International Journal of Contemporary Pediatrics
Rajshekhar CS et al. Int J Contemp Pediatr. 2016 Feb;3(1):96-99
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20160138

Research Article

Efficacy of vitamin D supplementation in the treatment of severe pneumonia in children aged less than five years

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Received: 18 August 2015
Revised: 05 November 2015
Accepted: 18 November 2015

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ABSTRACT

Background: Vitamin D supplementation is useful in preventing respiratory tract infections, but there is no clear evidence to support the therapeutic efficacy of vitamin D in acute pneumonia.
Methods: This study was conducted to evaluate the efficacy of vitamin D supplementation in addition to routine treatment of severe pneumonia in children less than 5 years of age. Vitamin D was supplemented at a dose of 1000 IU and 2000 IU for children <1 year and for children >1 year, respectively. Equal number of children received placebo.
Results: The primary outcome was the time to resolution of severe pneumonia. Hurried breathing was present in 87.5% of drug group children and 43% of placebo group children (the difference was not significant, p=0.74).Cyanosis was present in 12.5% of children in the vitamin D group and 8.3% in children in the placebo group, with no significant difference between the treatment groups (p=0.50). Poor oral intake was reported in 22.9% cases of vitamin D group and 33.3% in placebo group.
Conclusions: Short-term supplementation with vitamin D failed to show any evidence of improvement in resolution of severe pneumonia in children under the age of five.

Keywords: Vitamin D, Children, Severe pneumonia, Respiratory tract infections, Mortality

INTRODUCTION

Worldwide, 15% of mortality related to infections in children under the age of 5 years is attributed to pneumonia. In 2013, an estimated 935000 deaths in children under the age of 5 years has been caused by pneumonia.[1] Nearly 50% of the global mortality (approximately 3.7 lakh deaths, annually) related to pneumonia occurs in India. In India, 69% children with pneumonia seek medical attention and of them, only 13% are treated with antibiotics.[2] Pneumonia caused by viruses, bacteria or fungi is preventable through immunization, adequate nutrition and minimization of exposure to environmental factors.

Vitamin D regulates the calcium and phosphate homeostasis and thereby plays an important role in bone metabolism. In addition, vitamin D is known to regulate the immune system. Besides causing rickets, vitamin D deficiency has been linked to respiratory infections such as pneumonia, tuberculosis and bronchiolitis.[3] Vitamin D deficiency is a common and important nutritional deficiency in children in India. Low serum vitamin D levels are a risk factor for pneumonia, wherein a study showed that subjects with lowest vitamin D levels were at a 2.5 times greater risk for pneumonia than those with high vitamin D levels.[4] In addition to intravenous antibiotics, oxygen, or assisted ventilation (in severe cases), researches have tried nutritional supplements such as zinc and vitamin A but the results were not encouraging. A systematic review and meta-analysis by

Charan et al concluded that vitamin D supplementation is useful in preventing respiratory tract infections.[5] However; there is no clear evidence to support the therapeutic efficacy of vitamin D in acute pneumonia. Therefore, we planned to study if vitamin D supplement along with routine management helps in improving the treatment outcome in children under the age of 5 years. The objective of this study is to evaluate the efficacy of vitamin D supplementation in addition to routine treatment of severe pneumonia in children less than 5 years of age. In addition, we compared the effect of vitamin D on the time to resolution of the illness (tachypnea, lower chest in drawing, hypoxia, and inability to feed), and duration of hospitalization with that of placebo.

METHODS

The study was conducted at HSK Hospital, Bagalkot, Karnataka, India. Children aged between 2 months and 5 years admitted to pediatric ward and pediatric intensive care units, with severe pneumonia were enrolled into the study. The study was conducted between January 1, 2012 and June 30, 2013.

Written and informed consent was obtained from parents of eligible children and each patient was allotted a study number. These numbers corresponded to the order of patients entering the study. Each of the patients were thoroughly evaluated and the baseline demographic data (history [nature and duration of symptoms], feeding practices [breastfeeding history and age of introduction of complementary foods], immunization status, socio-demographic variables [parental education, occupation, family income, number of siblings, housing, cooking fuel used in the household, smoking, and history of lower respiratory tract infections in a family member] and the practice of exposure of the child to sunlight) was obtained.

Inclusion criteria

- Children aged between 2 months and 5 years.
- Clinical diagnosis of severe pneumonia [clinical presentation with cough, fever, tachypnea and crepitation's on auscultation, along with presence of either lower chest in drawing or at least one other danger sign (inability to feed, lethargy, cyanosis)] as per World Health Organization [WHO] guidelines for acute respiratory infection control program.

Exclusion criteria

- Receipt of vitamin D supplementation within last 4 weeks before admission.
- Severe malnutrition (weight for height <70%; and/or height for age <85%, or presence of edema as per WHO classification of under nutrition). Congenital heart diseases, congenital deformities of chest and thorax.
- Immunodeficiency states

Study medication allocation

A 2×2 computerized block randomization was carried out by Meyer Organics Private Ltd. to allot the test medications and placebo. Vitamin D and placebo were administered in the form of tablets. Each tablet of vitamin D contained 1000 IU and 2000 IU for children <1 year and for children >1 year, respectively. The placebo contained lactulose. Both the drug and placebo looked alike in terms of appearance, taste and colour.

Children with severe pneumonia were randomly assigned to receive supplementation of placebo (N=48) or vitamin D (N=48). The dose of vitamin D was prescribed according to the Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Vitamins issued by The Food and Nutrition Board, Institute of Medicine, National Academics6 along with antibiotics as per Indian Association of Pediatrics (IAP) protocol for treatment of severe pneumonia.[2]

The study medications were dispensed in milk and administered 4 hours after admission to hospital. This was followed by once-a-day dosing for next 4 hours. Those unable to take the medications orally were given through naso-gastric tube. The drug was repeated if an episode of vomiting occurred within 15 min of ingestion of drug.

Clinical monitoring

Data including respiratory rate, retractions, oxygen saturation, fever, feeding, cyanosis and mental status were recorded every 8 hours. Worsening of any one sign was qualified as 'deteriorating' condition and no change as 'failure to improve'. Children were reclassified from severe pneumonia to non-severe pneumonia when chest indrawing and hypoxia (saturation <95% on room air) were absent for 24 hours and respiratory rate was less as per age cut off, at which oral antibiotics were started. Oral feeding was also started at this point of time. If any signs recurred, the children were classified as severe until these conditions were met. All children received a minimum of 5 days of antibiotics either intravenously or orally.

Children were discharged when tachypnea had subsided for a minimum of 24 hours. Children with clinical rickets were given a mega dose (6,00,000 IU) of vitamin D at the time of discharge. All children were observed for adverse effects and compliance.

Primary outcome

The primary outcome was the time to resolution of severe pneumonia. Resolution of severe pneumonia was considered when lower chest retraction and danger signs

(inability to feed, cyanosis or hypoxia) were no longer present.

RESULTS

Study outcome

The mean age of the children who received vitamin D or placebo was not significantly different (1.94±1.46 versus. 2.08±1.92 years). There was no significant difference in the gender distribution between the children <1 year and >1 years of age. Literacy rate among parents of drug group and placebo was 47.9% and 29.2%, respectively.

Hurried breathing was present in 87.5% of drug group children and 43% of placebo group children (the difference was not significant, p=0.74). There was no significant difference between the two treatment groups in terms of previous history of respiratory tract infections (35.4% versus. 39.6%; p=0.67). Family history of respiratory tract infections was significant in the placebo group (2% versus 9% in vitamin D versus placebo groups; p=0.02). Children in the placebo group had been more adherent to vaccination schedule than those in vitamin D group, (93.8% versus 79.2% in placebo versus vitamin D group; p=0.03). Family history of tuberculosis was not significantly different between the two treatment groups (p=0.50). Equal proportion of children had been breast fed in both the treatment groups (87.5%, 89.6% in drug versus vitamin D). Exclusive breast feeding was given in 75% cases of drug group and 79.2% in placebo group children (difference was not significant, p=0.74). Top feeding was given to 79.2% of children in the vitamin D group and 18.8% of children in the placebo group. Poor oral intake was reported in 22.9% of children in the vitamin D group and 33.3% in placebo group (no difference between the treatment groups; p=0.25).Children in both groups were equally exposed to passive smoking. Presence of significant febrile period was noted in 89.6% of children in the vitamin D group and 85.4% in placebo group (difference was not significant, p=0.53).Cyanosis was present in 12.5% of children in the vitamin D group and 8.3% in children in the placebo group, with no significant difference between the treatment groups (p=0.50). Poor oral intake was reported in 22.9% cases of vitamin D group and 33.3% in placebo group. The primary objective of time taken for resolution of severe symptoms was as observed in Table 1.

Table 1: Distribution of study subjects according to time taken for severe symptoms to subside.

Time in hours	Proportion of children	
	Vitamin D treated group	Placebo treated group
<24 h	10(20.8%)	30(62.5%)
24–48 h	30(62.5%)	28(58.5%)
>48 h	30(62.5%)	15(31.3%)

p=0.14 (not significant)

DISCUSSION

Pneumonia is a severe form of acute lower respiratory infection caused by bacteria, virus or fungi. Children with pneumonia may have a range of symptoms depending on their age and the cause of the infection. Bacterial pneumonia usually causes more severe illness in infants and children with symptoms high fever, chills and rapid breathing. The onset of viral pneumonia is slow but the symptoms worsen over time. The common signs and symptoms of pneumonia in children and infants include rapid or difficult breathing, cough, fever, chills, headaches, loss of appetite and wheezing. Children aged <5years with severe pneumonia have difficulty in breathing with their chests moving in or retracting during inhalation (known as 'lower chest wall indrawing'). Some infants may also present with convulsions, unconsciousness, hypothermia, lethargy and feeding problems. Although chest X-rays and laboratory tests are confirmatory for pneumonia, clinical symptoms are the key to diagnosis in settings with poor-resources. Therefore, cough and difficult breathing in children and infants prompts the diagnosis of pneumonia.[7]

Nutritional deficiencies including inadequate zinc intake, comorbid illness (AIDS or measles), and environmental factors (living in crowded homes and exposure to parental smoking or indoor air pollution) are the factors that predispose infants to risk of pneumonia.

The protective action of vitamin D in preventing respiratory tract infections is attributed to their role in regulating natural antibodies through induction of monocyte differentiation and inhibition of lymphocyte proliferation.[5] Vitamin D may enhance the phagocytic activity of macrophages. Vitamin D inhibits monocyte production of inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-12 and tumor necrosis factor (TNF)-α.[8]

Vitamin D should always be adjuvant treatment in patients with serious illnesses and but not as a substitute for standard treatment. Hypothetically, researchers suggest that a short-term course of vitamin D (2,000 IU per kg per day for three days) might be adequate to produce sufficient quantity of the naturally occurring antibiotic, Cathelicidin to cure common viral respiratory infections, including influenza and the common cold.[9]

In our study, the baseline characteristics did not differ between the two treatment groups, except for family history of respiratory tract infections, completion of vaccination and supplementation of top feeding. Family history of respiratory tract infections was significant in the placebo group. Vaccination was complete in significantly higher proportion of children in the placebo group compared to the vitamin D group. Greater proportion of children in the vitamin group had received top feeding than children in the placebo group.

Similar to the outcome of study by Choudhary et al. our study did not find any significant difference in the outcome of time to resolution of severe pneumonia between the two treatment groups.[10] Choudhary et al randomized 200 children (median age 10 months) to vitamin D or placebo. Fever, cough, coryza, irritability and decreased oral intake were reported in all the children enrolled in the study. The median duration for resolution of severe pneumonia was comparable in both the treatment groups. The time for resolution of symptoms of severe pneumonia (tachypnea, chest retraction, hypoxia, fever, inability to feed and lethargy/irritability) was also comparable between the two groups. This study showed that short-term supplementation with vitamin D did not reduce the duration of resolution of severe pneumonia, duration of hospitalization, and time taken for resolution of individual symptoms of severity of pneumonia in under five children.[10]

Since our study had certain limitations, it was not possible to generalize the results to all lower respiratory tract infections. Owing to safety concerns, the dose of vitamin D was kept below the No Observed Adverse Effect Level. A higher dose was not administered because of lack of safety data in children and absence of vitamin D level monitoring system. It might also be true that the recruited children would have had vitamin D deficiency and therefore the dose of vitamin D given to the children might have not been sufficient to show any clinical effect. This could have been overcome by measuring the vitamin D level at baseline, however due to financial constraints; the levels could not be checked. Despite daily supplementation of vitamin D, the blood levels of vitamin D might have been sub-optimal in our study population.

CONCLUSION

Short-term supplementation with vitamin D does not decrease the duration of resolution of severe pneumonia, duration of hospitalization, and time taken for resolution of individual symptoms of severity of pneumonia in children under the age of five.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Rajshekhar CS, Vanaki R, Badakali AV, Pol RR, Yelamali BC. Efficacy of Vitamin D supplementation in the treatment of severe pneumonia in children aged less than five years. Int J Contemp Pediatr 2016;3:96-9.