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ORIGINAL ARTICLE

Effect of Vitamin D Supplementation in the Prevention of Recurrent Pneumonia in Under-Five Children

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Abstract

Objective To assess the effect of vitamin D supplementation in the prevention of recurrent pneumonia in under-five children.

Methods The present one year 8 months longitudinal, community-based randomized controlled study included a total of 100 under-five children with pneumonia. Children were divided into two groups: intervention group (Group I: standard treatment with vitamin D 300,000 IU; $n = 50$) and control group (Group C: standard treatment only; $n = 50$). As nine samples were hemolyzed, groups I and C comprised of 46 and 45 children, respectively. The children were followed up for 1 y and signs of upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), vitamin D deficiency, and vitamin D toxicity were recorded.

Results The male to female ratio in group C and I was 1.27:1 and 1.5:1, respectively ($P = 0.420$). Age, gender, birth, anthropometric and clinical characteristics, and feeding habits were not statistically significant ($P > 0.05$) between both the cohorts (Group C and I). Children with reduced vitamin D levels were high in group C (25) when compared to the group I (15). During all the follow-ups, the URTI and LRTI episodes, severity of pneumonia, number of hospital admissions, complications, mean episodes of LRTI, and mean duration of LRTI were comparable between group I and group C ($P > 0.05$).

Conclusions Overall, the present study highlights that oral vitamin D (300,000 IU bolus dose quarterly) has some beneficial effect in the prevention of recurrent pneumonia in under-five children, although, not to a significant degree. Hence, it is recommended that further studies are required to demonstrate a significant effect of vitamin D in the prevention of pneumonia.

Keywords Lower respiratory tract infections · Recurrent pneumonia · Upper respiratory tract infections · Vitamin D · Under-five children

Introduction

Pneumonia, a pulmonary infectious disease, is the leading cause of mortality among young children [1]. Globally, every year, 43 million new cases of pneumonia are diagnosed with a mortality rate of 322 per 100,000 under-five population [1, 2]. Despite advances in the management of pneumonia, there is a need for effective novel therapies [3]. Along with antibiotics, zinc, micronutrients, and vitamin C and A supplementations have a substantial role in the management of pneumonia among young children [4].

Research indicates that vitamin D may have a potential role in protection from acute respiratory tract infections (ARTIs) by increasing the body's production of naturally-acting antibodies [5]. A study conducted also reported that children with vitamin D deficiency were 2.5 times more predisposed to pneumonia than those with normal levels of vitamin D [6]. It has also been reported that vitamin D might be used in the treatment of opportunistic and antibiotic-resistant infections [1].

Till date, various observational studies and clinical trials have been conducted in children and adults to emphasize the role of vitamin D in the treatment of pneumonia [6–10]. A randomized controlled trial reported that a single high dose of vitamin D in children with severe pneumonia reduced the recurrence of pneumonia [9]. In contrast, a recent case-control study in adults reported no significant association between vitamin D supplementation and pneumonia. Also, the study stated that vitamin D supplementation without the administration of drugs increased the risk of pneumonia [11].

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The concentrations that relate to optimum stores of vitamin D in the body are still debatable [9].

However, there is limited evidence regarding the effect of vitamin D in the resolution of pneumonia. Hence, the present study assessed the effect of vitamin D supplementation in the prevention of recurrent pneumonia in under-five children by comparing vitamin D deficiency with severity, duration, and complications of pneumonia.

Material and Methods

The present 1-y 8 mo longitudinal, community-based randomized controlled study was conducted between January 2013 and September 2014 at the Department of Pediatrics. The study was approved by the Institutional Ethical and Research Committee. All the parents/caregivers of the children were explained about the purpose of the study and a written informed consent was obtained from them before enrollment in the study. A total of 100 children with recurrent pneumonia were allocated into two groups: intervention group (Group I: standard treatment with vitamin D 300,000 IU; n = 50) and control group (Group C: standard treatment only; n = 50). As nine samples were hemolyzed, vitamin D levels were measured among 91 children in the present study (Group I = 46) and control group (Group C = 45).

All the children aged below 5 y diagnosed with pneumonia, according to World Health Organization criteria were included in the study. While, children diagnosed with rickets, vitamin D deficiency, congenital heart disease, wheezing associated with lower respiratory tract infections (LRTI), neurological illnesses, congenital anomalies (Kyphosis, scoliosis, cleft lip, and palate), measles, whooping cough, tuberculosis, and human immunodeficiency virus (HIV) infection were excluded from the study. Also, the children who were on vitamin D supplements in the last few months and did not reside for more than 1 y in the given locality were exempted from the study.

Demographic data, socioeconomic characteristics, history of the patients, and clinical presentation were obtained through an interview. Children were subjected to thorough physical examination including anthropometry, vitals, and general physical examination followed by a thorough respiratory system and systemic examination.

All the subjects enrolled in the study were subjected to venous blood sampling; 2 ml of venous blood was sampled by venipuncture and collected in a plain vacutainer. The vacutainer was placed away from light in a light proof carry box. The collected blood samples, sent to the laboratory were subjected to Electrochemiluminescence (Cobas e 411, Roche Diagnostics, USA) for the quantitative determination of total 25-hydroxyvitamin D in human serum and plasma.

Children in group I received standard treatment for pneumonia along with quarterly doses of 300,000 IU of vitamin D for 1 y in approximately 100–120 ml of milk. The vitamin D samples were individually packaged in butter paper and placed in self-sealing plastic bags. The brand used was Torflash, which constituted Cholecalciferol (Torrent Pharmaceuticals, India). The weight of the drug was 5 g (~300,000 IU). Children in group C (placebo group) received standard treatment for pneumonia with 5 g of finely ground sugar (castor sugar) packaged and used similarly as vitamin D samples.

Children in both the groups were provided with an ID card to facilitate the follow-up. They were called every 15 d, calls were made to the families to investigate for any signs of vitamin D toxicity or worsening of symptoms. Thereafter, they were followed up every 3 mo for a total of 4 visits. Medical officers were trained to examine the children and inquire for the details of the upper respiratory tract infections (URTI) (flaring of nose, throat, tonsils, sinus tenderness), LRTI (palpitation, percussion, and auscultation), signs of vitamin D deficiency (irritability, bone pain, delay in gross motor development, and seizures), and signs of vitamin D toxicity (tremors, abdominal cramps, nausea, and vomiting) encountered during the study period. Outcome variables were documented in terms of the number of episodes (URTI and LRTI), hospital admissions, duration, severity, and complications.

The data were analyzed using SPSS v 20. The categorical data were expressed as rates, ratios, and proportions; and continuous data were expressed as the mean ± standard deviation (SD). Categorical data were analyzed using chi-square and Fisher's exact test. Continuous data were compared by independentt-test. P value ≤ 0.05 was considered as statistically significant.

Results

Baseline sociodemographic and clinical characteristics of the study groups are shown in Table 1. The male to female ratio in group I and group C was 1.27:1 and 1.5:1, respectively. Most of the children in groups I (15) and C (28) were in between 4 and 5 y, and 1 and 3 y, respectively. All the patients in group C (50) and 49 patients in group I reported cough as the major symptom. History of similar complaints was reported in 45 and 48 patients in groups I and C, respectively. Three-fourths of the children in both the groups were (group I = 32; group C = 31) raised in overcrowded houses. On stratifying the duration of exposure, group I (19) and group C (23) had an exposure of 3–4 h of sunlight. Nearly three-fourths of children in both the groups had dark skin tone. However, no significant difference was found between both the groups regarding baseline characteristics such as gender (P = 0.42), age (P = 0.44), symptoms (P > 0.05), complaints noted (P > 0.22), living conditions (P > 0.05), skin tone (P = 0.67), and exposure to sunlight (P = 0.70).

Table 1 Sociodemographic and clinical characteristics of the study groups

Variables	Group I, $n = 50$	Group C, $n = 50$
Gender		
Male	28 (56)	30 (60)
Female	22 (44)	20 (40)
Age-group (years)		
≤ 1	5 (10)	5 (10)
> 1–2	11 (22)	14 (28)
> 2–3	11 (22)	14 (28)
> 3–4	8 (16)	10 (20)
> 4–5	15 (30)	7 (14)
Symptoms		
Cough	49 (98)	50 (100)
Fever	48 (96)	46 (92)
Hurried breathing	13 (26)	8 (16)
Difficulty in feeding	14 (28)	8 (16)
Convulsions	3 (6)	1 (2)
Vomiting	11 (22)	12 (24)
Lethargy	0	1 (2)
History of similar complaints	45 (90)	48 (96)
Hospital admission in the past 2 mo	5 (10)	2 (4)
Clinical signs		
Heart rate (beats/min)	101.06 ± 10.35	102.44 ± 9.48
Respiratory rate (beats/min)	32.24 ± 5.09	32.44 ± 5.47
Tachypnea	17 (34)	14 (28)
Adventitious sounds	18 (36)	16 (32)
Living conditions		
Type of house (Kucha)	19 (38)	24 (48)
Ventilation	28 (56)	26 (52)
Overcrowding	32 (64)	31 (62)
Exposure to sunlight (hours)		
Nil	6 (12)	3 (6)
1–2	13 (26)	13 (26)
3–4	19 (38)	23 (46)
5–6	12 (24)	11 (22)
Skin tone		
Dark	32 (64)	34 (68)
Fair	18 (36)	16 (32)

Data are presented as 'number (%)' or 'mean ± SD'; *C* Control group; *I* Interventional group

Table 2 shows anthropometric and birth characteristics, feeding patterns, and vitamin D levels of the study groups. Mean anthropometrical indices *i.e.*, height, weight, and head circumference were quite high in group I compared to group C. However, the difference was not statistically significant ($P > 0.05$). Vaginal mode of delivery was recorded in most of the patients in both the groups I (46) and C (47). Birth weight of 2.5–3.5 kg was recorded in most of the patients in both the groups I (35) and C (34). Three-fourths of the children in group I (44) and C (37) were born at full-term. All the children in group I (50) and 49 children in group C were completely immunized. Most of the children in both the groups received exclusive breastfeeding (41 in each group) with a duration of 6 mo (22 in each group). At the time of the study, most of the children (34 in each group) followed a mixed diet (vegetarian diet complemented with eggs). However, no significant difference was observed in both the groups in terms of anthropometrical indices, birth characteristics, history of breastfeeding, duration of breastfeeding, and details of complementary feeding ($P > 0.05$). Children with vitamin D levels < 20 mg/ml were high in group C when compared to group I; (25 *vs.* 15; $P = 0.07$). The mean vitamin D levels were high in

Table 2 Birth characteristics, anthropometric indices, feeding pattern, and vitamin D levels in the study population

Variables	Group I, $n = 50$	Group C, $n = 50$	P value
Anthropometric indices			
Height (cm)	92.24 ± 16.07	90.50 ± 14.93	0.576
Weight (kg)	14.70 ± 4.94	13.46 ± 4.96	0.213
Head circumference (cm)	47.99 ± 3.45	47.67 ± 2.83	0.614
Chest circumference (cm)	51.66 ± 3.68	51.96 ± 3.16	0.663
Birth characteristics			
Mode of delivery			
Vaginal	46 (92)	47 (94)	0.50
LSCS	4 (8)	3 (6)	
Birth weight (kg)			
1.5–2.49	8 (16)	10 (20)	0.96
2.5–3.5	35 (70)	34 (68)	
> 3.5	2 (4)	2 (4)	
Not known	5 (10)	4 (8)	
Gestation			
Full-term	44 (88)	37 (74)	0.07
Preterm	6 (12)	13 (26)	
History of breastfeeding			
Prelacteal feeds	21 (42)	16 (32)	1.00
Exclusive breastfeeding	41 (82)	41 (82)	
Formula feeds	9 (18)	8 (16)	
Duration of exclusive breastfeeding (months)			
< 6	9 (18)	9 (18)	1.00
6	22 (44)	22 (44)	
> 6–9	6 (12)	6 (12)	
9–12	13 (26)	13 (26)	
Details of complementary feeding			
Initiation of complementary feeding (months)			
< 6	8 (16)	8 (16)	0.98
6	21 (42)	23 (46)	
> 6–9	15 (30)	14 (27)	
9–12	6 (12)	5 (10)	
Type of complementary feed started			
Veg	49 (98)	48 (96)	1.00
Mixed	1 (2)	2 (4)	
Present diet			
Veg	16 (32)	16 (32)	1.00
Mixed	34 (68)	34 (68)	
Vitamin D levels (ng/ml)	Group I, $n = 46$	Group C, $n = 45$	0.071
< 20	15 (32.61)	25 (55.56)	
20–30	20 (43.48)	11 (24.44)	
> 30	11 (23.91)	9 (20)	

Data are presented as 'number (%)' or 'mean ± standard deviation'; *C* Control group; *I* Interventional group; *LSCS* Lower segment cesarean section

group I compared to group C, however, the difference was insignificant (22.93 ± 10.68 *vs*. 19.83 ± 13.09; $P = 0.22$).

Table 3 shows outcome variables in both the groups during the follow-up period of 1-y for every 3 mo. At the end of the fourth visit, URTI and LRTI episodes, hospital admissions, complications, and severity of pneumonia (mild and severe) were low in group I when compared to group C ($P > 0.05$). But in the 4th follow-up the number of hospital admissions were higher in intervention group compared to the control group. Of all the 26 children admitted to the hospital, the number was marginally low in intervention group than control group (11 *vs*. 15).

Table 3 Outcome variables in both the groups during the follow-up period of 1 y

Follow-up visits for every 3 mo	Group I, $n = 46$	Group C, $n = 45$	P value
URTI episodes (follow-up)			
First	29 (63.04)	27 (60)	0.765
Second	21 (45.65)	24 (53.33)	0.464
Third	15 (32.61)	10 (22.22)	0.267
Fourth	22 (47.83)	25 (55.56)	0.461
LRTI episodes (follow-up)			
First	28 (60.87)	34 (75.56)	0.133
Second	27 (58.70)	29 (64.44)	0.573
Third	26 (56.52)	27 (60)	0.737
Fourth	19 (41.30)	25 (55.56)	0.174
Hospital admissions (follow-up)			
First	2 (4.35)	6 (13.33)	0.126
Second	3 (6.52)	5 (11.11)	0.345
Third	0	1 (2.22)	0.495
Fourth	6 (13.04)	3 (6.67)	0.254
Complications (follow-up)			
First	1 (2.17)	2 (4.44)	0.492
Second	0	1 (2.22)	0.495
Third	0	0	–
Fourth	1 (2.17)	2 (4.44)	0.492
Severity of pneumonia (mild; follow-up)			
First	9 (19.56)	10 (22.22)	0.490
Second	11 (23.91)	8 (17.77)	0.678
Third	13 (28.26)	8 (17.77)	0.449
Fourth	5 (10.86)	13 (28.88)	0.070
Severity of pneumonia (moderate; follow-up)			
First	17 (36.79)	20 (44.44)	0.490
Second	13 (28.26)	18 (40)	0.678
Third	12 (26.08)	18 (40)	0.449
Fourth	11 (23.9)	6 (13.33)	0.070
Severity of pneumonia (severe; follow-up)			
First	2 (4.35)	4	0.490
Second	3 (6.52)	3 (6.67)	0.678
Third	1 (2.17)	1 (2.22)	0.449
Fourth	3 (6.52)	6 (13.33)	0.070

C Control group; *I* Interventional group; *LRTI* Lower respiratory tract infection; *URTI* Upper respiratory tract infection; Data are presented as number (%)

At the end of the fourth follow-up, the mean LTRI episodes were slightly low in group I when compared to group C (1.42 ± 0.69 *vs.* 1.72 ± 1.02; $P = 0.79$); while, the mean duration of LRTI was slightly high in group I than in group C (4.53 ± 1.93 *vs.* 3.88 ± 1.36; $P = 0.62$; Table 4).

Discussion

The prognostic role of vitamin D supplementation in the management of pneumonia among under-five children has been elucidated in present study. In the current randomized controlled study, it was observed that administration of standard treatment along with 300,000 IU of vitamin D in under-five children with pneumonia displayed beneficial effect in terms of reduced URTI and LRTI episodes, complications, and severity of pneumonia, although it was not significant.

A systematic review conducted by Kearns et al. [12] reported that quarterly mega bolus doses (~300,000 IU) of vitamin D are safe and not associated with any signs of toxicity. However, other doses (~100,00 IU) employed in the previous studies yielded little benefit [9]. Hence, a dose of 300,000 IU of vitamin

Table 4 Recurrence of lower respiratory tract infections in both the study groups

Variables	Group I, $n = 46$	Group C, $n = 45$
Mean LRTI episodes (follow-up)		
First	1.61 ± 0.83	1.32 ± 0.59
Second	1.52 ± 0.80	1.38 ± 0.62
Third	1.69 ± 0.84	1.63 ± 0.93
Fourth	1.42 ± 0.69	1.72 ± 1.02
Mean LRTI duration (follow-up)		
First	4.07 ± 1.78	3.74 ± 1.91
Second	3.96 ± 1.81	3.62 ± 1.05
Third	3.88 ± 1.51	3.67 ± 1.71
Fourth	4.53 ± 1.93	3.88 ± 1.36

C Control group; *I* Interventional group; *LRTI* Lower respiratory tract infection; Data are presented as mean ± standard deviation

D was administered in present study for a year in the group I. The vitamin D administered in all the age groups in the group I was well-tolerated without any major side effects.

In the present study, there was no significant difference between the two cohorts (Group I and Group C) regarding the baseline sociodemographic, anthropometric, birth, and clinical characteristics and the feeding patterns. Most of the patients in the age-group of 1–3 y were at risk of developing respiratory infections. The age-specific data in the present study was similar to other studies in the literature [9, 13]. Male gender was one among the risk factors in developing respiratory tract infections. These findings are in concordance with a study conducted by Dhungel et al. [14], wherein, they reported that respiratory infections are slightly higher among boys. The bias of overcrowding is a well-proven risk factor in the development of pneumonia [13]; similar to present study, wherein, most of the children grew up in overcrowded families, however the difference was insignificant. Exposure of sunlight was an insignificant risk factor in the development of respiratory infections in the present study, which is comparable to the study conducted by Oduwole et al. [15]. In the present study, birth characteristics and feeding patterns in both the groups were similar; therefore, mode of delivery, low birth weight, prelacteal feeds, formula feeds, and inadequate breastfeeding are not attributed as the risk factors in developing respiratory infections in the study groups. Premature birth can be attributed as a risk factor of vitamin D deficiency [16]. However, in the present study, although most of the children in group C were preterm babies, the difference was insignificant. Cough followed by fever were the most common symptoms encountered among the children in both the groups, in this study. The observation is similar to other studies conducted in different countries [17, 18].

Various studies concluded that children with rickets are at high risk of developing LRTI or pneumonia [19, 20]. However, despite vitamin D deficiency, none of the children in the current study had rickets or clinical signs of rickets.

Although, at the end of the fourth follow-up, children in group I reported low LRTI and URTI episodes, complication rate, and severity of pneumonia when compared with group C; however, it was insignificant. The mean episodes of LRTI were low in group I when compared to group C. However, the mean duration of LRTI was slightly longer, which could be due to pleural effusion and bronchoscopy in two of the children that required a longer duration of hospital stay. A similar randomized controlled study conducted by Holland et al. [21], reported that vitamin D supplementation along with antibiotic treatment significantly reduced the new episodes of pneumonia over a 90-d period, however severe recurrences did not differ significantly in between the groups. The study also concluded that a high-dose supplementation of vitamin D may not immediately influence the recovery from pneumonia. To authors' knowledge, this is the first longitudinal, community-based randomized controlled study, which assessed the effect of vitamin D supplementation with a higher dose (300,000 IU bolus dose, quarterly). Hence, the findings of this study could not be compared and commented upon.

Other studies reported use of different doses of vitamin D varying from daily doses of 1000–1200 IU or 2000 IU per day, to bolus doses of 100,000 IU as a single dose or repeated quarterly doses [5, 6, 9, 10, 22]. Hence, there is a need to conduct further studies to evaluate the effective optimal dose and to determine the frequency of administration (single dose or daily dose) in preventing pneumonia. Also, further studies should be conducted to determine several predisposing factors in the development of recurrent pneumonia, such as socioeconomic and nutritional status, suboptimal immunization, ethnicity, air pollution, tobacco exposure, and other underlying chronic diseases or infant prematurity among children with vitamin D supplementation.

In the present study, although the results are encouraging and supporting in determining the role of vitamin D in the prevention of pneumonia in under-five children, the results are insignificant. The probable reason might be the quarterly administration of bolus doses of vitamin D, which were not efficient in preventing pneumonia, significantly. Along with this, the study has few noting limitations. Therapeutic drug monitoring of vitamin D, which is required to assess the appropriate dose of vitamin D for clinical resolution of pneumonia, was not conducted. Only after such studies, one can conclude the effectiveness of vitamin D supplementation in the prevention of pneumonia.

Conclusions

Overall, the present study highlights that oral vitamin D (300,000 IU bolus dose, quarterly) has some beneficial effect

in the prevention of recurrent pneumonia in under-five children, although not to a significant degree. Hence, further studies are required to signify the effect of vitamin D supplementation in the prevention of pneumonia. However, addressing the issue of isolated vitamin D deficiency may not be an effective strategy to prevent recurrent pneumonia.

Authors' Contribution NS, DK, and NSM: Conceptualized the study; NS: Collected the data, literature search, and developed the manuscript; DK and NS: Analysis of data and literature search; DK and NSM: Overall supervision and intellectual input in final drafting. All authors contributed to the critical revision of the manuscript. DK is the guarantor for this article.

Compliance with Ethical Standards

Conflict of Interest None.

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