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Original Research Article

Effect of zinc therapy in remission of pediatric nephrotic syndrome

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ABSTRACT

Background: Zinc has been used in diarrhea since long but their efficacy in nephrotic syndrome still requires evidences. The objectives of this study were to determine the effect of Zinc in nephrotic syndrome among the children in rural population.
Methods: Randomized control trial. We included 60 children of age group 6 months - 15 years diagnosed as nephrotic syndrome and fulfilling the inclusion criteria. All children were given standard steroid therapy for duration depending on initial or relapse cases while intervention arm (n=30) were given zinc syrup at the dose 10 mg for less than 1 year and 20 mg for more than 1 year for 14 days apart from standard steroid therapy. Duration of remission in both the groups was measured as primary outcome while secondary outcome was duration of hospital stay in both control and study group.
Results: Mean number of days taken in remission in study group was 11.8±3.96 days and in control group 18.3±5.14 days ($p < 0.001$). Total duration of study in hospital in study group was 13.07±4.86 days and in control group was 20.50±7.06 days ($p < 0.001$).
Conclusions: Zinc significantly reduced the duration of hospital stay and remission in children suffering from nephrotic syndrome.

Keywords: Efficacy, Nephrotic syndrome, Remission, Steroids, Zinc

INTRODUCTION

Nephrotic syndrome is an important chronic disease in children. Nephrotic syndrome can be idiopathic as well as non-idiopathic in nature. However, idiopathic nephrotic syndrome is more common, affecting nearly 90% of children.[1] INS result from any of several well-described primary glomerulopathies that are defined by histopathology and clinical criteria About 80% children with idiopathic nephrotic syndrome show remission of proteinuria following treatment with corticosteroids, and are classified as 'steroid sensitive'.[2]

Steroid therapy results in remission of proteinuria in steroid sensitive nephrotic syndrome (SSNS) but develop relapses in 40-50% of cases usually following infections.[3]

Adequate oral corticosteroid therapy is recommended at the initial episode of nephrotic syndrome in children. The commonly used preparations are prednisone (USA) or prednisolone (most other countries including India).

On the basis of the ISKDC Study Around 95% of children with steroid-responsive nephrotic syndrome will demonstrate resolution of proteinuria with 4 weeks of daily glucocorticoid therapy and 100% after an additional 3 weeks of alternate-day therapy.[4]

Zinc is a vital micronutrient in humans and is essential for protein synthesis, cell growth, and differentiation. Epidermal, gastrointestinal, central nervous, immune, skeletal, and reproductive systems are the organs most affected clinically by zinc deficiency.[5] Severe zinc

deficiency has been shown to be associated with stunting of growth, hypogonadism, impaired immune function, skin disorders, cognitive dysfunction, and anorexia.

Low Zinc levels have been described in children with severe malnutrition, malabsorption and nephrotic states due to either lack of intake, decreased absorption or loss of zinc in diarrheal stool and in urine. Zinc supplementation can reduce morbidity and mortality, especially among children due to gastro-intestinal and respiratory diseases.[6] So, this study is being conducted to know whether the zinc also have any role in hastening the remission of nephrotic syndrome.

METHODS

This prospective randomized control was conducted in department of pediatrics of UP University of Medical Sciences Saifai Etawah after taking institutional ethical approval, between January 2015-June 2016. All children age group of 6 months -15 years attending the out patient department and in patient department of pediatric department with complains of Generalised swelling and decreased urine output were admitted and diagnosed as case of nephrotic syndrome by bedside urine protein 3+/4+ (significant nephrotic range proteinuria 40mg/m2/24 hour), Hypoalbuminemia (serum albumin <2.5 g/dl) and Hyperlipidaemia (serum cholesterol >200 mg/dl). Patients were defined as newly diagnosed (patient with initial episode) and relapse cases (Urine albumin 3+ or 4+ (or proteinuria >40 mg/m2/h) for three consecutive early morning specimens, having been in remission previously.

Children diagnosed with nephrotic syndrome according to above mentioned Criteria and age more than six month and less than fifteen years were included in the study. Patients with Nephritic syndrome, Steroid resistant nephrotic syndrome, Patient taken zinc therapy within last 3 months, Nephrotic syndrome with secondary causes Nephrotic syndrome patient refuse from giving consent were excluded. According to the previous one year admission of nephrotic syndrome in our pediatrics ward the sample size of 60 was taken. Baseline data including age, gender, height, weight, and blood pressure were recorded. Detail history were taken and proper physical examination was done. Complete blood count, urine routine / microscopy, urine culture and sensitivity, 24-hour urinary protein, total serum protein, serum. albumin, serum globulin, serum cholesterol, serum electrolytes – serum calcium, serum sodium, serum potassium, serum creatinine, blood urea mantoux test, gastric aspirate /sputum for AFB and X-ray chest were done in every patients.

Patients were randomized into two groups by computer based random number generator program and they were treated accordingly. Group 1 had received standard steroid therapy along with short course zinc therapy (For 2 weeks) and Group 2 had received standard steroid therapy alone. Standard steroid therapy for Newly diagnosed patients contained prednisolone at a dose of 2 mg/kg per day (maximum 60 mg in single or divided doses) for 6 weeks, followed by 1.5 mg/kg (Maximum 40 mg) as a single morning dose on alternate days for the next 6 weeks; therapy is then tapered and discontinued and in Relapse cases. Prednisolone is administered at a dose of 2mg/kg/day (single or divided doses) until urine protein is trace or nil for three consecutive days. Subsequently, prednisolone is given in a single morning dose of 1.5 mg/kg on alternate days for 4 weeks, and then discontinued. Oral zinc therapy was given only to group 1 patient of nephrotic syndrome. Patients of zinc groups received oral Zinc Gluconate (SYRUP ZIORAL) for 2 weeks and were followed till remission of nephrotic syndrome (proteinuria nil for 3 days on BSUP/urine dipsticks). Zinc was given in maintenance dose of 10 mg/day in less than one years of age group and 20mg/day in more than one years of age group for 2 weeks. Daily nephrotic charting was done which included Weight, Fluid intake, 24 hour urine output, Blood pressure, Bedside urine protein and Abdominal girth. Protein was evaluated by 2 technique, bedside urine protein (daily) and urine dipstick test (at time of admission). Patients were monitored for remission and any other complications of nephrotic syndrome. Remission was defined as Urine albumin nil or trace (or proteinuria <4 mg/m^2/h) for three consecutive early morning specimens. Primary outcome was measured by remission of nephrotic syndrome i. e. 3 days BSUP nil while Secondary outcome was measured by Duration of hospital stay.

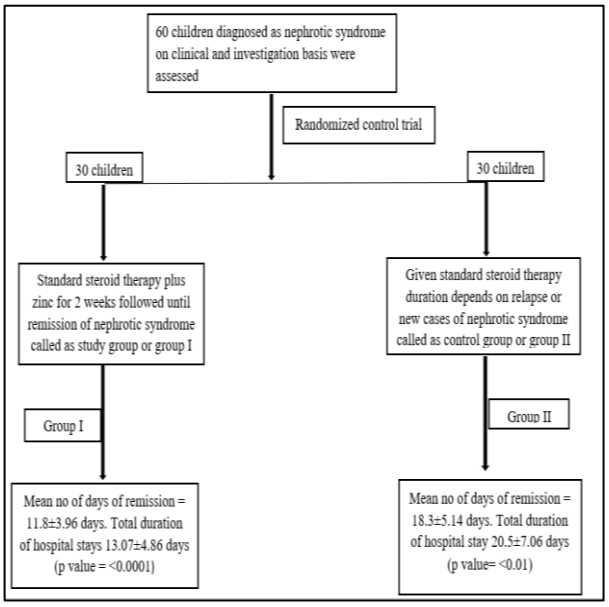

Figure 1: Flow chart of the study.

Statistical analysis

Statistical analysis was done by using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical

Analysis Software. The results of the continuous measurements were presented as mean+SD (Min-Max) and the result of the categorical measurement and Chi Square were present in number (%). Tukey HSD test was used to find the significance of the study parameter on a categorical scale between two groups. The 95% confidence interval was computed to find the significant feature.

RESULTS

Out of a total of 60 patients included in the assessment, a total of 30 (50%) underwent steroid therapy with zinc supplementation and comprised the Group I of study whereas remaining 30 (50%) underwent steroid therapy alone and comprised the Group II of study.

Majority of patients were aged 1-5 years (58.3%) followed by those aged >5 years (40%). There was 1 (1.7%) patient aged <1year. Demographic and clinical profile of patients are given in Table 1.

Table 1: Demographic characteristics and clinical profile of study and control population.

Characteristics	Study group	Control group
Number of patients	30	30
Male:Female	3.2:1	3.2:1
New:relapse cases	1.5:1	1.7:1
Mean age in years	4.94±1.85 years	4.96±1.88 years
Common Clinical profile		
Edema	12 (40%)	21(70%)
Infection	12 (40%)	17 (56.7%)
Hypertension	06 (20%)	05 (16.7%)
Steroid toxicity	2 (6.7%)	11 (36.7%)

In both the groups 76.7% patient were males and remaining 23.3% were females. Male to female ratio of study population was 3.29.

In Group I, a total of 18 (60%) were new cases whereas in Group II, a total of 19 (63.3%) were new cases. Though the proportion of relapse cases were slightly higher in Group I (40%) as compared to that in Group II (36.7%) et this difference was not significant statistically (p=0.791).

Table 2: Outcome (number of days of remission).

No. of days	Total (n=60)		Group I (n=30)		Group II (n=30)	
	No.	%	No.	%	No.	%
≤15 days	32	53.3	24	80.0	8	26.7
>15 days	28	46.7	6	20.0	22	73.3
Mean±SD (Range) in days	14.97±5.34 (7-29)		11.8±3.96 (7-22)		18.13±5.40 (11-29)	

χ^2= 17.143; p<0.001 (S), 't'=5.181; p<0.001

Number of days for remission ranged from 7 to 29 days with a mean value of 14.97±5.34 days. Majority (n=32; 53.3%) had remission within 15 days.

In Group I, 24 (80%) had remission within 15 days and mean time taken for remission was 11.8±3.96 days, however, in Group II, majority (n=22;3.3%) had remission after 15 days and mean time taken for remission was 18.13±5.40 days. Statistically, there was a significant difference between two groups with respect to time taken for remission (p<0.001) (Table 2).

Mean time taken for remission ranged from 11.50±4.15 days (Group I New cases) to 20.73±6.65 days (Group II Relapse cases). In Group I relapse and Group II new cases, mean time taken for remission was 12.25±3.79 and 16.63±4.00 days respectively.

Statistically, there was a significant difference in mean time taken for remission among different groups (p<0.001). On evaluating the data further, statistically significant difference in mean time taken for remission was observed between Group I new and Group II new and Group I new and Group II relapse cases and Group I relapse and Group II relapse cases (Table 3).

Table 3: Association of remission time in new and relapse cases with zinc and without zinc therapy.

Group	No. of cases	Mean duration	SD
New case zinc therapy (Group I New)	18	11.50	4.15
Relapse case zinc therapy (Group I Relapse)	12	12.25	3.79
New case no zinc therapy (Group II New)	19	16.63	4.00
Relapse case no zinc therapy (Group II Relapse)	11	20.73	6.65

F= 11.437; p<0.001

Duration of hospital stay ranged from 7 to 38 days. Overall, majority of cases (53.3%) had <15 days of hospital stay. Overall mean duration of hospital stay was 16.78±7.08 days.

In Group I, duration of hospital stay ranged from 7 to 26 days with a mean of 13.07±4.86 days. A total of 24 (80%) had duration of hospital stay <15 days.

In Group II, duration of hospital stay ranged from 13 to 38 days with a mean of 20.50±7.06 days. In Group II, a total of 22 (73.3%) patients had hospital stay >15 days. Statistically, there was a significant difference in duration of hospital stay of two groups (p<0.001) Table 4.

Table 4: Distribution of hospital stay in both group.

No. of days	Total (n=60)		Group I (n=30)		Group II (n=30)	
	No.	%	No.	%	No.	%
≤15 days	32	53.3	24	80.0	8	26.7
> 15 days	28	46.7	6	20.0	22	73.3
Mean±SD (Range) in days	16.78±7.08 (7-38)		13.07±4.86 (7-26)		20.50±7.06 (13-38)	

χ^2= 17.143; p<0.001 (S); 't'= 4.74; p<0.001

Table 5: Association of hospital stay in new and relapse cases with zinc and without zinc therapy.

Group	No. of cases	Mean duration	SD
New case zinc therapy (Group I new)	18	12.67	5.44
Relapse case zinc therapy (Group I relapse)	12	13.67	3.98
New case no zinc therapy (Group II New)	19	18.11	4.67
Relapse case no zinc therapy (Group II Relapse)	11	24.64	8.70

F= 11.578; p<0.001

Mean time taken for remission was 12.67±5.44, 13.67±3.98, 18.11±4.67 and 24.64±8.70 days respectively for Group I new, Group I relapse, Group II new and Group II relapse cases respectively. Statistically, this difference among groups was significant (p<0.001) (Table 5).

DISCUSSION

Reactive oxygen species (ROS) are involved in the etiopathogenesis of nephrotic syndrome (NS). It has been proposed that ROS stimulate lipid peroxidation, which is resulted in cell injury; disruption of structural integrity of tubular epithelial cells, enhances glomerular permeability to proteins and changes glomerular hemodynamics.[11-13] So oxidative stresses, an imbalance between the production of reactive oxygen substances and the antioxidant defensive mechanism, contributes to an enhanced permeability of the glomerular capillary wall.[7-8]

Cellular defence mechanisms against ROS including enzymatic systems such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and non-enzymatic antioxidant defense system containing albumin, reduced glutathione, uric acid, vitamin C, vitamin E, carotenoids, selenium and zinc. Total antioxidant capacity (TAC) of the system is the sum of endogenous and food-derived antioxidants.[9] Albumin is the major and most predominant plasma antioxidant which decreases during active phase of nephrotic syndrome and may be related to nephrotic syndrome.[8] Antioxidants prevent the production of reactive oxygen substances, so they can play a major role in decreasing the injury in nephrotic syndrome. Zinc is very important antioxidant and component of various antioxidant enzymes e. g enzymatic systems such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx).

Low Zinc levels during active nephrotic state might lead to a down regulation of type-1 cytokine, a relative type-2 cytokine bias and an increased risk of infections.[10-13] Zinc supplement may lead to decreased episodes of infections presumably due to augmentation of gene expression for IL-2 and interferon, thereby restoring the cytokine-1 immune response.[13-14] Zinc deficiency is common and associated with a high mortality in developing countries

There is paucity of literature regarding remission in nephrotic syndrome on zinc therapy. We were able to find only few studies which is showing effect of zinc on relapse of nephrotic syndrome. Sherali AR et al conducted a double blind randomized placebo controlled trial in Karachi from January 2008 to June 2009 Sixty children with FRNS were enrolled (30 in each group) but 54 completed the trial. Six lost to follow-up, 5 from Zinc group (Zg) and one from placebo (Pg). they found that Zinc supplementation in children with SSNS may be beneficial in prevention of infectious and infection associated relapses.[14] Similar results were also seen by Arun et al in a randomized controlled trial in which Zinc supplementation was associated with fewer relapses and higher likelihood of maintaining remission in frequent and infrequently relapsing NS.[15] Various interventions like use of prophylactic antibiotics, intravenous immunoglobulin, pneumococcal vaccine and Chinese medicinal herbs (Tiajining) in addition to nonpharmacological strategies have been studied for prevention of infections and infection associated relapses.[16]

Aggarwal et al emphasized that zinc is a vital micronutrient in humans and is essential for protein synthesis, cell growth, and differentiation.[6] Severe zinc deficiency has been shown to be associated with stunting of growth, hypogonadism, impaired immune function, skin disorders, cognitive dysfunction, and anorexia. Use of zinc supplementation for a short period of 2 weeks among children in attempts to treat and to prevent common childhood infections was found to be beneficial.

Cogan MG observed that there is increased urinary excretion of high density lipoproteins and of transport proteins for iron, copper and Zn in patients with nephrotic syndrome. Not only the transport proteins are lost in urine but even there is increased excretion of trace metals.[17]

Freeman RM et al reported a linear correlation between proteinuria and zincuria in nephrotic syndrome patients. Albumin bound to a variety of essential and toxic metal ions including Cu, Zn, Ca and Ni by its metal binding sites with clear specification for different metal ions. A positive correlation was found between serum Zn and Cu

levels and serum albumin level.[18] So, all these studies show deficiency of zinc in nephrotic syndrome and present study also have added evidence that zinc therapy administration in these patients lead to early remission.

Strength of present study is our pin point approach to see the effect of zinc on remission of nephrotic syndrome in paucity of studies and literature. If we see from social and economic point of view, drug we tried to study is inexpensive, effective and easy to administer, short course in therapy, negligible side effect and good compliance.

Limitations of present study is that blinding could not be possible, we did not measured the serum zinc level, did not take into consideration the beneficial effect of zinc supplementation on linear growth, which is often cited as another benefit of zinc supplementation and there was no follow up done after remission to access the long term.

CONCLUSION

Our study concluded that Zinc administration along with standard steroid therapy is effective in early remission in pediatrics nephrotic syndrome.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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