Effect of Vitamin D supplementation in under-5 children with pneumonia: A randomized controlled trial

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ABSTRACT

Objective: The objective of the study was to study whether Vitamin D supplementation in under-5 children presenting with pneumonia and severe pneumonia reduces its duration and recurrences. **Study Design:** This study was designed as a double-blind, randomized, placebo-controlled trial. **Setting:** Pediatric unit of a teaching institute. **Methods:** A total of 80 children aged between 2 months and 5 years with the diagnosis of pneumonia and severe pneumonia (as per the WHO definition) admitted over a period of 1 year were included in the study. Children with features of rickets, severe malnutrition, asthma, any underlying medical disorders, and if received Vitamin D supplementation over the past 12 months were excluded from the study. Children were randomized into two groups. Intervention group received 300,000 IU (international units) of Vitamin D (1 ml), and the control group received 1 ml of sterile water as a placebo along with antibiotics and supportive care. Children were monitored for the resolution of symptoms. The two groups were comparable for baseline demographic, socioeconomic, clinical, and laboratory parameters. All the children were followed up for 3 months after discharge for any repeat episodes of pneumonia. **Results:** Time to resolution of symptoms (fever, tachypnea, and chest retractions) was not significant (3.63±1.27 days in intervention group/3.6±0.78 days in placebo group, p=0.933). On follow-up, recurrence of pneumonia was significantly high in placebo group than in intervention group (20 [40%] and 3 [7.5%], respectively, p<0.05). Risk of recurrence was 0.201 (95% confidence interval, 0.069–0.587) in intervention group. **Conclusion:** Supplementation with Vitamin D in under-5 children with pneumonia and severe pneumonia significantly reduces the risk of recurrence over the period of 3 months.

Key words: *Fast breathing, Fever, Pneumonia, Vitamin D supplementation*

Worldwide, pneumonia affects 156 million children aged <5 years old every year, and it is the leading cause of mortality in this age group [1]. More than 2 million annual deaths are estimated to occur because of pneumonia in <5 years old and almost all of these occur in the developing world. In India, 43 million cases and 0.4 million deaths are due to the pneumonia. The median incidence of pneumonia in India is estimated to be 0.37 episodes per child per year [2].

Studies in developing countries have suggested an association between nutritional rickets and pneumonia. There were 13-fold higher incidences of rickets among children with pneumonia than among controls in Ethiopian children [3]. Furthermore, low Vitamin D status was found to be an independent risk factor for treatment failure and for prolonged severe lower respiratory infection in a study on Nepalese children [4]. Vitamin D deficiency was also found to be significantly associated with children admitted to the pediatric intensive care unit with severe acute lower respiratory infection [5].

1,25-dihydroxy Vitamin D, the active form of Vitamin D activates Vitamin D receptor which induces antimicrobial peptides (cathelicidin and β-defensin 2). These are vanguards of innate immune responses against bacterial, fungal, and viral pathogens. Furthermore, the susceptibility to infection occurs before many of the overt manifestations of the nutritional rickets might occur [6]. Studies have shown an association of subclinical Vitamin D deficiency with severe acute lower respiratory infection [7,8]. Hence, an intervention of Vitamin D supplementation in resource poor settings might help in reducing the disease burden of pneumonia in the community. However, in spite of these evidence, there are very few studies done on Vitamin D supplementation in children with pneumonia [9,10]. Hence, we conducted this trial to test whether Vitamin D supplementation in under-5 children presenting with pneumonia and severe pneumonia reduces its duration and its recurrences.

METHODS

This double-blind, placebo-controlled, randomized trial was conducted on children between 2 months and 5 years with diagnosis of pneumonia and severe pneumonia admitted in pediatric unit of a teaching institute in north Karnataka during December 2014 to November 2015 over a period of 1 year. Prior

approval of institutional ethical committee was taken. Written informed consent was taken from either of the parents before recruitment.

Pneumonia was diagnosed (as per the WHO definition) in children presenting with cough, cold, and fast breathing (respiratory rate ≥50 per min in 2 months–12 months; ≥40 per min in 12 months–5 years). Children presenting with chest in drawing along with the above symptoms were diagnosed as severe pneumonia [11]. Children with clinical features of rickets (craniotabes, frontal bossing, rachitic rosary, Harrison groove, enlargement of wrist, and ankle), severe malnutrition (weight for height/length < −3 SD, with or without edema, and with or without midupper arm circumference <11.5 cm), history suggestive of asthma, underlying disorders (cough >2 weeks, tuberculosis, congenital heart diseases, retroviral disease, epilepsy, nephrotic syndrome, and bleeding disorder), and any Vitamin D supplementation over the past 12 months were excluded from the study.

Subjects were randomized into two groups according to a computer generated random number table. Group allocation was concealed in a brown opaque envelope. Intervention group (Group I) received 1 ml (300,000 IU Vitamin D3, Abbott India Limited) of Vitamin D intramuscularly, and the control group (Group II) received 1 ml of sterile water as a placebo over the lateral aspect of thigh, using 2cc disposable syringe with 24 number needle. The attached labels of the ampoules of Vitamin D3 and sterile water were removed, so they appeared similar and were given a unique identity number which was sealed by the pharmacist not aware of the groups. The identity was opened after the intervention, data collection, follow-up, and tabulation were completed. The ampoules were stored in a dry and cool environment according to the manufacturer's recommendations. The investigators and the caretakers of the subjects were unaware of the study groups.

Both the groups received antibiotics in the form of intravenous Penicillin G (200,000 units/kg/day in four divided doses) and supportive care in the form of oxygen, intravenous fluids, and antipyretics (paracetamol at 15 mg/kg/dose).

Detail history, demographic data, socioeconomic status (Kuppuswamy's socioeconomic status scale modified for 2007 [12]), immunization status, history of breastfeeding and complementary feeding practice, exposure to smoking, type of fuel used for cooking (liquefied petroleum gas [LPG]/non-LPG), and housing conditions were recorded in a structured pro forma. Clinical examination including anthropometry as per the standard techniques was also recorded. Respiratory rate was recorded for one full minute for 2 times after removing all the clothes when the child was awake and not crying. Axillary temperature was checked using digital thermometer with standard technique. Venous blood was drawn for hemoglobin, blood counts, serum calcium, and alkaline phosphatase and for blood culture (which was collected separately under all aseptic precautions). Chest radiograph was done in all the children and was reported by a qualified radiologist, not aware of the study groups.

All the children were clinically monitored and details of the pulse rate, respiratory rate, temperature, chest indrawing, feeding, and general condition were recorded every 8 h. Persistence for more than 48 h or worsening of the above-mentioned signs was considered as deterioration or failure to treat. In such cases, antibiotics were stepped up to cefotaxime (50 mg/kg/dose every 8 h intravenously). Improvement of tachypnea, fever, and chest indrawing persisting for ≥48 h was considered as recovery, after which the child was discharged. The duration of resolution was recorded from the time of study enrolment to that of recovery. All the children were given an identity card and were followed-up for 120 days after discharge for any repeat episodes of pneumonia.

All the children fulfilling the study criteria were included in the study over the period of 1 year of the study. Collected data were presented in percentage and proportions. Chi-square test was used to see the association, and *t*-test or non-parametric test was used to see the difference between two variables.

RESULTS

During the study period, 106 children were enrolled. Of which, 26 children were excluded as 13 lost to follow-up (7 in intervention group and 6 in placebo group), 11 parents refused consent, and 2 detected to have pulmonary tuberculosis (Fig. 1). Hence, results were analyzed for 80 children with 40 in each group.

Both the groups were comparable with respect to age, sex, low birth weight and preterm at birth, education of the parents, exposure to smoking, type of fuel used, overcrowding, and socioeconomic status (Table 1). Both the groups were similar with respect to previous history of pneumonia, nutritional status (weight for height), and presence of anemia (hemoglobin<11 g/dL) (Table 2). 24 (60%) children out of 40 in intervention group and 26 (65%) out of 40 in placebo group presented with pneumonia and the remaining (16 [40%] and 14 [35%], respectively) children presented with severe pneumonia ($p>0.05$). Hence, severity of pneumonia was also equally distributed between the two groups as difference was not statistically significant.

Chest radiograph showed the features of consolidation in 15 (37.5%) and 11 (27.5%) in intervention and placebo, respectively ($p>0.05$). Blood culture was positive in 1 (2.5%) and 2 (5%) in intervention and placebo groups, respectively ($p>0.05$). Both the groups were comparable with respect to radiological and microbiological parameters as the difference was not significant.

Most of the children in both the groups responded to Penicillin G. Antibiotics were stepped up to cefotaxime in 3 (7.5%) children of intervention group and 4 (10%) children of the control group. Time to resolution of symptoms (fever, tachypnea, and chest retractions) was almost similar (3.63±1.27 days in intervention group and 3.6±0.78 days in placebo group, $p=0.933$) and was not significant. On follow-up of these children, recurrence of pneumonia was significantly high in placebo group (20 [40%] in placebo group vs. 3 [7.5%] in intervention group, $p<0.05$). Risk of recurrence was 0.201 (95% confidence interval, 0.069–0.587) in the intervention group. All the children responded to

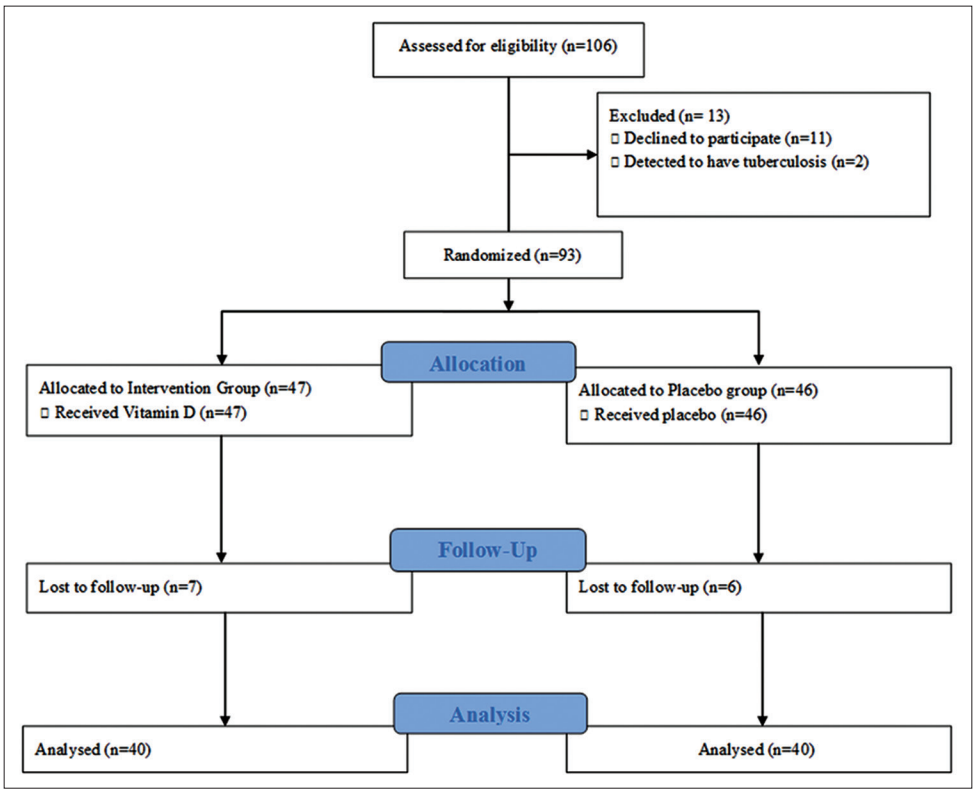

Figure 1: Flow diagram

Table 1: Baseline characteristics of the groups*

Parameter	Intervention group n (%)	Placebo group n (%)
Age		
2–12 months	19 (47.5)	22 (55)
12 months–5 years	21 (52.5)	18 (45)
Boys	22 (55)	26 (65)
Parental education		
Illiterate	8 (20)	9 (22.5)
Preterm birth	7 (17.5)	5 (12.5)
Low birth weight (<2.5 kg)	4 (10)	3 (7.5)
Immunization status		
Complete	32 (80)	34 (85)
Partial	8 (20)	6 (15)
Previous episode of pneumonia	4 (10)	3 (7.5)
Exclusive breastfeeding	29 (72.5)	32 (80)
Exposure to passive smoking	5 (12.5)	7 (17.5)
Type of fuel used		
Non-LPG	22 (55)	22 (55)
Overcrowding #	20 (50)	18 (45)
Socioeconomic status		
Middle (Class III)	9 (27.5)	11 (27.5)
Lower (Class IV, V)	31 (77.5)	29 (72.5)

***p>0.05, overcrowding: >2 persons per room, >3 persons per 2 rooms, >5 persons per 3 rooms [12]**

the treatment, and none of them developed complications of pneumonia or adverse effects of Vitamin D toxicity.

DISCUSSION

This well-conducted double-blind, placebo-control, randomized trial shows that supplementation with Vitamin D along with antibiotics in children with pneumonia and severe pneumonia significantly reduces the risk of recurrence over the period of 3 months. However, it has no effect on the duration of recovery of the present episode of pneumonia.

The major limitation of our study was the small sample size, as we included children with pneumonia and severe pneumonia over the period of 12 months. Other limitation was we could not do serum levels of Vitamin D in our subjects before or after supplementation due to financial constraints. Furthermore, we could not identify the viral causes of pneumonia due to the non-availability of the facility; however, it would be equally distributed between the two groups.

The factors associated with pneumonia (birth weight, gestation, immunization status, breastfeeding, exposure to passive smoking, type of fuel used at home, anemia, socioeconomic status, housing conditions, and parental education) were equally distributed between the two groups. These were the modifiable risk factors associated with children aged between 1 month and 5 years presenting with pneumonia in an Indian study by Savitha *et al.* [13]. We excluded children with severe malnutrition as they would be supplemented with micronutrients as a part of the management. Children in our study had no clinical signs of Vitamin D deficiency and hence many not receive any Vitamin D supplementation. However, subclinical Vitamin D deficiency can be a significant

Table 2: Disease-related characteristics

Parameter	Intervention group n (%)	Placebo group n (%)
Severity of pneumonia*		
Pneumonia	24 (60)	26 (65)
Severe pneumonia	16 (40)	14 (35)
Weight for length/height*		
Median	19 (47.5)	13 (32.5)
<−1 SD	13 (32.5)	21 (52.5)
<−2 SD	8 (20)	6 (15)
Anemia (Hb<11 g/dL)*	26 (65)	33 (82.5)
Chest radiograph showing consolidation*	15 (37.5)	11 (27.5)
Failure to recover on penicillin G*	3 (7.5)	4 (10)
Blood culture positivity*	1 (2.5)	2 (5)
Time for resolution of symptoms (days) mean (SD)#	3.6 (0.78)	3.625 (1.27)
Recurrence of pneumonia$	3 (7.5)	20 (50)

*p>0.05, #Mann–Whitney U-test P=0.933, $p<0.05, SD: Standard deviation, Hb: Hemoglobin

risk factor for severe acute lower respiratory infection as shown by Wayse *et al.* in Indian children [7]. Furthermore, susceptibility to infection occurs before many of the overt manifestations of nutritional rickets might appear [14]. Our study adds further evidence of Vitamin D supplementation playing a potential role in protecting from recurrences of respiratory tract infection which may be due to the underlying subclinical Vitamin D deficiency.

There were no gross side effects (nausea, vomiting, abdominal pain, constipation, and poor feeding) detected after giving such a high dose (300,000 IU) of Vitamin D by intramuscular route. Study on children in Istanbul (aged 6–30 months) treated with the same dose of Vitamin D for rickets was found to be safe and effective [15]. We chose to give Vitamin D as a single dose instead of daily or intermittent dosage due to the concerns of compliance and its effectiveness in maintaining the serum Vitamin D levels over 2–3 months as evident in previous studies [10]. A study in Kabul showed that supplementation with quarterly bolus doses of Vitamin D (100,000 IU) did not affect the incidence or severity of the pneumonia in infants [16]. Furthermore, reliability of intermittent dosing was poor because of wide variability in the serum Vitamin D concentration achieved. Studies have shown that single oral dose led to rapid peak followed by fall of Vitamin D concentration; however, single intramuscular dose led to long-lasting serum Vitamin D levels even though it sometimes took nearly 2 months to achieve the peak concentration and which remained higher for almost a year [17].

The follow-up duration of 3 months in our study though short was appropriate to assess the effect of supplementation. Studies show that it takes nearly 2months for the peak concentration of vitamin D to be achieved after receiving single intramuscular large dose [17]. This might also be the reason why Vitamin D supplementation in our study did not reduce the duration of the current episode of pneumonia. This was also evident in previous studies by Choudhary *et al*. on Indian children [9] and by Manaseki-Holland *et al*. in Kabul [10]. The possible cause might be blood levels of Vitamin D might still be suboptimal immediately after the administration of the dose for the effect to occur.

Even though India is located in tropical region with abundant sunlight, Vitamin D deficiency is common. Several studies in South Asian population have reported high prevalence of hypovitaminosis D, despite living in areas with abundant ultraviolet B radiation. Sun-avoidant behavior leaves many dependent on diets for intake of Vitamin D, which are inadequate in fulfilling Vitamin D requirements [14]. The average adult diet typically provides <10–20% of an individual's Vitamin D stores which in a child's diet is likely to provide even lesser [18]. Breastfeeding may not provide enough Vitamin D for infants, especially if mothers are also Vitamin D deficient [7,8,19]. The complementary or replacement foods in the diets of Indian infants and children are not fortified with Vitamin D [7]. Hence, supplementation with Vitamin D remains the most appropriate option available.

However, risk of hypervitaminosis D should be kept in mind, hence, measuring the levels of Vitamin D before supplementing wherever possible would be a more rational practice. At present, due to non-availability of an optimal Vitamin D supplementation regime for skeletal or immunological functions of Vitamin D [20], more studies are needed in different settings using different dosages with a large sample size. Furthermore, there is a scope for studies on Vitamin D supplementation in other childhood infections.

CONCLUSION

Our study shows that supplementation of single high dose (300,000 IU) of Vitamin D given intramuscularly significantly reduces the recurrence of pneumonia. The present study further strengthens the evidence of Vitamin D supplementation in pneumonia which is responsible for the highest burden of childhood mortality and morbidity worldwide. This has an importance from a public health point of view in resource poor settings as a simple measure of supplementing high dose of Vitamin D (300,000 IU) during the episode of pneumonia reduces the risk of recurrence which would help to reduce the disease burden and mortality.

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