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Efficacy of zinc as an adjuvant therapy in acute pneumonia in children of age 2 months to 2 years: A randomized controlled trial

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Abstract

Background: Pneumonia is the most common Illness affecting infants and children globally. Childhood pneumonia has been identified as the major "forgotten killer of children" by UNICEF and the WHO. The WHO and United Nations Children's Fund (UNICEF) in 2013, published the integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD) which outlined a framework for ending preventable child deaths due to diarrhoea and pneumonia by 2025.

Zinc is a vital micro element that is essential for a variety of fundamental biological processes due to its function as a transition metal, cofactor, structural component, and signalling molecule. Zinc is also an essential component of antibacterial immunity. The impaired immunocompetence due to low zinc states enhances the establishment of a particular infection due to a reduction in the clearance of infectious agents.

Recommend zinc nutritional intake is 10-20mg/day for children. It is estimated that 17-20% of the world's population may be zinc deficient. Zinc deficiency is common among children in developing countries because of inadequate food intake, particularly from animal source and limited bioavailability from local diet. It has been proposed that zinc can be a real potential in the prevention of pneumonia morbidity and mortality.

Objective: To study the effect of zinc supplementation as an adjuvant therapy on outcome of pneumonia.

Method: We conducted a randomised controlled trial from march 2023 to february 2024. All children in the the age group of 2 months to 2 years, who presented with the features of pneumonia to the department of Paediatrics in Akash institute of medical sciences and research centre Devanhalli, Bangalore rural. Ethics consent was obtained from Institutional ethical committee. Demographic details such as name, age, gender along with clinical profile was taken. After admission, detailed history and physical and systemic examination were carried out and necessary data collected.

Sample size being 50 cases, they were divided in two groups as case group (zinc group) and control group by stratified randomisation, 25 participants being in each group. Enrolled children were given standard treatment for pneumonia in the form of oxygen, intravenous fluids, bronchodilators, parenteral antibiotics. Enteral feeds were started once the child respiratory distress improved, oxygen saturations greater than 93%, baby was able to tolerate feed. Zinc group received 20 mg of elemental zinc per day as a single dose for 7 days.

Result : Out of the total 50 cases, two groups were divided with 25 cases in zinc group and 25 cases in non-zinc group. In zinc group 6 cases (50%) took 24-48 hours for disappearance of symptoms, another 3 cases (26%) less than 24 hours, in 1 case time for disappearance of symptoms was 48-72 hours, another case which took 72-96 hours. The mean duration of time taken for disappearance of danger signs was 42.33 ±13.89 hours.

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In the non-zinc group (36%) 5 cases took 24-48 hours for disappearance of danger signs, 3 cases (22%) which took 48-72 hours and 2 cases (14%) which took 96-120 hours, 2 more cases (14%) which took 120-144 hours. The mean duration of hospital stay in non-zinc group was 62.28 ±10.84 hours which is comparatively more than that of zinc group.

Conclusion: This study concluded that zinc supplementation shortens the time taken for resolution of respiratory distress and resolution of symptoms. However, it was not found to be of much help in improving oxygen saturation. It also did not show any significant decrease in time taken for disappearance of danger signs and duration of hospital stay.

Key words: Zinc; Pneumonia; GAPPD; UNICEF.

1. Introduction

Pneumonia is the most common illness affecting infants and children globally. Childhood pneumonia has been identified as the major "forgotten killer of children" by UNICEF and the WHO. According to WHO pneumonia killed 7,40,180 children under the age of 5 in 2019 accounting for 14% of all deaths and 22% of all deaths in children aged 1-5y. India has the highest number of global under 5 deaths due to pneumonia with estimated 508 deaths per day in 2017[1].

The WHO and United Nations Children's Fund (UNICEF) in 2013 published the integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD) which outlined a framework for ending preventable child deaths due to diarrhoea and pneumonia by 2025[2]. The GAPPD emphasises a "protect, prevent, treat" approach and includes proven effective interventions[2]. However, estimates suggest that the sustainable development goal to eliminate preventable child deaths by 2030 will remain improbable unless deaths due to childhood pneumonia are significantly reduced[3]. WORLD PNEUMONIA DAY - NOVEMBER 12th.

There are certain social, Economic and Environmental factors which are responsible for it, such as

Environmental factors like children living in kuccha houses had an increased risk of severe pneumonia.[4,5], overcrowding and poorly ventilated houses, higher levels of outdoor pollution in urban areas [1,6], high levels of solid fuel use causing indoor pollution in rural areas and poorly

constructed houses were the main reasons for the increased risk of pneumonia in children[1,7].

Zinc is a vital micro element that is essential for a variety of fundamental biological processes due to its function as a transition metal, cofactor, structural component, and signalling molecule[8]. Zinc is also an essential component of antibacterial immunity.

The impaired immunocompetence due to low zinc states enhances the establishment of a particular infection due to a reduction in the clearance of infectious agents[9].

Zinc deficiency was associated with reduced killing activity of phagocytes in pneumococcal infection[10]. Recommended zinc nutritional intake is 10 mg to 20 mg per day for children. It is estimated that 17 to 20% of the world's population may be zinc-deficient[11]. Zinc deficiency is common among children in developing countries because of inadequate food intake, particularly from animal source and limited bioavailability from local diet. There are several reports on the impact of supplementation with nutrients such as zinc and vitamin A for the treatment of pneumonia. zinc deficiency seems to enhance the airway inflammation and cellular damage in respiratory infections.

Zinc deficiency alters innate and adaptive immunity. Zinc supplementation improves immunity, ameliorates chronic dysfunctional inflammatory responses, and has been shown to shorten the duration and decrease severity in children with diarrhea, and since 2004, WHO and Unicef recommend zinc supplementation along with oral rehydration.

It has been proposed that zinc can be a real potential in the prevention of pneumonia morbidity and mortality[12].

Objective

To study the effect of zinc supplementation as an adjuvant therapy on outcome of pneumonia.

2. Methodology

We conducted a randomised controlled trial study for 12 months from march 2023 to february 2024, where we enrolled selective cases with age group between 2 months to 24 months, who presented with clinical features of pneumonia to the OPD in the department of paediatrics of Akash institute of medical sciences and research centre, Devanahalli, Bangalore rural.

Demographic details such as name, age, sex along with clinical profile was taken. After admission detailed history and physical and systemic examination were carried out and necessary data such as

- Respiratory rate for 1 minute, the count was done at a time when the child was not crying
- Oxygen saturations using pulse oximetry
- Axillary temperature measured by using standard mercury thermometer
- Auscultation findings [crepts, wheeze, bronchial breath sounds]
- Danger signs were recorded in the pro forma

About 50 children were selected they were grouped in to two study group by stratified randomisation, each group were allotted 25 children one were kept as a zinc group and another were kept as control. Enrolled children were given standard treatment for pneumonia in the form of oxygen,

intravenous fluids, bronchodilators, parenteral antibiotics.Enteral feeds were started once the child respiratory distress improved, oxygen saturations greater than 93%, baby was able to tolerate feed.

Zinc group received 20 mg of elemental zinc per day as a single dose for 7 days, observation are made in the terms of

- Time for disappearance of danger signs
- Time to reach O2 saturation > 90 % in room air
- Time for resolution of distress
- Time to became asymptomatic
- Duration of stay in the hospital

2.1. Statistical Analysis

Total number of cases is 50, out of 50, 25 belongs to zinc group and 25 belongs to non zinc group.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. We constructed Kapaln–Meyer plots of duration of each outcome for zinc and Non zinc groups.

3. Results

In our study, we included 50 cases with 25 cases in each group. There was no lost to follow up and all the 50 cases were included for analysis.

Mean time to be asymptomatic in zinc group was 64.32±35.13 hours and in non zinc group was 87.48±36.67 hours, which was statistically significant with p value of 0.008. Time taken to be asymptomatic was lesser with zinc.

In the zinc group mean time for 02 saturation to become more than 90 was 23.9+38.36. In the non-zinc group, the mean time taken was 45.8+53.42, higher than that of zinc group but, was not found to be statistically significant (P=0.130)

Time taken for resolution of respiratory distress was statistically significant with p value of 0.025. The time taken was lesser in zinc group that is 52.86±33.42 and in non zinc group it was 75.47±38.15.

Table 1 The baseline demographic details and the clinical presentation of the study groups.

Variable	Zinc	No zinc
Age(Mean +- SD)	14.23+-5.28	12.58+-7.85
Gender (n,(%))		
Male	17(68)	14(56)
Female	8(32)	11(44)
Oxygen saturation n,(%)		
<90	11 (44)	16(64)
>90	14(56)	9(36)
Danger signs*		
Lethargy	7(28)	8(32)
Inability to drink	16(64)	14(56)
Convulsions	0	1(4)
Stridor	3(12)	4(16)
Chest findings		
1. Crepts	20(80%)	19(76%)
2. Wheeze	1(4%)	1(4%)
Diagnosis		
Pneumonia	6(24%)	7(28%)
Severe pneumonia	19(76%)	18(72%)

* Danger signs numbers and percentages are not cumulative. Figures Only represent the cases with each sign. Few babies had multiple danger signs.

Similarly, hospital stay was also lesser in zinc group (6.24±3.55) compared to non zinc group(7.52±3.42). This difference was not statistically significant (p=0.368).

In the present study the variable such as Respiratory rate, O2 at RA, Zinc, time for disappearance of danger signs, time to reach O2 >90 in RA, time for resolution of distress, time to be asymptomatic, Duration of stay were used to compare between zinc and non zinc group. There was decrease in mean time taken for disappearance of danger signs , disappearance of danger signs, time to reach O2 >90 in RA time for resolution of distress, time to be asymptomatic, Duration of stay in zinc group compared to non zinc group. However statistically significant values were seen in (P value <0.05) time for resolution of distress and time to be asymptomatic.

Table 2 The outcome variables

Variables	**Zinc**	**Non zinc**	**P value**
Time to be asymptomatic	64.52±7.44	88.15±8.34	0.008
Time to reach O2 >90 in RA	24.9±8.72	44.85±9.12	0.13
Time for resolution of distress	51.47±6.42	74.57±8.17	0.025
Time for disappearance of danger signs	42.3±12.82	62.42±10.73	0.246

Mean time taken for disappearance of danger signs(lethargy, inability to drink, convulsions, stridor) in zinc group was 42.33±13.89 and non zinc group was 62.28±10.84. The time taken was lesser in zinc group however the difference was not statistically significant. (P= 0.246)

4. Discussion

Zinc plays an important role in the development and maintenance of host defence against infections[25]. The therapeutic benefit of oral zinc in diarrhoea has been well documented in a Cochrane review of 18 trials which showed that it shortened the recovery time in children with acute or persistent diarrhoea in the age group of 6 months to 5 years[26]. In the case of pneumonia, there are several trials and meta-analyses about zinc supplementation. Some found benefits,

others limited improvement and some found a lack of benefits compared to placebo. Further, it has also been shown that routine zinc supplementation lowers the risk of acute respiratory infections and clinical pneumonia in children[27]. In this backdrop, the present study was conducted to study the effect of zinc supplementation as an adjuvant therapy on outcome of pneumonia.

Age distribution, gender, population distribution in rural and urban localities in our study was similar to most other studies. Similar to other studies, our patients presented mostly with fever and cough.

In the present study, majority of the children in zinc and non-zinc group were diagnosed with severe pneumonia in 76% and 72% of the children respectively. In a study done by Shivalingaiah and Ramaraj, [28]pneumonia was found in 30% of the children which is low when compared to the present study.

In the present study the mean duration for the disappearance of danger signs in zinc groups was 42.33 ± 13.89 hours which was lower when compared to non-zinc group with duration of 62.28±10.84 hours and it was not significant.(p=0.246) Similarly in a study done by Vinayak and Behal[29], Duration of resolution of danger signs were not significant.

The use of zinc as adjunctive therapy for pneumonia was evaluated in several countries. Results from a randomised, double-blind, placebo-controlled trial of zinc supplementation (25 mg per day) with antibiotics for radiology-confirmed acute pneumonia in 94 hospitalised children aged 6 to 36 months in Tanzania showed no significant reduction in the duration of hospitalisation (incidence rate ratio [IRR] = 0.69; 95% CI 0.45 to 1.06; P = .09) or in the proportion of children hospitalised for less than 3 days (risk ratio [RR] = 0.85; 95% CI 0.57 to 1.25; P = .40) and less than 5 days (RR = 1.01; 95% CI 0.83 to 1.23; P = .92) when compared with placebo[30]. Similarly in our study, mean duration of hospitalisation in zinc group was 6.24±3.55 which was lesser than and non zinc group that is 7.52±3.42, but this reduction was not statistically significant.

Similarly, in another meta-analysis of 7 randomised controlled trials with 1066 children from developing countries, hospitalised for severe acute lower respiratory tract infection, compared the therapeutic role of zinc with placebo[31]. Time of resolution of severe illness (standardised mean difference of −0.15; 95% CI −0.5 to 0.2; P = .4) and duration of hospitalisation (standardised mean difference of −0.29; 95% CI −0.68 to −0.09; P = .13) were not statistically different between groups.

In our study, The mean time to reach SPO2 >90 in RA was 23.9±38.36 hours in zinc groups and 45.8±53.42 hours in non-zinc group and it was found to be non-significant. However, the duration was less in zinc group as compared to the non-zinc group. In a study done by Srinivasan et al[33] the time to normalisation of oxygen saturation 24 hours in zinc group and 18 hours in non zinc groups and its was found to be nonsignificant. In the study conducted by Bansal et al[34] the median (IQR) time taken to achieve oxygen saturation (SpO2) > 95% in room air was similar in zinc and placebo groups (0 (0–7) hours and 0 (0–6.5) hours, P=0.73). In a study by Bose et al[35] The median (95% CI) time taken for resolution of hypoxia was comparable between zinc (70.7 (65.5, 87.2) hours) and placebo group (72.3 (67.7, 76.2) hours), (P=0.575).

In this study the mean time for the resolution of the distress was lower in zinc group as compared to the non zinc group (52.86 ± 33.42 vs 75.47 ± 38.15 hours) and it was found to be significant with p value of 0.025. Similarly, Basavraj et al study[32] the mean duration for resolution of distress in zinc group was 52.47 ± 33.99 hours which was significantly lower as compared to non-zinc, 74.17 ± 37.76 hours (p=0.04).

In our study, the mean time to be asymptomatic was significantly less in zinc group as compared to non zinc group (64.32 ± 35.13 hours vs 87.48 ± 36.67 hours; p=0.008). Similarly, in a study done by Basavraj et al[32] the mean duration for the resolution of symptoms was 65.52 ± 36.03 hours in zinc group and 88.00±37.97 hours in non-zinc group and it was found to be significant (p=0.04).

Our study showed significant reductions in time required for recovery from symptoms of pneumonia and decrease in respiratory distress who received zinc supplementation along with standard antimicrobial therapy. Also, there was decrease in time to improve oxygen saturation, and mean duration of hospital stay, however, they were not statistically significant.

5. Conclusion

In our study we concluded that zinc supplementation shortens the time taken for resolution of respiratory distress and time taken for resolution of symptoms. However, it was not found to be of much help in improving oxygen saturations. It also did not show any significant decrease in time taken for disappearance of danger signs and duration of hospital stay.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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