*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*
*e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 14, Issue 12 Ver. VI (Dec. 2015), PP 04-11*
*www.iosrjournals.org*

# A Prospective Observational Study of Zinc As Adjunct Therapy In Pediatric Population With Severe Pneumonia

Dr.Vasudev Kompally[1], Sruthi Dyavanapally[2], Nagesh Adla[2], Vikram kumar Gourineni[2], Shabber Hussain[2]

[1]*Department of Paediatrics, Kakatiya Medical College, Mahatma Gandhi Memorial Hospital, Warangal, Telangana, India.*
[2]*Department of Clinical Pharmacy, Vaagdevi College of Pharmacy, Warangal, Telangana, India.*

***Abstract:*** *Worldwide, Pneumonia is the leading infectious cause of death in children, accounting for 15% of all deaths of children under 5 years old. Pneumonia killed an estimated 9, 35,000 children under the age of five in 2013 and can be prevented by immunization, adequate nutrition and by addressing environmental factors. The aim of study was to determine the role of Zinc as an adjunct therapy in paediatrics with severe pneumonia. This study is a randomized, double blinded, placebo-controlled clinical trial conducted between March 2014 to September 2014 at Department of Paediatrics. Children aged 1month-6years who were diagnosed with severe pneumonia are randomly assigned with zinc and placebo supplementation in 1:1 ratio. 20mg of zinc syrup/day was received by subjects along with antimicrobial therapy. All clinical signs and symptoms of severe pneumonia were assessed and recorded on standard forms, entered into computer, and edited with the use of GRAPH PAD PRISM, version 6. The time until cessation of severe pneumonia and duration of hospitalization was slightly shorter among the zinc recipients. We explored whether the effect of zinc was different in subgroups on the basis of duration of fever, presence of wheezing, creptations, and endpoint consolidation on chest x-ray. This trial yielded a moderate but not statistically significant efficacy estimate for zinc in the resolution of severe pneumonia in hospitalized 1month-6year old children with the standard antibiotic therapy. However, large trials are required to clarify the role of zinc in treatment of severe pneumonia*

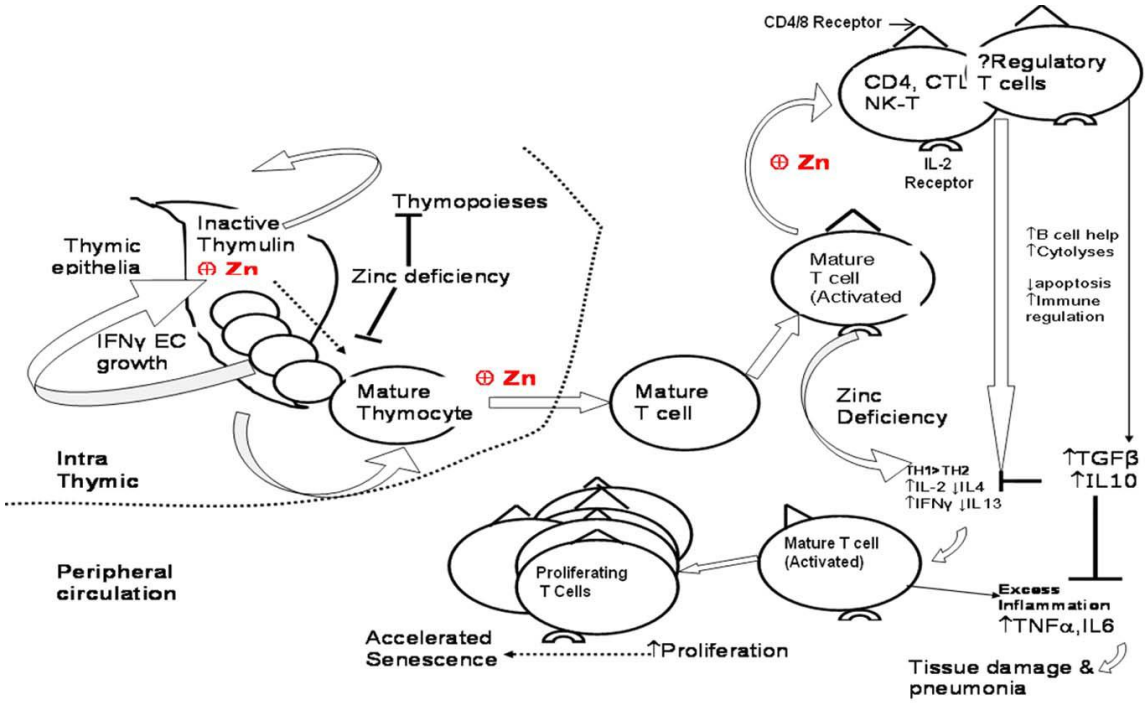
***Keywords:*** *Adjunct therapy, Pneumonia, Zinc*

## I. Introduction

Death from pneumonia is the leading single contributor to under-5 mortality globally, which presents a major challenge for the achievement of the fourth millennium development goal to reduce under-5 mortality two-thirds by 2015[1]. In southern Asia, macronutrient malnutrition and micronutrient deficiencies, especially deficiencies of zinc, iron and vitamin A are common in young children [2]. Pneumonia management, which relies on the early diagnosis and prompt antibiotic therapy, has been effective, reducing pneumonia-related deaths by 47%, but may be diminished by poor nutritional status [3-5]. Under nutrition is known to be associated with greater severity of pneumonia and of the micronutrients, zinc plays a crucial role in immunomodulation [6-9].

Zinc deficiency, a likely risk factor of pneumonia is a global problem affecting populations of low economic status [10]. It is estimated that zinc deficiency in association with diarrhoea, pneumonia and malaria contributed to 44% of deaths and 3.8% of loss disability adjusted life years among children aged 6-59 months in Africa, Latin America and Asia. Two distinctive roles of zinc in modulating pneumonia burden exist: firstly as a preventive element when administered prior to pneumonia disease; secondly, zinc may change the course of pre-existing pneumonia when added as an adjunct to conventional antibiotic treatment potentially to reduce the severity and duration of pneumonia in sufferers [11].

Proposed model of how zinc may influence T-cell immunity during severe pneumonia to alleviate lung damage: (Figure-1)




In the intra-thymic compartment, inactive thymulin generated by thymic epithelia, combines with zinc to result in functional thymulin, which drives thymocyte development in the direction of the broken arrow to export mature T cells into the peripheral circulation (right part of the dotted line). Zinc deficiency blocks intra thymic T cell development as shown. In the peripheral circulation zinc has the potential to drive further maturation, activation and differentiation into helper (CD4), effectors and cytotoxic T lymphocytes (CTL) and possibly including naturally occurring regulatory T cells, which originate from the thymus. Regulatory T cells may also produce TGF∞and IL10 to counteract potential immune pathology.

A recent clinical trial conducted in Bangladesh suggested that zinc supplements given with empiric antimicrobial therapy can significantly shorten the duration of severe pneumonia, tachypnea, hypoxia, and chest in drawing and duration of hospital stay for young children with pneumonia [12] other trials in India, Nepal and Australia found no effect [13,14]. As more research is needed to establish the role of zinc in treatment of severe pneumonia, we undertook a clinical trial to evaluate the effect of zinc supplementation with the standard antibiotic therapy and time taken for normalization of respiratory rate, temperature, oxygen saturation.

## II. Materials And Methods

***Study design and setting:***

This study is a randomized, double blinded, placebo-controlled clinical trial conducted between March 2014 to September 2014 at Department of Paediatrics, Mahatma Gandhi Memorial Hospital (MGMH), Warangal, Telangana, India. MGM Hospital is a large teaching hospital and medical centre that is accessed directly by the population of Telangana and by referrals from local medical practitioners.

The study was approved by the Institute Ethical Committee and project review board of Mahatma Gandhi Memorial Hospital. Written consent was obtained after the parents or guardians read study information. If the parents or guardians were illiterate, the content of the written consent was read to them, and consent was documented by a thumbprint impression of one of the parents or guardians in the presence of an unrelated witness.

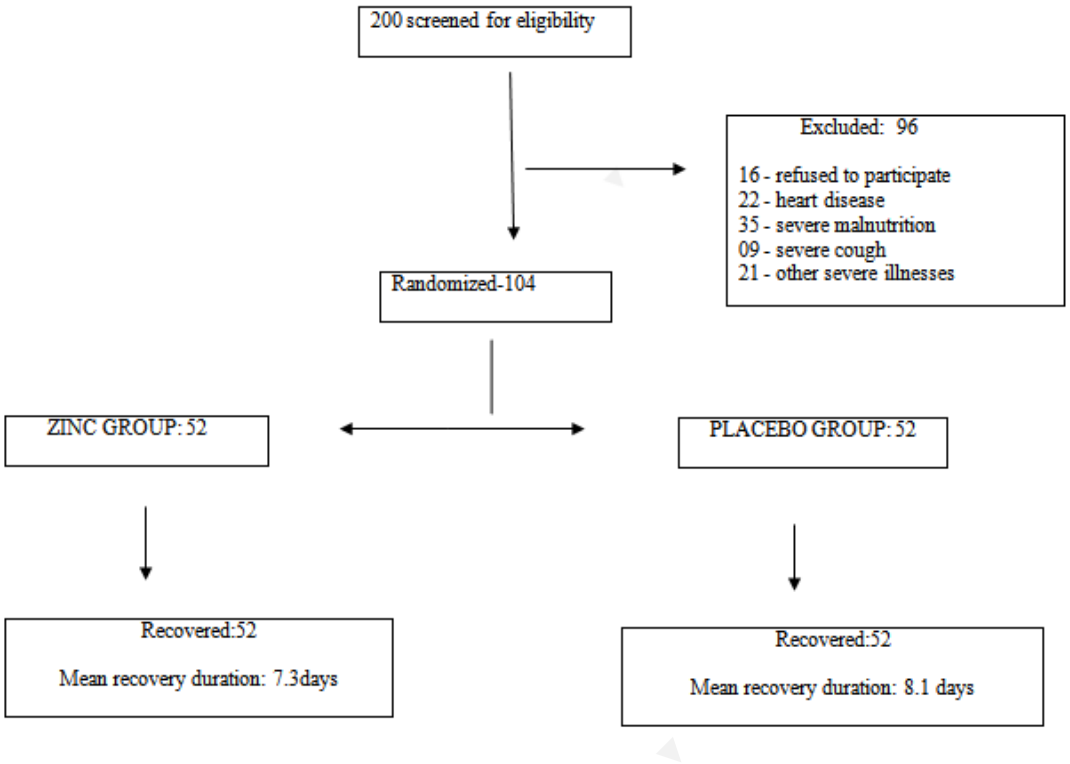
***Enrolment of subjects:***

Children aged 1 month to 6 years presenting to the Mahatma Gandhi Memorial Hospital emergency or outpatient departments were assessed by the study physicians and considered eligible for enrolment in the trial if they fulfilled the criteria for a diagnosis of severe pneumonia defined as per WHO/IMCI (Integrated Management of Childhood illness) guidelines. Severe Pneumonia is defined as a respiratory >50/min, which was accompanied with crepitations on auscultation and the presence of >1 of the following danger signs: lethargy, inability to feed, chest in drawing, or central cyanosis. Patients who had history of chronic cardiac or renal disease, illness severe enough to require ventilation, malnutrition therapy [i.e., weight for age <60% of the

reference for Indian children [7]], illness requiring hospitalization in the previous 21days or current zinc supplementation.

At the time of enrolment, study physicians collected information on demographics, current illness, and history of respiratory diseases for each subject. All physical findings, anthropometric data, chest X-ray findings, complete blood count results were recorded in a predesigned data sheet.

***Trial flow:***




## III. Intervention

The subjects were randomly assigned, following simple randomization procedures (1:1) to receive supplementation with Zinc acetate syrup. 5ml zinc acetate syrup contained 20 mg elemental zinc. The supplements were formulated and manufactured as syrups by Zuventus (Zinconia). Zinc supplementation is ceased once children were discharged. Children received 20mg (5ml) zinc acetate or placebo by mouth at the time of enrolment. All enrolled children were treated according to the standard protocol with a combination of Ampicillin (50-100mg/kg/day intravenously every 6 hours) and Amikacin (15-22.5mg/kg/day intravenously twice daily) parenterally. Patients who failed to improve after 48 hours on this regimen of first-line antimicrobial therapy were switched to a regimen of parenteral Ceftriaxone. Daily requirements of intravenous fluids are initiated for children unable to eat/breast feed. Oxygen supplementation was provided to children with documented hypoxia. During hospitalization, the child's condition was assessed at the beginning of each 8-hour shift by a study physician or a study nurse, and the assessment was recorded in the patient's chart. Respiratory rate, axillary temperature, the presence of cough, crepitations, wheezing, chest in drawing, cyanosis, inability to feed, and lethargy were also noted in the patient's chart.

***Sample size:***

On the basis of the consensus of the hospital paediatricians, 50% of the patients were expected to achieve "clinically cured" or "much improved" status after 5 d of treatment. With zinc as an adjunct therapy, we expected 75% of the children to achieve this status as judged by the clinician. The calculated number in each group (with 80% power and a 5%significance level) would be 52 children, assuming a withdrawal rate of 8% (24). On the basis of similar assumptions for the proportion of patients in whom tachypnea or fever would have resolved after 4 d of treatment, the calculated sample sizes would be similar. A total of 104 patients was the estimated sample size.

***Outcome definitions:***

The primary outcomes were the duration of hospitalization and the treatment failure requiring 2$^{nd}$ line agents for management of severe pneumonia. Duration of hospitalization was defined as time gap between

enrolment and discharge in hours. We also analyzed the time to normalize the clinical symptoms such as respiratory rate, temperature and oxygen saturation.

***Statistical analysis:***

Complete data was collected on standard forms and entered into computer after the manual checks. The statistical analysis were undertaken by using GRAPH PAD PRISM, version 6. The major objective of the study was to evaluate the effect of zinc on the clinical course of illness due to pneumonia in infants and young children based on P-values obtained using paired T- test. Differences were considered significant when a two-sided P-value was <0.05.

## IV. Results

From March 8, 2014 to September 30, 2014, we screened 200 children meeting inclusion criteria, of which 104 children were enrolled. Of the remaining 104 children, 52 were to receive zinc and 52 to receive placebo (figure 1). The results were drawn using Graph pad prism which is a scientific 2D graphing and statistical software.

***Baseline demographic characteristics (Table-1)****:*

Out of 104, 57 (54.8%) were male. The mean age group (months) is 13.4 in zinc group and 19.2 in placebo group. 37 out of 52 used antibiotics in week before admission in zinc group and 25 out of 52 in placebo group.

***Baseline clinical characteristics (Table-2):***

The mean haemoglobin level is 9.86g/dl in zinc group and 9.9g/dl in placebo group.

***Wheezing***: In the zinc group, 23 of the 26 (88%) infants and 24 of the 26 (95%) older children had wheezing. In the placebo group, 25 of the 26 (95%) infants compared with 18 of the 26 (78%) older children presented with wheezing. P value did not give any statistical significance.

***End point consolidation***: 104 chest x-rays available for interpretation, endpoint consolidation was identified in 12 (23%) in zinc group and 14 (27%) in placebo group. There is no statistical significance.

***Crepitations***: 13 out of 52 in zinc group and 9 out of 52 have crepitations. The P values between the groups did not give statistical inference.

***Oxygen saturation***: The mean oxygen saturation is 83 in zinc group and 85 in placebo group & the statistical values were not significant.

***Chest in drawing***: 50 out of 52 (96 %) in zinc group, 48 out of 52 (92%) in placebo group were said to have chest in drawing. 100.8F in zinc group and 100.5F in placebo group was the mean axillary temperature. The mean respiratory rate (breaths/min) was 64 in zinc group and 60 in placebo group <12 months, 65 in zinc group and 62 in placebo group 12-72months. A total of 10 patients are unable to breast feed and 7 have nasal flaring.

***Primary and secondary outcomes (Table-3):***

***Time to normalization of temperature, cough and respiratory rate:***

Mean duration of fever in zinc group (days) is 2.8 days and 2.9 in placebo group. The p- ***Value*** is 0.908 with no significance. Mean duration of cough in zinc group is 3.5 days and 3.8 days in placebo group. The p value is 0.44 which is not significant. The median time to normalization of respiratory rate is 90 hours in zinc group and 96 in placebo group. The p-value is 0.19 which is less significant.

***Subjects with severe pneumonia >90 hours (figure-2)****:* 37 patients of 52 (71%) in zinc group have severe pneumonia symptoms >90hours and42 out of 52 in placebo group.

***Duration of hospitalization (figure-3)***: The mean duration of hospital stay was 168hours in zinc group where as in placebo group the mean duration is 193 hours. The P value for two groups is 0.0676. The value is slightly closer to the significance (<0.05). The duration is reduced in zinc group.

***Treatment failure requiring 2nd line agents (figure-4)***: 10 out of 52 paediatric patients required 2nd line agent i.e., Ceftriaxone (IV) in zinc group, where as in placebo group 12 out of 52 required 2nd line agent. A total of 22 patients required other antibiotic for the treatment of severe pneumonia. The percentage of recovery rate with 1st line agents (Ampicillin and Amikacin) is 81% and 2nd line agents is 19%. The time until cessation of severe pneumonia was slightly shorter among the zinc recipients. The effect of zinc, however, was not significantly different between those with and without radiographic pneumonia, that is, the interaction was not statistically significant. These comparisons were also in favour of zinc, but none reach the statistical significance (Table 3). The risk of treatment failure was lower among the zinc recipients; however, this was also not statistically significant.

## V. Discussion

This study on zinc as adjunct therapy in children with severe pneumonia shows a modest but not statistically significant effect of daily zinc administration in reducing time to cessation of severe pneumonia defined as a 24-hour consecutive period of absence of LCI, hypoxia, and any other danger sign.

In the study by Maheswari G Srinivasan *et al*[10], there was no significant difference in normalization of respiratory rate, temperature and oxygen saturation between children receiving placebo and zinc.

Gauri S Shah *et al* [12] reported that there is no significant reduction in duration of severe pneumonia or reduction in hospital stay instead the duration has increased in zinc group which is contradictory to our study.

In other study in India (C. L. Coles *et al* [15]) on children 2-23 months showed that disease symptoms were improved faster and the duration of hospitalization decreased significantly in zinc-receiving patients. This finding is consistent with our study.

In a study undertaken in Bangladesh (W. Abdullah *et al* [16]), children who received zinc recovered faster, and fewer had treatment failure and duration of severe pneumonia lasting 72, 96, or 120 hours. This also reported that in children without wheezing, administration of zinc resulted in earlier resolution of clinical signs. The effect of zinc was not modified by wheezing status in our subgroup analysis (Table 5), a finding similar to that reported from South India. However, because there were only 9 children without wheezing, we had insufficient power to detect an effect of zinc in this subgroup.

Furthermore, other recent trial by Mohammad Javad Qasemzadeh *et al* [17], showed that zinc therapy can reduce resistance caused by antibiotic therapies and inferred that zinc can hasten the recovery from pneumonia and quickly resolve symptoms in children.

There were no differences in the time to resolution of respiratory signs either combined or individually between the zinc and placebo groups in Ecuadorian children. [18]

Trials in India have shown both beneficial[19,20] and non beneficial effect [21] of zinc in the recovery from severe pneumonia in young children and significant reduction the duration of hospital stay. In our neighbouring country Nepal, Tejesh Malla *et al*[22] emphasized that zinc recipients recovered marginally faster and recurrence of pneumonia was also significantly less ($p<0.001$) in zinc recipients.

All these studies, like our study, were double-blind randomized controlled trials assessing the efficacy of zinc in children with severe pneumonia. Inherent differences in the populations studied and differences in the illness characteristics including pre enrolment duration and definition of recovery would explain the discrepancy between studies.

## VI. Conclusion

This trial yielded a moderate but not statistically significant efficacy estimate for zinc in the resolution of severe pneumonia in hospitalized 1month-6year old children. The Zinc supplements were well tolerated, safe and no vomiting was noted. In the treatment of severe pneumonia Ampicillin and Amikacin are effective in 81% of our population. In light of conflicting study results, additional large trials in representative settings are required to help clarify the role of zinc and efficacy of Amikacin & Ampicillin in treatment of severe pneumonia.

## References


[1]. Pa Tamba Ngom, Stephen Howie, Martin O.Ota and Andrew M. Prentice. The potential role and possible immunological mechanisms of zinc adjunctive therapy for severe pneumonia in children. The open immunology journal, 2011, 4, 1-10.

[2]. Anuradha Bose, Christian L Coles, Gunavathi, Hemanth John, Prabhakar Moses, P Raghupathy et al. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 y old. Am J Clin Nutr 2006; 83:1089-96.

[3]. Sazawal S, Black RE. Meta-analysis of intervention trials on case-management of pneumonia in community settings. Lancet 1992:340; 528-33.

[4]. Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. Am J Clin Nutr 1997; 66(suppl): 464S–77S.

[5]. Brundtland GH. Nutrition and infection: malnutrition and mortality in public health. Nutr Rev 2000; 58:S1– 4.

[6]. Caulfield LE, de Onis M, Blossner M, Black RE. Under nutrition as an underlying cause of child deaths associated with diarrhoea, pneumonia, malaria, and measles. Am J Clin Nutr 2004; 80: 193–8.

[7]. Fishman SM, Caulfield LE, de Onis M, et al. Childhood and maternal underweight. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors.

[8]. Geneva, Switzerland: World Health Organization, 2004:39 –162.

[9]. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J Clin Nutr 1998; 68(suppl):447S–63S.

[10]. Prasad AS. Zinc: an overview. Nutrition 1995; 11:93–9.

[11]. Maheswari G Srinivasan, Grace Ndeezi, Cordelia Katureebe Mboijana, Sarah Kiguli, Gabriel S Bimenya, Victoria Nankabirwa et al. Zinc adjunct therapy reduces case fatality in severe childhood pneumonia: a randomized double blind placebo-controlled trial. BMC Medicine 2012, 10:14.

[12]. Ruel MT, Rivera JA, Santizo MC, Lonnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhoea and respiratory infections among rural Guatemalan children. Paediatrics 1997; 99; 808-13.

[13]. Gauri S Shah, Ashok K Dutta, Dheeraj Shah and Om P Mishra. Role of zinc in severe pneumonia: a randomized double bind placebo controlled study. Italian Journal of Paediatrics 2012, 38:36.
[14]. Sudha Basnet, Prakash S. Shrestha, Arun Sharma, Maria Mathisen, Renu Prasai, Nita Bhandari et al. A randomized controlled trial of zinc as adjunct therapy for severe pneumonia in young children. Paediatrics 2012; 129; 701.
[15]. Valentiner-Branth P, Shrestha PS, Chandyo RK. Randomized controlled trial of the effect of zinc as adjuvant therapy in children 2–35 mo of age with severe or non-severe pneumonia in Bhaktpur, Nepal. Am J Clin nutr doi.:10.3945/ajcn.2009;28907.
[16]. C. L. Coles, Anuradha Bose, Prabhakar D Moses, Leni Mathew, Indira Agarwal, Thomas Mammen et al. "Infectious etiology modifies the treatment effect of zinc in severe pneumonia," The American Journal of Clinical Nutrition, vol. 86, no. 2, pp. 397-403, 2007.
[17]. W. A. Brooks, M. Yunus, M. Santosham, Naheed A, MA_Wahed, Kamrun Nahar et al. "Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial," The Lancet, vol. 363, no. 9422, pp. 1683-1688, 2004.
[18]. Mohammad Javad Qasemzadeh, Mahdi Fathi, Maryam Tashvighi, Mohammad Gharehbeglou, Sohelia Yadollah-Damavandi, Yekta Parsa et al. "The effect of Adjunct Therapy on Recovery from Pneumonia in Hospitalized Children: A Double-Blind Randomized Controlled Trial. Hindawi Publishing Corporation Scientifica Volume2014.
[19]. Farnando Sempertegui Bertha Estrella, Oswaldo Rodriguez, Dinor Gomez, Myryam Cabezas, Gilda Salgado et al. Zinc as an adjunct to the treatment of severe pneumonia in Ecuadorian children: a randomized controlled trial. Am J Clin Nutr 2014;99:497–505.
[20]. Dilip Mahalanabis, Madhurima Lahiri, Dilip Paul, Susham Gupta, Atul Gupta, Mohammed A Wahed et al. Randomized, double-blind, placebo-controlled clinical trial of the
[21]. efficacy of treatment with zinc or vitamin A in infants and young children with severe acute lower respiratory infection. Am J Clin Nutr 2004;79:430–6.
[22]. Rajagembeeran V, Basavaraja GV, Nijaguna, Govindraj M. The Role of Zinc as an Adjuvant Therapy in Acute Pneumonia in Children in Age of 2 Months to 2 Years. Scholars Journal of Applied Medical Sciences 2015; 3(1D):267-271.
[23]. Nita Wadhwa, Aruna Chandran, Satinder Aneja, Rakesh Lodha, Sushil K Kabra, Mona K Chaturvedi et al. Efficacy of zinc given as an adjunct in the treatment of severe and very
[24]. severe pneumonia in hospitalized children 2–24 mo of age: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr 2013;97:1387–94.
[25]. Tejesh Malla, Kalpana K Malla, Brijesh Sathian, Prithuja poudyal, Eva Gauchan, Sahisnuta Basnet. Oral Zinc as Adjuvant Therapy for Pediatric Recurrent Pneumonia: A Prospective Study in a Tertiary Care Hospital. American Journal of Public Health Research, 2015, Vol. 3, No. 4A, 12-18.

**(Table-1) Baseline demographic characteristics of children aged 1-72months in a clinical trial evaluating efficacy of zinc as adjunct therapy for severe pneumonia**

| Characteristics | Zinc group (n=52) | Placebo group (n-52) |
|---|---|---|
| Mean age in month, SD | 13.4 (15.30) | 19.2 (22.06) |
| Age groups (months) | | |
| <12months, n% | 34 (65.3) | 32 (61.5) |
| 12-72months, n% | 18 (34.6) | 20 (38.4) |
| Male subjects, n% | 32 (61.5) | 25 (48) |
| Child still breastfeeding, n% | 45 (86) | 43 (82) |
| Mean of weight (kgs), SD | 6.99 (3.17) | 7.86 (3.79) |
| Antibiotic use in week before admission, n% | 37 (71%) | 25 (48%) |

SD- Standard Deviation, n- number of cases,

**(Table-2) Baseline clinical characteristics of children aged 1-72months in a clinical trial evaluating efficacy of zinc as adjuvant therapy for severe pneumonia**

| Characteristic | Zinc group (n=52) | Placebo group ( n=52) | P-value |
|---|---|---|---|
| Mean hemoglobin in g/dl (SD) | 9.89 | 9.91 | 0.91* |
| Mean respiratory rate in breaths per minute (SD) : | 61.62 (5.81) | 63.83 (4.42) | 0.04* |
| <12months | 50.76 (7.63) | 56.63 (8.15) | 0.02* |
| 12-72months | 83.78 (5.22) | 81.9 (7.02) | 0.12* |
| Mean oxygen saturation (SD) | 47 (90.3) | 43 (82.6) | 0.25** |
| Wheezing (%) | 50 (96.1) | 48 (92.3) | 0.40* |
| Chest in drawing (%) | 13 (25%) | 09 (17.3) | 0.337** |
| Crepitations (%) | 12 (23%) | 14 (27%) | 0.652** |
| Consolidation on chest x-ray (%) | | | |
| Signs and symptoms of severe pneumonia | 06 (11.5) | 04 (7.6) | 0.502* |
| Child unable to drink/breastfeed (%) | 04 (7.6) | 03 (5.7) | 0.696** |
| Nasal flaring (%) | | | |

S.D :- Standard Deviation, *Paired T-test, **Z-test

**(Table-3) Primary and secondary outcomes in a randomized placebo-controlled on oral zinc syrup as adjunct therapy for severe pneumonia in children 1-72 months of age**

| Characteristic | Zinc group (n=52) | Placebo group (n=52) | P-value |
|---|---|---|---|
| Mean duration of hospitalization in hours (SD) | 167.30 (47.19) | 188.19 (65.92) | 0.0521* |
| Number of subjects with duration of severe pneumonia in hours (>90hours), (%) | 37 (71%) | 42 (80%) | 0.25** |
| Treatment failure requiring 2nd line agents (%) | 10 (19.2%) | 12 (23.07%) | 0.631** |
| Time to normalization of respiratory rate in hours | 90 (22.37) | 96 (14.88) | 0.09* |
| Time to normalization of cough in hours (SD) | 71.38 (20.65) | 74.5 (20.06) | 0.41* |
| Time to normalization of temperature in hours (SD) | 67.78 (15.82) | 70.86 (22.76) | 0.39* |

SD- standard deviation, *Paired T-test, **Z-test

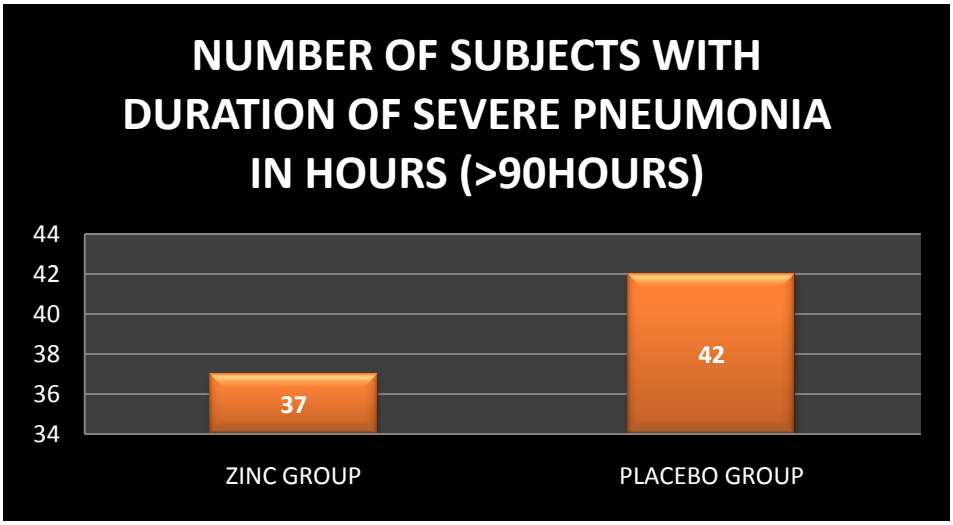



Fig 2: This figure explains about duration of severe pneumonia

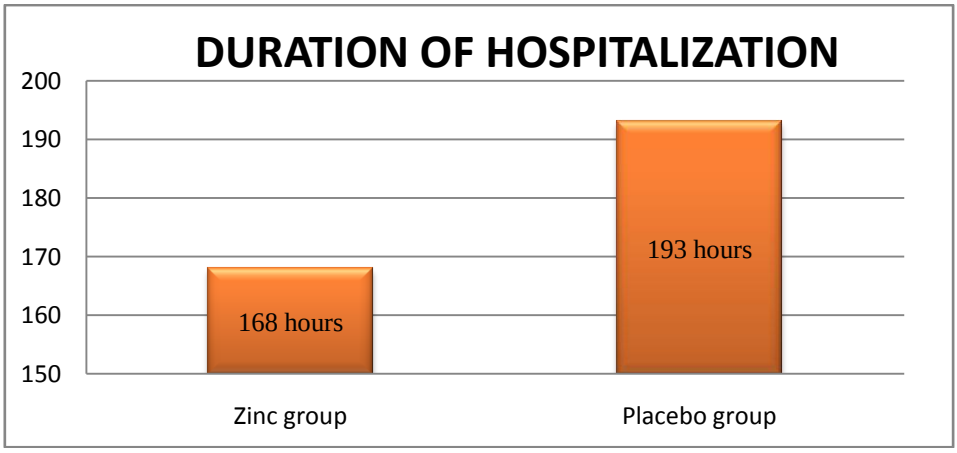



Fig 3: This figure explains about duration of hospitalization (in hours) in patients with Zinc group and placebo group

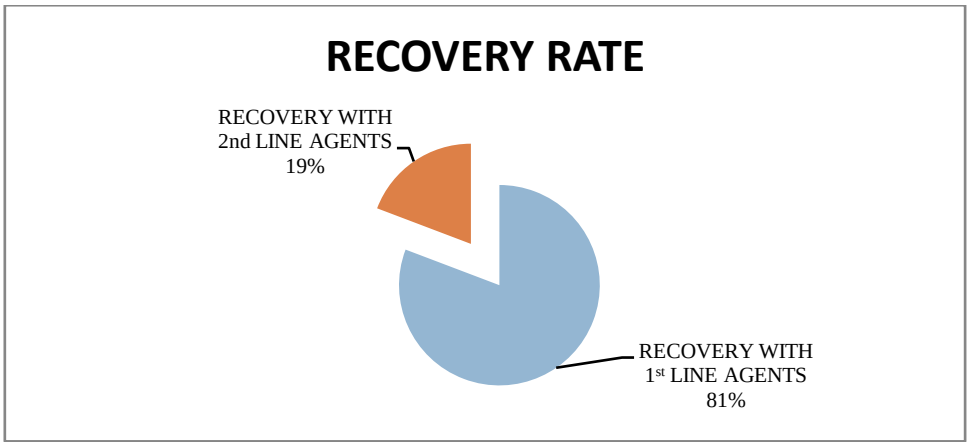



Fig 4. This figure explains about the Recovery rate of both the groups.