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The Role of Vitamin D Supplementation in the Prevention of Acute Respiratory Infections: A Double-Blind Randomized Controlled Trial

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ABSTRACT

We calculate the serum levels of 25 hydroxyvitamin D (25(OH)D) in patients who have been admitted to a rural hospital's paediatric ward due to acute respiratory tract infections (ARTI). We also determine the serum 25 hydroxyvitamin D [25(OH)D] levels in these patients in order to investigate the relationship between vitamin D insufficiency and respiratory tract infections. The patients were randomized into two groups (Groups A and B) using a computer-generated sequence: Group A (Vitamin D 120,000 IU with standard treatment., n=165) and Group B (placebo with standard treatment., n=153). The pharmacologist, who was not involved in the study, dispensed the identical containers (Abbott Healthcare Pvt. Ltd., India) containing Vitamin D and placebo to assigned random groups. Data regarding demographics, clinical history of patients, socioeconomic status of parents, clinical presentations and medication details were recorded in a predesigned pro forma. Out of 318 (*n*=165 in Group A and *n*=153 in Group B) patients, 200 (62.8%) were males and 118 (37.1%) were females with mean age and mean weight of 36±17.7 versus 37.2±16.4 months and 13.2±4.5 versus12.5±4.1 kg, respectively and no significant difference was found (P>0.05) between them. Majority (77., 26.2%) of the patients were in the age group of 11-20 months. Furthermore, a trend of gradual decrease in the number of ARTI patients was observed with the progression of age till 40 months of age. We draw the conclusion that vitamin D insufficiency and respiratory tract infections are related based on the findings of this study. Measuring the levels of vitamin D before beginning any supplementation is advised, as only a small number of patients had dangerous amounts of the vitamin. As a result, vitamin D treatment may not be recommended in every instance of ARTI.

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Key Words
Hydroxyvitamin D, pneumonia, immunomodulatory

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INTRODUCTION

Despite advances in the treatment of RTIs, pneumonia is the leading cause of death in 13%-16% of hospitalized pediatric patients in India[1,2]. Hence, there is a need for effective and novel treatment modalities[3]. In addition to antibacterials, micronutrients and vitamin supplementations (especially A and C) play a significant role in the clinical resolution of RTIs[4]. Researchers indicate that probably Vitamin D has a potential role in the prevention of ARTIs by increasing the production of natural antibodies in the body[5]. A study reported Vitamin D deficiency in children as a predisposing factor to RTIs and concluded that Vitamin D-deficient children were 2.5 times more prone to RTIs, especially pneumonia, than children with adequate Vitamin D levels[6]. Vitamin D supplementation coupled with standard treatment might be useful in the treatment of antimicrobial-resistant and opportunistic infections[7]. The active form of Vitamin D (cholecalciferol) has anti-inflammatory effects on the acquired immune system by shifting CD4+ T-cells pool from a T-helper cell 1/T-helper cell 17 response to a regulatory T-cell/T-helper cell 2-dominated response[8,9].

The immune system is your body's defense system Thereby helping children to fighting infections. In children, an association between nutritional rickets with respiratory infection has long been recognized[10]. Recent epidemiological studies clearly demonstrate the link between vitamin D deficiency and the increased incidence of respiratory infections[11]. There is a possible role for vitamin D supplementation in children with respiratory tract infection. In winter season a decrease in the immunomodulatory molecule i.e. vitamin D, remains an unexplored factor that might contribute to the increased occurrence of ALRI season. Several studies have associated vitamin D deficiency with an increased risk of ARTIs and vitamin D supplementation has been proposed as a possible preventive measure against ARTIs in children[12]. This study was undertaken to estimate a possible association between vitamin D deficiency and respiratory infection by estimating serum 25 hydroxy vitamin D [25(OH)D] levels in a group of young children with ALRI children.

MATERIALS AND METHODS

The present study was conducted in Sree Mookambika Institute of Medical Sciences, Kanyakumari, Tamil Nadu, India. After obtaining written informed consent from the parents or guardians, a total of 318 patients, aged 1-5 years, with the primary diagnosis of ARTI who had not received any antimicrobial therapy for the same or any other indication in the previous week, were included. Participants with congenital abnormalities (such as scoliosis, kyphosis, cleft lip and cleft palate) and diseases like as rickets, tuberculosis, or any other chronic RTI were not allowed to participate in the study. Additionally, children who had received continuous vitamin D treatment within the previous year were not included in the study.

Using a computer-generated sequence, the patients were randomised into two groups (Groups A and B): Group A (placebo with normal treatment., n=153) and Group A (Vitamin D 120,000 IU). The pharmacologist, who was not associated with the research, was allocated random groups identical Abbott Healthcare Pvt. Ltd., India containers containing vitamin D and a placebo. A pre-made pro forma was used to collect information on demographics, clinical histories of patients, parents' socioeconomic status, clinical presentations and prescription data. After a clinical evaluation of each kid, a systemic and respiratory examination was performed. Samples of sputum or throat swabs were taken aseptically and they were submitted straight to the microbiology lab for sensitivity testing and culture. Following the collection of blood samples, the children in Group A were administered normal treatment for their individual infections in addition to once-daily oral administration of 1,20,000 IU of vitamin D3 (cholecalciferol). Afterwards, every youngster was monitored for five days in a row by consistent phone calls to gauge progress. The child was deemed completely cured the day the fever broke and they resumed acting normally and eating. After then, the patient underwent monthly follow-up for a duration of six months, during which the recurrence of an acute attack of ARTI was documented. Frequent phone conversations were used to track treatment compliance as well.

R version 3.6.0 software (Revolution Analytics, Mountain View, CA, United States) was used for statistical analysis. The Shapiro-Wilk test was used to determine whether the data were normal. The paired t-test was utilised to compare continuous variables with a normal distribution that were represented as mean±standard deviation, whereas the Chi-square test was applied to dichotomous data. In order to test for variables without a normal distribution, the Mann-Whitney U-test was used. Frequencies and percentages were used to display the category variables. Statistical significance was defined as $P<0.05$ with a 95% confidence interval (CI).

RESULTS AND DISCUSSIONS

Out of 318 (165 in Group A and 153 in Group B) patients, 200 (62.8%) were males and 118 (37.1%) were females with mean age and mean weight of 36±17.7 versus 37.2±16.4 months and 13.2±4.5 versus 12.5±4.1 kg, respectively and no significant difference was found ($P>0.05$) between them. Majority (77., 26.2%) of the patients were in the age group of 11-20 months. Furthermore, a trend of gradual decrease in the number of ARTI patients was observed with the

progression of age till 40 months of age. Later, it increased in the 51-60 (67., 23.2%) month age group. Statistically, no significant association was found between the different age groups with respect to ARTI [P=0.397., Table 1].

Table 1: Age and Gender Wise Distribution of Acute Respiratory Tract infection Patients

Age group (month., mean±SD)	Males, n (%)	Females, n (%)	Total, n (%)	P*
11 20 (15±4.1)	54 (27)	25 (21.1)	80 (25.1)	0.397
21 30 (27±3.5)	42 (21)	25 (21.1)	67 (21.0)	(χ^2=4.095)
31 40 (37±2.7)	23 (11.5)	22 (18.6)	45 (14.1)	
41 50 (44.4±5.2)	35 (17.5)	22 (18.6)	57 (17.9)	
51 60 (57±3.2)	46 (23)	24 (20.3)	69 (21.6)	

*Chi Square Test., Age Group Expressed in Mean±SD. SD=Standard Deviation., ARTI=Acute Respiratory Tract Infection

Before Vitamin D supplementation, the frequency of ARTI ranged from 3-12 per year. Only one patient in each group experienced three attacks of RTIs, while one patient in Group A experienced 12 attacks of ARTI in the previous year. In both the groups, majority of the patients experienced five or six attacks per year [Table 2]. Before Vitamin D supplementation, the mean ARTI episodes during the last 1 year in Groups A and B were 6.61±2.21 and 6.52±0.96, respectively, with no significant difference (P=0.832).

Table 2: Frequency of Acute Respiratory Tract Infection in the last 1 year Before Vitamin D Supplementation.

	Frequency (%)		
Episodes/year	Group A (n=165)	Group B (n=153)	P*
3	2 (1.2)	2 (1.3)	1
4	18 (10.9)	16 (10.4)	1
5	62 (37.5)	57 (37.2)	0.963
6	51 (30.9)	57 (37.2)	0.320
7	20 (12.1)	15 (9.8)	0.489
8	4 (2.4)	6 (3.9)	0.637
9	3 (1.8)	0	-
10	3 (1.8)	0	-
12	2 (1.2)	0	-

None of the patients in either group recovered from ARTI within 3 days after Vitamin D supplementation. On the 4th day, majority of the patients in Group A (40.6%) had recovered completely compared to Group B [5.6%., Table 3]. Group A patients were 7 times (odds ratio [OR]: 7.98, CI: 4.3-14.7., P<0.0001) more likely to have a high recovery rate compared to Group B patients.

Table 3: Recovery Speed in the Groups Before Vitamin D Supplementation

Recovery speed	Group A, n (%)	Group B, n (%)	OR (95% CI)	P*
<4 days	67 (40.6)	13 (8.4)	5.32 (3.0 11.2) <0.0001	<4 days
<5 days	148 (89.6)	95 (62.0)	8.99 (4.6 14.9) <0.0001	<5 days

*Chi Square Test. OR=Odds Ratio., CI=Confidence Interval

In both the groups, the frequencies of ARTI reduced from 3-12 (during the last 1 year before treatment) to 1-4 (during treatment post 6 months). ARTI frequencies were found to be decreased in both the groups during treatment post 6 months [Table 4]. The proportion of three or four episodes of ARTI was significantly less in Group A (7.2%) compared to Group B (32.6%., P<0.00001).

Table 4: Frequency of Acute Respiratory Tract Infection During 6 Months After Vitamin D Supplementation

	Frequency (%)		
ARTI Episodes	Group A (n=165)	Group B (n=153)	P*
1	24 (14.5)	6 (3.9)	0.004
2	127 (76.9)	95 (62.0)	0.001
3	12 (7.2)	50 (32.6)	<0.00001
4	2 (1.2)	2 (1.3)	1

*Proportion Z Test. ARTI=Acute Respiratory Tract Infection

The effect of Vitamin D supplementation in ARTI in under five children was studied at a bolus dose of 120,000 IU only once as previously established studies reported little benefit at smaller doses (10,000 IU). It is reported that quarterly doses of Vitamin D (up to 300,000 IU) are more safe and effective and not associated with any Vitamin D related toxicity.13 Accordingly, none of the patients in this study experienced any signs of Vitamin D toxicity. In the current study, majority of the patients in Group A (40%) recovered completely within 4 days compared to Group B (5.6%), indicating that the speed of recovery was better in patients who received Vitamin D along with standard treatment of ARTI. Wayse *et al.* conducted a study in under five children with lower RTI and reported that low levels of Vitamin D3 were one of the risk factors for severe acute lower RTIs[14]. Ginde *et al.* performed the secondary analysis of the third National Health and Nutrition Examination Survey regarding the association between serum Vitamin D3 level and upper RTI[15]. They concluded that serum Vitamin D3 levels are inversely associated with ARTI. However, they had included all age groups in their study and not studied the recovery rate of ARTI after correction of Vitamin D deficiency[15].

Similarly studies conducted by Mc Nally[16] found that significantly more children admitted to the pediatric intensive care unit with ALRI were vitamin D deficient. In a study by Esposito[17] Here they found that associated vitamin D deficiency is with an increased risk of RTIs and vitamin D supplementation has been proposed as a possible preventive measure against RTIs in children. In this regard, it is very important to understand the definition and insufficiency of vitamin D and when and how to treat this condition. Unfortunately, there is no consensus, although a level of at least 10 ng/mL 25-hydroxycholecalciferol (25[OH] D) is thought to be necessary to promote bone mineralization and calcium homeostasis and a concentration between 20 ng/mL and 50 ng/mL is considered adequate to provide an immunomodulatory effect. Available data support a role for vitamin D deficiency in reducing the risk of

pediatric tuberculosis, recurrent acute otitis media, and severe bronchiolitis, whereas further studies are needed to confirm an association in children with recurrent pharyngo-tonsillitis, acute rhinosinusitis and community-acquired pneumonia. In our study we also found that 15% (n=8) had the levels in the toxic range, this figure is quite alarming as Frequent and unnecessary supplementation of vitamin D in treatment of respiratory infections is practiced by many doctors before they are referred to our hospital. Antibiotics are the mainstay of treatment for pneumonia. In the developing countries, zinc and vitamin A supplementation has been studied for the prevention and treatment of ARI. There is bombardment of the fact that Vitamin D is considered to be important for a healthy immune system. Vitamin D supplementation reduces frequency of respiratory tract infections (RTIs) and prolongs the time of the second ARTI in adult patients with frequent RTIs. This practice of supplementation is sometimes followed in pediatrics, but it is absolutely essential that the levels of vitamin D should be checked and then only the supplements should be given[3].

Although the findings are encouraging in demonstrating Vitamin D's role in the prevention of ARTI in under five children, the results are not conclusive, probably due to single dose administration of Vitamin D. In addition, this study has a major limitation that therapeutic drug monitoring (TDM) of Vitamin D was not performed to assess the optimal therapeutic dose of Vitamin D and its frequency of administration for resolution of RTIs. Further studies should be encouraged on TDM of Vitamin D and to determine the predisposing factors such as nutritional and socioeconomic status in RTIs.

CONCLUSION

Children who took supplements of vitamin D recovered from ARTIs more quickly and had fewer ARTI attacks overall. We draw the conclusion that vitamin D insufficiency and respiratory tract infections are related based on the findings of this study. Measuring the levels of vitamin D before beginning any supplementation is advised, as only a small number of patients had dangerous amounts of the vitamin. As a result, vitamin D treatment may not be recommended in every instance of ARTI.

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