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Role of Vitamin D supplementation in severe pneumonia in children of age group 2 months to 5 years: A Randomized Controlled Trial

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Abstract

Objective: To study the efficacy of Vitamin D supplementation in the treatment of severe pneumonia in children of age group 2 months to 5 years.
Study design: Randomized double blind placebo controlled clinical trial.
Material and methods: Eligible subjects included patients (between 2 months to 5 years) with a clinical diagnosis of WHO defined severe pneumonia, presenting in the pediatric emergency of Bebe Nanki Mother and Child hospital of Medical College Amritsar, India. Patients were randomized to two groups and 1000-2000IU of Vitamin D (n=100) or placebo (n=100) was given for 7 days, starting from day of admission. Outcome variables were time to resolution of illness (tachypnea, lower chest retractions, hypoxia and inability to feed) and duration of hospitalization, in children receiving vitamin D supplementation with the control group receiving placebo, in addition to routine antibiotics and supportive therapy.
Results: The clinical resolution in both the groups was comparable with mean difference being statistically insignificant. The mean time for resolution of tachypnea was (109.25 hours vs 110.52 hours), for resolution of chest retractions was (103.06 hours vs 104.99 hours),for resolution of hypoxia was (19.67 hours vs 20.35 hours) ,for resolution of inability to feed was (93.55 hours vs 95.90 hours) and for duration of hospital stay was (183.13 hours vs 184 hours) in Vitamin D and placebo group respectively.
Conclusion: Vitamin D supplementation does not decrease time for resolution of clinical symptoms and duration of hospitalization for WHO defined severe Pneumonia in children aged 2 months to 5 years.

Keywords: Vitamin D, Pneumonia

Introduction

Pneumonia continues to be the biggest killer worldwide of children under five years of age. Although the implementation of safe, effective and affordable interventions has reduced pneumonia mortality from 4 million in 1981[1] to just over 1 million in 2013,[2,3] it still remains the leading cause of childhood mortality accounting for 15% of all deaths in children below 5 years of age[4]. Many observational studies have shown an association between Vitamin D deficiency and acute lower respiratory tract infections[5-9], thus bringing into focus the immunomodulatory properties of Vitamin D. But the results of only few trials are available to document the efficacy of Vitamin D supplementation in severe pneumonia.

Vitamin D deficiency is known to cause rickets and retards the skeletal growth. Studies in developing countries have suggested an association between nutritional rickets and pneumonia. Researchers have found that vitamin D deficiency predisposes children to infection, and thus vitamin D has been labeled as "antibiotic vitamin"[10]. New York Times has claimed vitamin D as a potential new miracle drug[11]. Clinical and subclinical vitamin D deficiency in children has been reported to be a significant risk factor for severe acute lower respiratory tract infection[12]. Increased susceptibility to respiratory infections in vitamin D deficiency may be explained on the basis of it leading to hypotonia and chest wall deformity, leading to reduced lung volume, poor compliance of the chest wall, atelectasis and fibrosis. Apart from this, new knowledge of the biological and clinical importance of the active form of vitamin D and its receptor has generated interest in its role in improving immune function[13]. This has been already demonstrated experimentally in tuberculosis, a major pulmonary disease. The immune enhancing actions of vitamin D include induction of monocyte differentiation, inhibition of lymphocyte proliferation, stimulation of phagocytosis dependent and antibody-dependent macrophages, and modulation of T and B lymphocytes that produce cytokines and antibodies[14-16.] The stimulation of phagocytosis dependent and antibody-dependent macrophages contributes to antimicrobial properties of vitamin D[17.] All these factors contribute to a higher incidence of pneumonia in children with severe vitamin D deficiency.

In a systemic review by RR Singh M, Panigrahi I, Naik SS et al[18] (Two RCTs with 653 patients) comparing treatment of pneumonia in children under 5 years of age with vitamin D3 versus placebo, no significant difference in the mean (± SD) number of days to recovery between the vitamin D3 and placebo group(P= 0. 17) was found. Another trial conducted in University College of Medical Sciences, Delhi evaluated oral Vitamin D (1000-2000IU) for 5 days to children with clinical diagnosis of severe pneumonia and observed no difference in time to resolution of severe pneumonia, between the two groups.[19]

Since there have been mixed views regarding role of vitamin D supplementation in severe pneumonia, we planned to study the role of Vitamin D supplementation in severe pneumonia keeping the dose same (1000-2000IU) which is in accordance to tolerable upper limit as specified by the Food and Nutrition Board of the Institution of Medicine, USA[20], but for an extended period of 7 days as compared to previous trials. Such research is important given the increasing evidence that subclinical Vitamin D deficiency is common even in countries at low latitude and with plentiful sunshine, including India[21-23.] The main objective of our study was to evaluate the effect of adding Vitamin D in the routine treatment of severe pneumonia, in terms of clinical recovery.

Materials and Methods

This double blind randomized placebo controlled clinical trial was done in Pediatrics department of Bebe Nanki Mother and Child Health center of Medical College Amritsar, India from April 2015 to July 2017. Children aged between 2 months to 5 years presenting with severe Pneumonia (according to WHO classification)[24] were included after taking informed consent. Those who had received vitamin D or calcium supplementation within last 4 weeks before admission, severely malnourished (weight for

height SD- score < -3; and/or height for age SD-score< -3 or presence of edema), concurrent empyema thoracis or illness severe enough to require ventilation or clinical evidence of any heart disease, renal insufficiency and hepatic insufficiency were excluded from study. Simple randomization was done according to a computer generated random number table on a master list to one of two treatment strategies. Allocation concealment was done by sealed envelope technique, the envelope was opened at the time of intervention. Both the caregiver and the subject were blind regarding the content of the drug being given. Baseline data was recorded for feeding practices, immunization status, and socio-demographic variables. Physical examination included vital signs, cyanosis, mental status, chest auscultation for crepitations or wheezing, or both; and anthropometrical measurements. Respiratory rate was counted for full 60 seconds, chest in drawing was observed at the same time. The average of two readings was recorded. Axillary temperature was taken with a digital thermometer, fever defined as temperature >38˚C. Baseline oxygen saturation was measured using a pulse oximeter with a probe on a finger or toe, in room air and hypoxia defined as oxygen saturation <95% in room air. The eligible children were randomly assigned into 2 groups – D and P, to receive either vitamin D supplementation or placebo. Control group was P (n=100), who were given 5 ml unfortified regular milk. Group D (n=100), was given 5ml regular milk fortified with Vitamin D which was available in syrup form. The dose of vitamin D supplementation was 1000 IU per day for 7 days for infants (age < 1 yr), and 2000 IU per day for 7 days for older children .The drug was administered at the time of enrollment, with the first dose of parenteral antibiotic on the day of admission, and then once daily for the next 6 days. Patients were treated for severe pneumonia as per IAP protocol. The primary outcome was the time to resolution of illness (tachypnea, lower chest retractions and hypoxia and inability to feed) and the duration of hospitalization. The duration of hospitalization was defined as the time (in hours) between study enrolment and discharge. The effect of vitamin D supplementation on outcome variables was analyzed on an intention to treat basis. The data was analyzed by using SPSS software (version 11: SPSS; Chicago). Chi square test or Fisher's Exact test was used to compare categorical variables. All quantitative variables were compared by unpaired t test or analysis of variance (ANOVA). P < 0. 05 was considered as significant.

Observations

This double blind randomized placebo controlled clinical trial was done in Pediatrics department of Bebe Nanki Mother and Child Health center of Medical College Amritsar, India and included 200 patients with 100 in each group.The subjects in both the groups were comparable in terms of baseline personal characteristics. Mean age was 16.72 ± 11.66 vs 13.98 ± 11.79 months in Vitamin D and placebo group respectively (p=0.057). Male female ratio was 69:31 vs 59:41 in Vitamin D group and placebo respectively. In both the groups, males were more than females. Mean weight of study population was 9.37 ± 3.13 vs 8.17 ± 3.14 kg in Vitamin D and placebo group respectively (p=0.176). Most children (186 out of 200) had received breastfeeding. 95 out of 100 children in Vitamin D group and 91 out of 100 children in placebo group had history of receiving breast milk at some point of time in life. Out of 186 children receiving breast feed, only 37 (19. 8%) were receiving exclusive breastfeeding, 20 being in Vitamin D group and 17 in placebo group. Regarding Socio-economic status maximum cases (94/200) belonged to category 4 i.e. upper lower class of modified kuppuswami scale of socioeconomic status, followed by category 3(86/200) i.e. lower middle class. Of the individual groups also, similar pattern followed maximum being in category 4 (49/94 in Vitamin D group as compared to 45/94 in placebo) (p =0.80). Out of 200, 79% (158/200) children were completely immunized (81 of Vitamin D group and 77 of placebo group). 38 children (17 of Vitamin D group and 21 of placebo group) were partially immunized whereas 4(2 of Vitamin D group and 2 of placebo group) were unimmunized (p =0.77). Table 1 depicts the final outcome of study population in both the groups.

Table 1: Final outcome of study subjects

Final outcome	Group P		Group D		Total
	No.	%	No.	%	
Improved and discharged	81	81. 0	85	85. 0	166
Not improved					
• LAMA	8	8. 0	7	7. 0	15
• Continued treatment	11	11. 0	8	8. 0	19

Overall 166 (83%) children improved and were discharged. 34(17%) did not improve, out of which 15 could not complete the study because parents left against medical advise and the rest 19 continued the treatment.

The primary outcome measures were the time of resolution of illness (tachypnoea, lower chest retractions, hypoxia and inability to feed) and duration of hospitalization, in children receiving vitamin D supplementation and the control group receiving placebo, in addition to routine antibiotics and supportive therapy in both the groups. Children were monitorited every 8 hourly in terms of various clinical parameters. Table 2 provides a comparison of outcome measures between the two groups in terms of mean number of hours for resolution of clinical symptoms.

Table 2: Outcome measures in the two study groups.

	Group P		Group D		p-value
	Mean(hrs)	SD	Mean(hrs)	SD	
Tachypnea	110. 52	11. 32	109. 25	10. 10	0. 446
Retraction	104. 99	9. 99	103. 06	9. 02	0. 193
Inability to feed	95. 90	9. 83	93. 55	8. 73	0. 105
Hypoxia	20. 35	6. 69	19. 67	7. 25	0. 535
Duration of hospital stay	184. 00	13. 08	183. 13	12. 23	0. 658

Thus there was no difference in the outcome between the 2 groups in relation to resolution of various clinical symptoms and duration of hospital stay.

Discussion

Micronutrients in the current global health scenario are being considered as the magic bullets, and routine use of vitamin A and zinc is being advocated in measles[4] and diarrhea[6,8]. Role of zinc, vitamin A, vitamin C, iron and folic acid and multiple micronutrients has been studied earlier in acute respiratory infections[25].Vitamin D is the latest projected micronutrient that may have a potential protective role in acute respiratory infection; however ,this is not supported by any randomized controlled trial in children. It is a unique vitamin and hormone whose origin dates back to nearly 750 million years[26]. There is a mounting evidence for a pivotal role of vitamin D in the immune system. Monocytes continuously exprime the vitamin D receptors.

Our trial was planned to study the role of oral vitamin D supplementation in the treatment of severe pneumonia. Children of age 2 months to 5 years with severe pneumonia were included in the study. Both the groups were similar with regard to baseline characteristics. The clinical resolution in terms of tachypnea, chest retractions, inability to feed and hypoxia in both the groups was comparable with mean difference being statistically insignificant. These results are important; however, they need further deliberations. Our study has certain limitations as well and thus it may not be justified to generalize the results to all acute lower respiratory tract

infections at all ages and all settings. We will discuss the findings of our study in view of these limitations.

Similar study by Choudhary N, Gupta P et al was conducted at University College of Medical Sciences, Delhi in 2012.Two hundred children between 2 months to 5 years with severe pneumonia were enrolled. Oral vitamin D (1000 IU for <1 year and 2000 IU for >1 year) (n=100) or placebo (lactose) (n=100) once a day for 5 days, from enrolment. Median duration of resolution of severe pneumonia was similar in the two groups. Duration of hospitalization and time to resolution of tachypnea, chest retractions, and inability to feed were also comparable between the two groups concluding that short-term supplementation with oral vitamin D (1000-2000 IU per day for 5 days) has no beneficial effect on resolution of severe pneumonia in under-five children[19].

A study was conducted at Sanjeevani Paediatrics Hospital, a private hospital in Indapur, India to determine whether subclinical vitamin D deficiency in Indian children under 5 y of age is a risk factor for severe acute lower respiratory infection (ALRI). A total of 150 children including 80 cases and 70 controls, aged 2–60 months, were enrolled. It concluded that subclinical vitamin D deficiency and nonexclusive breastfeeding in the first 4 months of life were significant risk factors for severe acute lower respiratory tract infections in Indian children[27].

In another study in New Zealand, 112 patients admitted with community acquired pneumonia during the winter were found to have low vitamin D levels. The researchers found that vitamin D deficiency was associated with higher mortality within the first 30 days after hospital admission for pneumonia. The authors conclude that improved understanding of Vitamin D and its role in immunity may lead to better ways to prevent and or treat pneumonia[28].

In another study conducted in Mongolia, it was suggested that serum levels of 25-hydroxyvitamin D (25[OH]D) are inversely related with incidence of acute respiratory infections (ARIs). By using cluster randomization, classrooms of 744 Mongolian schoolchildren were randomly assigned to different treatments in winter (January-March). This analysis focused on a subset of 247 children who were assigned to daily ingestion of unfortified regular milk (control; n = 104) or milk fortified with 300 IU of vitamin D3 (n = 143). This comparison was double-blinded. The primary outcome was the number of parent-reported ARIs over the period of 3 months. Compared with controls, children receiving vitamin D reported significantly fewer ARIs during the study period (mean: 0. 80 vs 0. 45; P =. 047), with a rate ratio of 0. 52 (95% confidence interval: 0. 31-0. 89). Adjusting for age, gender, and history of wheezing, vitamin D continued to halve the risk of ARI[29].

In a systematic review and meta-analysis to assess the preventive effect of vitamin D supplementation on respiratory tract infection (RTI) was seen. Randomized, controlled trials of vitamin D for prevention of RTI were used for the analysis. Of 1137 citations retrieved, 11 placebo-controlled studies of 5660 patients were included in the meta-analysis. Overall, vitamin D showed a protective effect against RTI (OR, 0. 64; 95% CI, 0. 49 to 0. 84). The protective effect was larger in studies using once-daily dosing compared to bolus doses (OR = 0. 51 vs OR = 0. 86, p = 0. 01). Results indicate that vitamin D has a protective effect against RTI, and dosing once-daily seems most effective[30].

Though there is enough data to suggest a link between low Vitamin D status and increased risk of respiratory tract infections and its role in prevention of pneumonia but till date very few studies has been published on the role of Vitamin D supplementation in the treatment of severe pneumonia. Further there are limitations like no standard definition or diagnostic criteria for pneumonia, which often leads to misdiagnosis and Inability to check Vitamin D levels which is the best indicator to define Vitamin D deficiency, insufficiency, hypovitaminosis and toxicity.

Although our results do not show any significant effect of vitamin D supplementation on resolution of severe pneumonia or duration of hospitalization, yet there can be preventive role of vitamin D against pneumonia as proved by many studies. To know more about therapeutic effects of Vit D, further large studies need to be conducted with measurement of Vitamin D levels in study subjects and studies with different doses and duration of vitamin D supplementation, and with more stringent definition of pneumonia.

Conclusion

We conclude that the clinical resolution in both the groups was comparable with mean difference being statistically insignificant in terms of resolution of illness concluding that short-term supplementation with oral vitamin D (1000-2000 IU per day for 7 days) has no beneficial effect on resolution of severe pneumonia in under-five children. So it is worthwhile to explore this subject further and conduct more trials, before we conclude that Vitamin D supplementation has no role in severe pneumonia.

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