But this method is unreliable in the pediatric age group. Alternatively, a single first-morning urine sample is preferable.[1] Among the glomerular pathologies, nephrotic syndrome is one of commonest glomerular diseases in the pediatric age group with an annual incidence of 2/100000 cases.[2] Despite its low incidence, the disease burden is high because of relapsing nature of disease after prior

remission and response to conventional therapy i.e. corticosteroids.[3]

The Kidney Disease recommends the following criterion for the nephrotic syndrome: In the Improving Global Outcomes (KDIGO) group, dip-stick proteinuria of 3+ or the urine protein/creatinine ratio of ≥ 2000 implies 'nephrotic-range' proteinuria.[4,5] The management of youngsters with the frequent relapsing syndrome (FRNS) is challenging one and plenty of strategies are accustomed treat and forestall these relapses.[5] Research studies suggest that the zinc deficiency in active nephrotic syndrome causes the down regulation of type-1 cytokine, and increased the risk of infections due to relatively greater type-2 cytokine levels.[5] Zinc supplementation prevents these phenomena and results in effective defense system due to restoration of cytokine-1immune reaction, decreasing the risks of infections.

Diet is commonly deficient in Zinc leading to high morbidity in third world countries. Zinc deficiency manifests as a malnourished state. The documented causes of Zinc deficiency are loss of Zinc in diarrheal stool and in urine, inadequate intake, or inefficient absorption.[6]

In this regard a study reported that a combination regimen given to the participants caused a 20% decline in the frequency of relapses, sustained remission was achieved in 44.7% of the patients while only 27.5% within the B-Complex group ($p>0.05$).[7] Another study reporting steroid sensitive nephrosis demonstrated 72% remission with zinc supplementation as compared to 65.5% in placebo ($p > 0.05$).[6] Zinc deficiency disease was reported 24% in one study while another study reported in mere 6.17%. [6-7]

The rationale of this study is to work out the exact role of zinc in reducing relapses in steroid-sensitive syndrome. The present data show insignificant differences in Zinc supplementation and B-Complex but there's huge variability between the results of the above cited studies. together study reported 44.7%7 of the patients having sustained remission while another reported 72%.[6] At the tip of study (6 months) deficiency disease is additionally given during a very big selection i.e.24%6- 6.17%.[7]

Keeping in mind the low Zinc levels in causing relapses into consideration, we hypothesized that Zinc supplementation gives better results to decrease relapse rate.

In Pakistan, just one study is conducted6 whose results were inconsistent with other available studies of same region (that was exhausted India).[7]

This study can help us to grasp the precise role of zinc in reducing relapses in steroid-sensitive syndrome. If we discover better results using Zinc then in future we will alter our practice to boost the prognosis.

Methodology

The randomized controlled trial was conducted at OPD Pediatric Medicine, Shaheed Zulfiqar Ali Bhutto University, PIMS Children's Hospital Islamabad. The study period was 6 months (October 3, 2016 until April 2, 2017). The sample size was 192 (96 patients per group) calculated using a frequency of 44.7% of continuous remission in the Zinc group compared with 27.5% in the B-Complex group. 7 We have used 80% learning ability and 5% value. The sampling techniques used were random, consecutive sample.

Inclusion Criteria: Children aged 1-12 years of age with a history of SSNS recurrence (> 2 relapses 6 months) were included in our study.

Exclusion Criteria: Patients with severe malnutrition (average upper extremity <115mm), with Chronic Diseases (e.g. tuberculosis) in medical history and those with Concurrent or recent (six months) preventive treatment without prednisolone were excluded from our study.

192 patients were included in the study after meeting the procedure for admission to Pediatric OPD Shaheed Zulfiqar Ali Bhutto University PIMS children's Hospital Islamabad. Informed consent from parents or guardians was obtained before determining population size (name, age, gender) and clinical history (duration of disease, no. Patients were randomly assigned to two groups (Zinc and B-Complex) to receive Zinc sulphate orally (10 mg / day) or B-complex using a random number table. Patients are monitored every 2 months to 4 months. Remission and non-relapse were measured every 2 months to 4 months follow-up as prescribed performance.

Data were entered and analyzed using SPSS 21. Numerical data such as age, duration & no. repetition presented in the form of Mean ± SD Appropriate information such as gender, reducing the frequency of continuous forgiveness is presented in the form of frequency and percentages. The Chi-Square test was used to compare exemption and retrieval for both study

groups. Data were categorized by age, gender, duration of disease and no. going back before starting treatment. Chi-square post-stratification test was used and a value of p = 0.05 is considered significant.

Results

Our study shows mean age of cases was 6.38 ± 3.42 years with minimum and maximum age of 1 and 12 years (Figure 1). In B-Complex and Zinc group the mean age of cases was 6.51 ± 3.42 years and 6.25 ± 3.43 years. A total of 102(53.1%) were 1-6 years old and 90(46.9%) cases were 7-12 years of age.

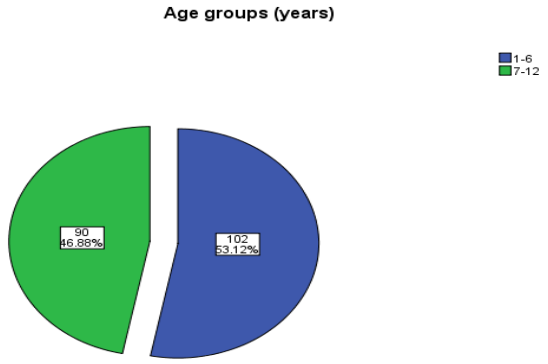

Figure 1. Frequency distribution of age groups.

There were 88(45.8%) male and 104(54.2%) female cases in our study (Figure 2). In B-Complex group there were 52(54.17%) male and 44(45.83%) female while in Zinc group there were 36(37.50%) male and 60(62.50%) female cases.

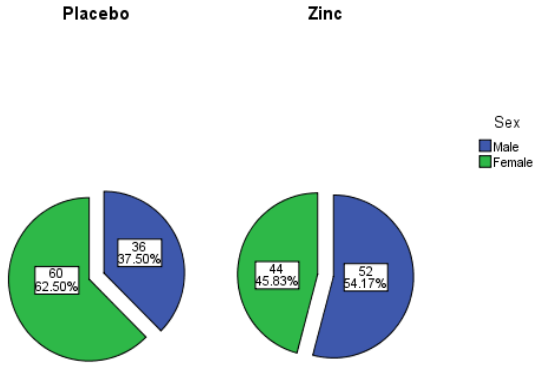

Figure 2. Gender distribution in both groups

In zinc and B-Complex group the mean duration of disease was 13.73 ± 4.20 months and 13.85 ± 4.37 months. In zinc and B-Complex group the mean number of replace was 6.52 ± 1.73 and 6.46 ± 1.69. There were 111(57.8%) cases had duration of disease 7-14 months and 81(42.2%) had 15-21 months as duration of disease. Before treatment there was 100(52.1%) who had 4-6 number of relapse and 92(47.9%) had 7-9 number of replace. (Table I)

Table 1: Descriptive Statistics of duration of disease (months) in both groups & number of relapse (before treatment) in both groups (n=96)

		Mean	SD	Min.	Max.
Duration of disease (months)	Zinc)	13.73	4.20	7.00	21.00
	B-Complex	13.85	4.37	7.00	21.00
	Total	13.79	4.28	7.00	21.00
Number of relapse (before treatment)	Zinc	6.52	1.73	4.00	9.00
	B-Complex	6.46	1.69	4.00	9.00
	Total	6.49	1.71	4.00	9.00

In B-Complex group there were 22(22.9%) and in Zinc group there were 47(49%) of cases had sustained remission. The sustained remission rate in Zinc group was significantly higher than B-Complex group, p-value < 0.001.Chi-square = 14.14. p-value < 0.0001 (Table II).

When data were stratified for age, gender, duration of disease and number of relapse before treatment we found

Table II: Comparison of sustained remissions in both study groups (n=96)

		Study groups		Total
		B-Complex	Zinc	
Sustained remission	***Yes***	22	47	69
		22.9%	49%	35.9%
	No	74	49	123
		77.1%	51.0%	64.1%
Total		96	96	192
		100.0%	100.0%	100.0%

significantly lower sustained remission rate in zinc than B-Complex, p-value < 0.05. (Table III & IV)

Discussion

Nephrotic syndrome (NS) could be a chronic childhood illness characterized by heavy proteinuria, hypoalbuminemia and oedema. About 80%-85% of the patients with NS shows initial response to corticosteroids and labeled as steroid sensitive nephrotic syndrome (SSNS). Remaining 15%-20% of the patients, who don't reply to steroid therapy are labeled as steroid resistant nephrosis (SRNS).[8] About 40%-50% of patients

Table III: Comparison of sustained remissions in both study groups with respect to age groups & gender.

Age groups (years)	Sustained remission	Study groups		p-value
		B-Complex	Zinc	
1-6	*Yes*	9	22	0.016
		18.8%	40.7%	
	No	39	32	
		81.2%	59.3%	
7-12	*Yes*	13	25	0.002
		27.1%	59.5%	
	No	35	17	
		72.9%	40.5%	
Male:	*Yes*	8	16	0.003
		15.4%	44.4%	
	No	44	20	
		84.6%	55.6%	
Female:	*Yes*	14	31	0.044
		31.8%	51.7%	
	No	30	29	
		68.2%	48.3%	

with SSNS have either frequent relapses (FRNS) or steroid dependent (SDNS) courses resulting in prolonged course of illness. Relapses are related to an increased risk of complications like sepsis, thrombosis, dyslipidemia and malnutrition.[9] Although, relapses is successfully treated with corticosteroids, repeated usage of high dose cortico¬steroids cause significant side-effects like avascular necrosis of hip, hypertension, diabetes and behavioral disorders.[10]

Table IV: Comparison of sustained remissions in both study groups with respect to duration of disease & Number of relapse.

Duration of disease (months)	Sustained remission	Study groups		p-value
		B-Complex	Zinc	
7-14	*Yes*	13	29	0.002
		23.6%	51.8%	
	No	42	27	
		76.4%	48.2%	
15-21	*Yes*	9	18	0.028
		45.0%	45.0%	
	No	32	22	
		78.0%	55.0%	
Number of relapse (before treatment)	**Sustained remission**	**Study groups**		**Total**
		B-Complex	**Zinc**	
4-6	*Yes*	11	26	37
		22.0%	52.0%	37.0%
	No	39	24	63
		78.0%	48.0%	63.0%
7-9	*Yes*	11	21	32
		23.9%	45.7%	34.8%
	No	35	25	60
		76.1%	54.3%	65.2%

Relapses of NS often follow minor infections of the upper respiratory (URI) or gastrointestinal tracts, and therefore the estimated frequency is around 50%-70% among children in developing countries. Other infections like tract infection, diarrhea, peritonitis and skin infections have also been implicated as triggers for relapse.[7] Several theories like cytokine release, immune dysfunction, increased glomerular permeability, and podocytopathy are pro-posed, but none of them is conclusive. Variety of interventions are tried to prevent/ decrease relapses in NS. Relapses are significantly reduced when daily corticosteroids are given during onset of viral URIs or when the upkeep doses of corticosteroids are increased at the onset of viral URIs.[11]

Studies have shown that zinc supplementation reduces relapses in children with SSNS.[7] It's proposed that deficiency disease might result in down-regulation of T-helper 1 (Th1) cytokines, a relative T-helper 2 (Th2) bias, and an increased risk of infection. As a result, zinc supplementation augments the organic phenomenon for IL-2 and IFN-γ, thereby restoring the Th1 immune reaction. Since the Th1-Th2 cytokine imbalance is additionally believed to end in relapses of SSNS, it had been proposed that the advantages of supplementation in these patients is also related to its ability to rectify the immune defect.[12]

A study was done on 60 children, 54 completed trial (Zg = 25, Pg = 29). Forty (74%) were males and 14 (26%) females.[13] In the current study the mean age of cases was 6.38 ± 3.42 years with minimum and maximum age of 1 and 12 years. There have been 88(45.8%) male and 104(54.2%) female cases. The gender distribution in the current study and the above study is different.

We found in the current study that in B-Complex group there have been 22(22.9%) and in Zinc group there have been 47(49%) of cases had sustained remission. The sustained remission rate in Zinc group was significantly on top of B-Complex group, p-value < 0.001.

In this regard a study reported that subjects receiving zinc showed a 20% lower frequency of relapses, with 44.7% of the patients having sustained remission compared to 27.5% within the B-Complex group (P>0.05).[7] Another study was done on steroid sensitive nephrosis and that they reported 72% in the Zinc group maintained remission compared to 65.5% in B-Complex, p-value > 0.05.6 The findings are different as found in the current study.

Pre-study relapses in the two groups were similar (Zg vs. Pg = 96 vs. 96.6%) whereas post study relapses in Zg were lower (7, 28%) compared to Pg (10, 34.5%). Post study mean relapse rate in Zg was 1.14 ± 0.37 PPPY compared to 2.71 ± 1.11 in pre study (p = 0.005). In Pg, post study mean relapse rate PPPY was 1.30 ± 0.48 compared to 1.70 ± 0.48 in pre study period (p = 0.037). Relapse rate reduction was 43% after Zinc supplementation compared to 27% reduction in B-Complex. Metallic taste was observed in 10% of cases. Thus it is often concluded from the study result that zinc supplementation helped reduce relapses in syndrome.[13] We found better outcome in zinc group as reported in above study.

Recently a systemic review is performed to judge the role of zinc as add on treatment to the "recommended treatment" of syndrome (NS) in children. That concluded that Zinc could also be a useful additive within the treatment of childhood NS. The evidence generated mostly was of "very low-quality". More good quality RCTs are required in numerous country settings in addition to different subgroups of kids before any firm recommendation will be made.[14]

Conclusion

The findings of this study suggest that Zinc supplementation is more preferable to B-Complex supplementation as the rate of continuous remission was higher in the zinc group, so in the future may be added to the treatment regimen to treat steroid-sensitive nephrotic syndrome.

References

1. Uwaezuoke SN. Steroid-sensitive nephrotic syndrome in children: triggers of relapse and evolving hypotheses on pathogenesis. Italian J Pediatr 2015;41(1):19-24. https://doi.org/10.1186/s13052-015-0123-9
2. Larkins N, Kim S, Craig J, et al. Steroid-sensitive nephrotic syndrome: an evidence-based update of immunosuppressive treatment in children. Archiv Dis Child 2015:doi:10.1136. https://doi.org/10.1136/archdischild-2015-308924
3. Hodson EM, Craig JC. Corticosteroid therapy for steroid-sensitive nephrotic syndrome in children: dose or duration? J Am Soci Nephrol 2013;24(1):7-9. https://doi.org/10.1681/ASN.2012111093
4. Lombel RM, Gipson DS, Hodson EM. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol 2013;28(3):415-26. https://doi.org/10.1007/s00467-012-2310-x
5. Kumar D, Arya P, Sharma IK, Singh MV. Effect of zinc therapy in remission of pediatric nephrotic syndrome. Int J Contemp Pediatr 2017;4:2036-40.
6. Malik M, Ahmed I, Abdulraoof HI, Almosawy JM. Serum zinc level in children with relapsing nephrotic syndrome. International Journal of Current Research, 10, (11), 75137-75145 nephrotic syndrome. JCPSP 2014;24(2):110-3.
7. Arun S, Bhatnagar S, Menon S, Saini S, Hari P, Bagga A. Efficacy of zinc supplements in reducing relapses in steroid-sensitive nephrotic syndrome. Pediatr Nephrol 2009;24(8):1583-6. https://doi.org/10.1007/s00467-009-1170-5
8. Santín S, Bullich G, Tazón-Vega B, et al. Clinical utility of genetic testing in children and adults with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol 2011;6(5):1139-48. https://doi.org/10.2215/CJN.05260610
9. Webb NJ. Epidemiology and general management of childhood idiopathic nephrotic syndrome. Evid Based Nephrol 2008:763-73. https://doi.org/10.1002/9781444303391.ch66
10. Hall A, Thorley G, Houtman P. The effects of corticosteroids on behavior in children with nephrotic syndrome. Pediatr Nephrol 2003;18(12):1220-3. https://doi.org/10.1007/s00467-003-1295-x
11. Gulati A, Sinha A, Sreenivas V, Math A, Hari P, Bagga A, et al. Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol 2011;6(1):63-9. https://doi.org/10.2215/CJN.01850310
12. Prasad AS. Zinc: mechanisms of host defense. J Nutr 2007;137(5):1345-9. https://doi.org/10.1093/jn/137.5.1345
13. Pardede S, Striratnaputri A, Kadim M. Selenium level in steroid-resistant and steroid-sensitive nephrotic syndrome. PI [Internet]. 23Nov.2020 [cited 10Nov.2021];60(6):316-0. Available from: https://www.paediatricaindonesiana.org/index.php/paediatrica-indonesiana/article/view/2452
14. Bhatt GC, Jain S, Das RR. Zinc supplementation as an adjunct to standard therapy in childhood nephrotic syndrome-a systematic review. World J Clin Pediatr 2016;5(4):383. https://doi.org/10.5409/wjcp.v5.i4.383