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Role of Zinc in Severe Pneumonia.

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ABSTRACT

Pneumonia is the leading cause of mortality and morbidity in young children in developing countries. Our objective was to evaluate the efficacy of zinc supplementation as an adjuvant therapy in treatment of severe pneumonia in children admitted at Sri Venkateswara Ramnarain Ruia Government General Hospital, Tirupati.Ours is a randomized double blind placebo controlled study. Children in the age group 6-60 months presenting with features of severe pneumonia as per IMNCI guidelines were included. Eligible children were allotted to zinc (n=54) and control (n=53) groups. Zinc group received 20mg of elemental zinc per day. Outcome was measured in terms of duration of hospital stay, nil per oral duration, oxygen use days, treatment requiring 2nd or 3rd line antimicrobial drugs. The mean time to reach O2>90% in room air is 34.12 hrs in zinc and 49.35 hrs in Placebo (p=0.009). The mean time of nil per oral duration is 15.5 hrs in Zinc and 40.75 hrs in Placebo (p=0.003).The mean duration of stay was 7.2 days in zinc and 8.9 days in Placebo (p=0.001).Treatment requiring 2nd or 3rd line antimicrobial drugs is significantly low in Zinc group (p=0.016)The results suggest that adjuvant treatment with zinc accelerates recovery from pneumonia and reduces the duration of hospital stay.
Keywords: children, zinc, pneumonia, supplementation, adjuvant therapy.

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INTRODUCTION

Worldwide pneumonia is the leading cause of morbidity and mortality in children [1]. WHO has estimated that each year pneumonia kills up to 2.4 million children, which accounts for 19% of all deaths in the under-five age group[2].The incidence of pneumonia is more than 10-fold higher and the number of childhood related deaths due to pneumonia approximately 2000-fold higher in developing countries than in developed countries[3]. Approximately 95% of the pneumonia related deaths occur in developing countries and the younger age group have the highest risk of death[4].India contributes nearly 20% of it [5].

There are certain social, economic, and environmental factors which are responsible for pneumonia. Low Socioeconomic status, severe malnutrition and lack of breast feeding particularly in early months of life contribute to development of pneumonia [6]. Elimination of most of the environmental risk factors of pneumonia is very difficult, but some nutritional factors need a simple intervention [7].Malnutrition is estimated to contribute up to half of pneumonia deaths .While much emphasis is placed on PEM and vitamin A, it has been proposed that zinc can be a real potential in the prevention of pneumonia morbidity and mortality [8]. Zinc deficiency is common among children in developing countries because of inadequate food intake, particularly from animal sources and limited zinc bioavailability from the local diets. Zinc deficiency impairs the immune system and increases the rate of serious infections such as pneumonia [7].

Zinc is reported to prevent pneumonia, and also prevent and treat diarrhoea. It might act in the acute phase response to infection, helps to boost the body immune response through a defence cascade, beginning with mobilisation and sequestration of zinc to metallothionein-rich tissue, rapid up regulation of immune defence specific protein synthesis, activation of immune defence activity such as macrophages, lymphocytes and natural killer cells and antibody dependent cytotoxicity. Children with good zinc status may have a more robust immune response than with poor zinc status. Zinc given together with antimicrobial therapy to young children with pneumonia was associated with a significant reduction in the duration of pneumonia [9].According to report from W.H.O zinc supplements are the most effective of all the available nutritional supplements to help prevent pneumonia. Zinc efficacy trials conducted in children with mild to moderate zinc deficiency have shown zinc supplementation has significant efficacy in the prevention of pneumonia and improved outcomes during episodes of severe diseases. Recommended zinc nutritional intake is 10 mg to 20 mg per day for children. Normal zinc levels is 65 -150 microgram%[10].

Objectives

To evaluate the efficacy of zinc supplementation as an adjuvant therapy in treatment of severe pneumonia in children admitted at Sri Venkateswara Ramnarain Ruia Government General Hospital, Tirupati.

MATERIALS AND METHODS

A Randomized double blind placebo controlled study included 110 Children in the age group of 6 months to 5 years with features of severe pneumonia as per IMNCI guidelines admitted to Department of Pediatrics, Sri Venkateswara Ramnarain Ruia Government General Hospital, Tirupati for a period of one year from September 2013 to September 2014.Children with congenital heart disease, congenital anomalies,tuberculosis,hyperactive airway disease and malnutrition were excluded from the study.The study was approved by institutional ethics committee,Sri Venkatewara medical college Tirupati.

Study Technique

About 110 children were selected and 3 (1 CHD from zinc group and 2 CHD from placebo group) were excluded as per criteria defined. They were grouped into two study groups by stratified randomization in 1:1 ratio. Zinc group was allotted 54 children and placebo group was allotted 53 children. One was kept as zinc group and another group was kept as control and are analysed.

At admission, we calculated respiratory rate for one minute and chest indrawing was observed. The oxygen saturation (by pulse oximetry), auscultation findings (crepts, wheeze, bronchial breath sounds) and danger signs (cyanosis, inability to feed, lethargy, unconsciousness, convulsions, stridor) were recorded.

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During hospitalization, the child's condition was assessed 8 hourly. Respiratory rate was measured for a full one minute. The count was done at a time when the child was not crying. Pulse oximetry was measured with the use of a probe placed on a finger or toe. Axillary temperature was measured by using a standard mercury thermometer. The presence of cough, crepitations, wheezing, chest indrawing, cyanosis, inability to feed, and lethargy/unconsciousness were also noted.

Enrolled children were given standard treatment for severe pneumonia in the form of oxygen, intravenous fluids, bronchodilators and parenteral antibiotics. Intravenous fluids were removed once the child's respiratory distress improved and oxygen saturation was ≥90%, and the baby was able to tolerate small sips of feeds. Feeds were started as early as possible to optimally balance fluid and caloric intake. Oral antibiotic was started when the child was feeding well and when oxygen saturation and respiratory rate were stabilized. Once the patient was on oral antibiotic, he or she remained under observation in the ward for a further 24 hr before discharge. Study subjects were discharged when they were being fed entirely with oral feeds, the respiratory rate was normalized, oxygen saturation was ≥90% with room air, and the attending pediatrician decided that the patient's clinical condition had resolved and did not require further hospital stay.

Zinc group received 20 mg of elemental zinc per day as a single dose for fourteen days. Placebo group received sugar tablets as control and they were similar to zinc tablets in size, shape and colour. The zinc and placebo tablets were packaged and labeled with study identification numbers by a pharmacist not directly involved in the care of the patients. Observations are made in terms of duration of hospital stay, nil per oral days, time to reach oxygen saturation more than 90% with room air, treatment requiring 2^{nd} or 3^{rd} line antimicrobial drugs.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

OBSERVATION AND RESULTS

Out of 107 cases enrolled in the study, the mean duration of age in the zinc group was 26.7±16.5 months and in the placebo group was28.3±14.3 months. Our study population includes more of rural children contributing to about 56.1% and male children were more in ratio of 2:1. 63 children had oxygen saturation < 90% at the time of admission which is just above 50% of study population. Statistically both groups are similar and no difference. Accessory muscle use is statistically similar in both groups withP value = 0.72.Time to reach SpO_2 >90% with room air is low in zinc group with P value – 0.008. Nil per oral duration was less in zinc group with P value = 0.005. Treatment requiring 2^{nd} or 3^{rd} line antimicrobial drug were less in zinc group with P value = 0.016.The mean duration of hospital stay is less in zinc group with P value = 0.008.

Table 1: Age distribution of patients studied

AGE	Zinc	Placebo
< 1year	15	9
1 – 5 years	39	44
Total	54	53
Mean ± SD (in months)	26.7±16.5	28.3±14.3

Table 2: Table showing respiratory rate in two groups of patients studied

Respiratory rate	Zinc	Placebo
< 1 year		
50 – 60	5	4
>60	10	5
Total	**15**	**9**
1 – 5 years		
40 – 50	5	2
>50	34	42
Total	**39**	**44**

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Table 3: Table showing O_2 saturation at RA during admission in two groups of Patients studied

SpO_2 at RA	Zinc	Placebo
<90%	32	31
≥90%	22	22
Total	**54**	**53**

Table 4: Table showing time to reach O_2 > 90% with RA in two groups of patients studied

Time to reach O_2 >90 in RA	Zinc (n=32)	Placebo (n=31)
< 24 hrs	9	5
24 – 48 hrs	19	10
48 – 72 hrs	2	11
>72 hrs	2	5

Table 5: Table showing nil per oral duration in two groups of patients studied

Nil per oral duration	Zinc (n = 54)	Placebo (n = 53)
Nil hrs	25	19
< 48hrs	26	15
48-96 hrs	3	10
>96hrs	0	9

Table 6: Table showing the duration of hospital stay in two groups of patients studied

Duration of hospital stay	Zinc	Non zinc
< 7 days	27	15
7 – 10 days	24	24
11 – 14 days	3	10
>14 days	0	4
Total	54	53

Table 7: Comparison of study variables in two groups of patients studied

Study variables	Zinc	placebo	P value
Age in months	26.7 ± 16.5	28.3 ± 14.3	0.59
Respiratory rate	63.3 ± 8.72	63.47 ± 9.42	0.92
SpO_2 at room air	88.62 ± 5.28	87.67 ± 6.64	0.41
Time to reach SpO_2 >90% at room air	34.12 ± 19.72	49.35 ± 24.67	0.0091
Duration of hospital stay in days	7.2 ± 1.95	8.9 ± 3.12	0.0011
Nil per oral duration	15.5 ± 18.15	44.50 ± 44.50	0.0003

DISCUSSION

In the present study, about 110 children in the age group of 6 - 60 months were approached for study during the period of September 2013 to August 2014 in department of pediatrics, Sri Venkateswara Ramnarain Ruia Government General Hospital, Tirupati. Of these, 3 children were excluded as per the criteria (1 member from zinc group and 2 members from placebo group have been detected to have congenital heart disease). About 107 children were allotted to two groups, zinc group containing 54 children and placebo group containing 53 children.

Baseline characteristics of the children were well balanced between the treatment groups. The efficacy of zinc as an adjuvant therapy in severe pneumonia was analyzed with outcome strategies as follows:

- Nil per oral duration
- Time to reach O_2 saturation > 90 % in room air
- Treatment requiring 2^{nd} or 3^{rd} line antimicrobial drug
- Duration of hospital stay

Our study included the children belonging to age group of 6 - 60 months. This is similar to the age group undertaken by Srinivasan et al[11], Ehsan et al[7], Shah et al[12] and Ajvith et al[13] studies. The mean age (in months) of distribution in our study is 26.7 vs. 28.3 whereas in Srinivasan et al[11] it was 17.9 vs. 18.1, Ajvith et al[13] it was 17 vs. 10 and Ehsan et al[7] it was 15.4 vs. 15.8 in zinc and placebo group respectively.

The gender distribution was nearly about 2:1 in favour of males. This is consistent with Ajvith Ganguly et al (2:1) and Bose et al (2:1) studies. In Tielsch et al study 2007 in Nepal [14] reported that children older than 12 months and boys were at lower relative risk of death if they received zinc.In our study there were more of rural children compared to urban children both in zinc and placebo groups. Rural children contribute to about 56.1% of total children. In our study 63 children had oxygen saturation < 90% at the time of admission which is just above 50% of study population. Statistically both groups are similar and no difference. In the zinc group of our study about 58.2% required O_2 supplementation and it was about 58.4% in placebo group. In Ajvith et al[13] it is 38.8% vs. 44.9%, in Bose et al[15] it is about 46% vs. 42% and in Srinivasan et al[11] study it is 27.7% vs 31.4% in zinc and placebo group respectively where the difference between two groups is not significant.Accessory muscle use is statistically similar in both groups with predominant subcostal and intercostal retractions.

The mean time taken to reach oxygen saturation of more than 90 percent with room air was less in zinc group. The mean time was 34.12 hrs. in zinc and in placebo it was 49.35 hrs (p value – 0.009) which is similar to Brooks et al[16] study (95% is taken as cut off) of 88 hrs Vs. 96 hrs in zinc and placebo group respectively. In Srinivasan et al[11] study it is 24 hrs vs 18 hrs in zinc and placebo groups respectively and doesn't correlate with present study although the difference is not statistically significant.Time taken to reach oxygen saturation > 90% with room air is relatively low in present study compared to Brooks et al study[16].

Nil per oral duration in zinc group is 15.5 hours compared to 40.75 hours in placebo group which is statistically significant with P value – 0.005 and it is about 10 hours in zinc group and 12 hours in placebo group in Shah et al[12] study and this is not statistically significant. The nil per oral duration is more in present study is compared to Shah et al[12] study.

Treatment requiring 2nd or 3rd line antimicrobial drug were less in zinc group compared to placebo with P value – 0.016, which is statistically significant. Treatment requiring 2nd line anti microbial drugs is more in present study compared to Shah et al[12] study

The duration of stay was less in zinc group when compared with placebo group. It took about 7.2 days in zinc group and 8.9 days for placebo group (p= 0.008). This is statistically significant. It is about 4 vs. 5 days in Brooks et al[16], 5 vs. 5.5 days(p=<0.001) in Ehsan et al study[7] and 3.06 vs 3 days in Shah et al[12] study.In our study only severe pneumonia group were included with out Non severe pneumonia group.

The zinc efficacy in our study may be because most of our children belong to severe pneumoniaThis is consistent with Valentiner - Branth et al[17], Ehsan valavi et al[7], Brookset al[16] and Anuradha Bansal et al[2] studies. All these studies concluded that zinc role as an adjuvant is significant in severe pneumonia.

Our study showed clinically and statistically reductions in the time required for recovery from symptoms of pneumonia. There is reductions in the mean time required to reach SO_2 > 90% with room air, mean time of nil per oral days and mean duration of days of hospital stay and treatment requiring 2nd or 3rd line antimicrobial drugs.

Limitations of the Study

- Serum zinc levels are not estimated.
- Sample size is small.
- Follow up for recurrence of respiratory tract infections was not done.

Recommendations for Further Study

According to the present findings and those of other randomized clinical trials, the benefit of zinc supplementation in acute pneumonia is debatable.

However, although the present study shows statistically significant benefit with zinc, it is not enough to confirm clinical benefit of zinc supplementation, since there is only a few hours difference in resolution of symptoms and duration of hospitalization. It appears that the effect of zinc supplementation in each population varies because of multi factorial interrelationships. Additional basic studies could help elucidate the mechanisms for these varying effects. However, zinc supplementation in populations at a risk of zinc deficiency would be beneficial.Further the limitations of present study like estimation of serum zinc levels should be done. Sample size should be more and follow up for recurrence of respiratory tract should be done.

CONCLUSIONS

The results suggest that adjuvant treatment with zinc 20 mg per day for 14 days accelerates the recovery from severe pneumonia in young children between 6 months to 5 years by reducing the

- Nil per oral duration.
- Time to reach O_2 saturation > 90 % in room air.
- Treatment requiring 2^{nd} or 3^{rd} line antimicrobial drug.
- Duration of hospital stay.

Zinc supplementation accelerates the recovery in severe pneumonia not only in malnourished children but also in non-malnourished children, as children with severe acute malnutrition were excluded in our study.

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