The Professional Medical Journal
www.theprofesional.com

DOI: 10.29309/TPMJ/18.4508

ORIGINAL PROF-4508

VITAMIN D AND PNEUMONIA;

ROLE OF VITAMIN D SUPPLEMENTATION IN CHILDREN WITH PNEUMONIA, A RANDOMISED CONTROL TRIAL.

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Article received on:
14/11/2017
Accepted for publication:
15/02/2018
Received after proof reading:
05/04/2018

ABSTRACT… Background: Pneumonia is lower respiratory tract infection (LRTI) and represents inflammatory conditions of the lungs i.e of the lower respiratory tracts, air sacs and lung parenchyma.[1] **Objectives:** To determine the role of vitamin D supplementation in reducing morbidity in children with pneumonia. **Study Design:** Randomized Controlled trial. **Place and Duration of Study:** Pediatric Department, Mayo Hospital Lahore from December 2014 to May 2015. **Patient & Methods:** Two hundred children of age 2 – 59 months with pneumonia (fever, cough, tachypnea, and subcostal recessions) and low vitamin D level (< 20 ng/ml) were included in the study. One Hundred pneumonia patients received antibiotics (group A) and vitamins D (100,000 IU) while another group of hundred patients received only antibiotics without vitamin supplementation (group B). When respiratory distress settled, length of stay in hospital was calculated at the time of discharged. All patients were followed in pediatric OPDs for 3 months after in-hospital treatment to pick recurrence of pneumonia symptoms (if any). **Results:** The mean recovery time for vitamin D group (5.7 +2.8 days) and non-vitamin D (6.1+2.8 days) was almost same with P=0.29. But the frequency of repeated episodes of pneumonia within 30 days of treatment was lower in intervention group n=4 (2%) than the non-intervention group n=18 (9%) (P = 0.002). **Conclusion:** 100,000 IU of vitamin D given once during treatment of pneumonia decreases the chances of recurrence in the next 30 days.

Key words: Vitamin D Supplement, LRTI, Pneumonia, Vitamin D Deficiency.

Article Citation: Shamaoon M, Maryam, Ahsan M, Ahmad R. Vitamin D and Pneumonia; Role of vitamin D supplementation in children with pneumonia, a randomised control trial. Professional Med J 2018; 25(4):532-537.
DOI:10.29309/TPMJ/18.4508

INTRODUCTION

Lower respiratory tract infections (LRTI) including pneumonia represent inflammatory conditions of the lungs i.e of the lower respiratory tracts, air-sacs and parenchyma. These infections lead to major morbidity and mortality in children in developing nations.[1,2] Patients presents with fever, cough, tachypnea and breathing difficulty. Clinical examination of the chest and plain x-ray of the chest is required for diagnosis.[2] Infants with severe respiratory tract infection may develop cyanosis, grunting and poor respiratory effort. Older children may present with associated chest pain or gastrointestinal symptoms as abdominal pain, vomiting, diarrhea, anorexia.[1]

According to an estimate by WHO, more than one and a half million pneumonia patients are seen in an year and children of less than 5 years of age and about 20 million cases requiring hospital admission.[1] Around 7 – 13% of these cases are serious enough that can lead to drastic results if not properly managed. Pneumonia is the main etiology behind the mortality of patients of age <5 years, about one and a half million patients die of pneumonia every year (18% of total deaths).[2,3]

Activated vitamin D_3 promotes growth of bones, especially in growing children and deficiency can lead to vitamin D deficiency rickets. Deficiency of vitamin D in children makes them more prone to develop respiratory infections.[2] Sunlight exposure of the skin promotes the synthesis and activation of vitamin D for body use. Various dietary sources of vitamin D include egg yolk and cod liver oil.[2] Binding of activated cholecalciferol to specific receptors promotes the synthesis of cathecilidins, these are integral part of innate immunity in the

body.[2] Activated cholicalceferol also promotes monocyte production and there conversion into macrophages, thus promoting body's immune response.[2] Charan et al reported that 21.8% patients on vitamin D supplementation vs 30% patients in non-vitamin D supplemented group had recurrent infections.[9] Semira Manaseki-Holland et al reported that pneumonia recurrence in 3 months after discharge was 45% vitamin D supplemented (100,000 IU) children compared to 58% in the control group; but no additional effect on the duration of hospital stay.[2]

Salem M. Banajeh reported that compared to normal children rickets is associated with fourfold increase chances of treatment failure.[2] Bergman P et al reported that the patients with vitamin D supplementation had less number of positive microbiological findings and bacterial cultures (36% vs. 41%) than the placebo group. These findings significantly support the preventive role of vitamin D from infections in the body and possibly diminish the duration of antibiotic required.[2]

Roth DE et al studied polymorphisms in the gene encoding for vitamin D rickets had strong association with increased risk of infection of the lower respiratory tract.[2] Choudhary N and Gupta P reported that supplementation of vitamin D orally for five days has no benefit in patients of less than five years with severe pneumonia.[2]

Manaseki-Holland S et al concluded after a study that stat doses of vitamin D given orally in children after every quarter was not effective in the reduction of the incidence and severity of pneumonia in those infants.[8]

We designed a study to test the hypothesis that 100,000 units of vitamin D3 supplementation once on the first day of admission in children with pneumonia decreases the duration of hospitalization. In addition, it also decreases the recurrence of pneumonia within three months following the episode of lower respiratory tract infection.

PATIENTS & METHOD

Two hundred children with pneumonia and low vitamin D level (< 20 ng/ml) of age 2 – 59 months admitted in emergency or pediatric ward, Mayo Hospital, Lahore between December 2014 to May 2015 were included in this randomized clinical trial after approval from the Mayo hospital ethical committee through non-probability purposive sampling. A child with history of cough and/or difficulty in breathing with fever (axillary temperature > 99°F), tachypnea (more respiratory rate for the age) with or without chest in-drawings (as observed by a person who is blind regarding the treatment) and consolidation seen on chest x-ray was diagnosed as pneumonia.[31,32] Sample size of 200 patients (100 in each group) was calculated by using 80% power, 95% confidence level, 9% absolute precision and 0.05 level of significance and by taking expected percentage of repeat episode of pneumonia in patients who were given and not given vitamin D as 45% and 58% respectively.[10]

Patients having very severe disease (total score >2), acute asthma, tuberculosis, congenital heart disease (CHD) or any of these is suspected after examination, 3rd degree malnutrition (weight-for age < -2SD and those already on vitamin D supplements or have normal vitamin D level (>20 ng/ml) were excluded.

After written informed consent from the parents, age, gender, height, weight, relevant history and physical exam, all the findings were documented and blood sample was sent to check vitamin D level along with other required lab and radiological investigations. Using computer table generated numbers, children were randomly assigned a group i.e. the group A and group B. Appropriate antibiotics were given as treatment of pneumonia. Patients in group A received intramuscular one lakh units of vitamin D on the first day of hospital treatment in addition to antibiotics. Children of the other group B only received suitable antibiotics. Any improvement or deterioration in the condition of the patient was noted. Patients with normal respiratory rate for age and no intercostal and subcostal recessions were discharged.

Outcome of the trial included length of stay at hospital and recurrence of symptoms within 3

months after discharge. All patients were kept on regular follow-up in the next three months for any recurrence of symptoms. The mother was trained during the hospital stay to detect tachypnea and chest in-drawings at home and was advised an immediate visit to the follow-up clinic or pediatrician during any such episode. Data were entered and analyzed through SPSS-20. Mean ± SD was calculated for quantitative variables. Frequency and percentage was calculated for qualitative variables.

Chi-square test was applied for categorical variables and t- test for continuous variables. (P-value < 0.05 was taken significant). Effect modifier like type of antibiotic used was stratified and post-stratification chi square was applied.

RESULTS

Of the total 200 patients, the mean age was 7.5 month whereas SD, median and range among both the groups were nearly same. Each group had equal number of patients and none of the patients was dropped out from the study. The male to female ratio was 1.6:1, males n=122 (61%) and females n=78 (39%). Predominant symptoms at presentation were tachypnea (99%), chest in-drawings (43%), cough (94%) and fever (85%). Symptoms were equally distributed in both the genders. Irrespective of gender the illness duration before admission was 3.5 days. Mean respiratory rate in both genders was fairly equal. On clinical examination, 68.5% patients had crepitation in chest. While examining each patient, 36% had no malnutrition, 25% had grade I malnutrition and 39% grade II malnutrition. Homogenous consolidation of the lungs was seen on chest x-ray of more than fifty percent patients (Figure-1). The respiratory rate and chest auscultation at the time of discharge of both groups were normal. Mean of hospital stay was 5.7 days in the interventional group whereas 6.1 days for non-vitamin D group. It clearly shows that patients on vitamin D supplementation had lesser duration of hospital stay (Table-I), with a p value of 0.28 (non-significant).

Table-II shows the follow-up of patients after discharge after 1st, 2nd and 3rd month for any episode of lower respiratory tract infection. During 1st month, 22/200 children had recurrence of pneumonia including 4 cases receiving vitamin D therapyvs18 children in the other group. P value was calculated and came significant (p=0.002).

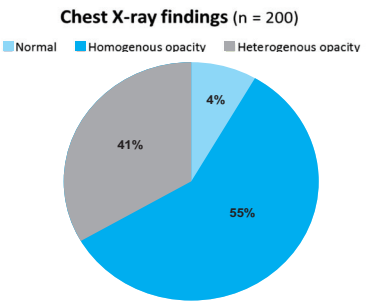

Figure-1. Showing chest X Ray findings in the patients

	Hospital stay (days)				
	Mean	p	SD	Median	Range
Vitamin D group	5.7	0.28	2.7	5.3	1.3-14.7
No vitamin D	6.1		2.8	5.7	1.1-14.4
Total	5.9	-	2.8	5.7	1.1-14.7

Table-I. Showing comparison of hospital stay between two groups

	Intervention	No.	%	Chi sq.	P
1st month	Vitamin D given	4	4	10.0	**0.002**
	No vitamin D	18	18		
	Total	22	22	-	-
2nd month	Vitamin D given	4	4	1.4	0.23
	No vitamin D	8	8		
	Total	12	12	-	-
3rd month	Vitamin D given	0	0	2.0	0.16
	No vitamin D	2	2		
	Total	2	2	-	-

Table-II. Comparison of patients with repeat episodes of pneumonia between the intervention and non intervention groups

On further follow-up, 12 patients came with symptoms of respiratory tract infection in the second month; 4 in vitamin D group and 8 in other group (p=0.23). Similarly in 3rd month two patients not of the control group came with symptoms of respiratory infection, (p value = 0.16). As a whole, the recurrence of pneumonia or lower respiratory tract infection symptoms was more in the group of patients who were not given vitamin D_3 (14%) as compared to the group of patients receiving vitamin D_3 (4%). Limitations of the study included

DISCUSSION

In our study, average age of patients having pneumonia was 7.5 months. Demographic survey of Pakistan showed age of presentation of children with pneumonia is 6 to 11 months.[2] In this study, male to female ratio was 1.6:1, which is in contrast to the other studies with no difference in gender distribution.[8,10] Demographic survey of Pakistan also showed no difference among male and female children with pneumonia.[15] Cause of male predominance may be due to social setup with lesser number of female children brought for treatment. Tachypnea, cough and fever, these were the major symptoms with which patients with admitted. Most of these had crepitation in the chest.[1,2] This study showed very few children with bronchial breathing and decreased air entry.[1]

Nearly 2/3rd of the patients were malnourished showing direct relation of pneumonia with nutritional status of a child. The more the child is malnourished more are the chances of pneumonia.[2,3,4,5] A study showed that the proportion of moderately malnourished children included in the studies was around 25%.[2] Another study conducted at Peshawar, showed 35% children had malnutrition, 33% with grade I and 43% with grade II malnutrition which were comparable with this study.[2]

In this study, treatment protocol followed for pneumonia management was almost same for all the patients to remove bias. This clinical trial showed that vitamin D given with treatment of lower respiratory tract infection reduces the risk of recurrence of symptoms over three months. Length of stay in hospital varied from patient to patient. At the end we came with a conclusion that vitamin D given in any dose during treatment have no significant role in early recovery from disease, but may decrease the chances of recurrence of symptoms. Our results were close to many other clinical trials done previously.[10,12]

A study conducted in Kabul also proved the preventive role of vitamin D supplements in young patients with lower respiratory tract infection and decreases the risk of recurrence of symptoms for a quarter of a year. The risk of recurrence of symptoms was more (58%) in placebo group compared to the vitamin D group (45%).[10] In a review article on the role of vitamin D supplementation in children with lower respiratory tract infection, Charan et al concluded in favor of vitamin D supplementation as it decreases the chances of infections and vitamin D deficiency increases the risk of respiratory infections.[9] Another study conducted in Japan showed significant decline in influenza among school children.[2] In two different studies one in India and other in Afghanistan vitamin D supplementation in pneumonia patients showed no effect on the recovery time.[8,14]

Das R et al compared single dose vs multiple daily doses of vitamin D.[14] Many studies showed that daily dose schedule shows a better therapeutic effect than a large bolus dose, daily doses were more effective.[3,4,5,6]

This study supports the prevention given by vitamin D from infections by enhancing immunity. Studies show that the biologically active metabolite of vitamin D promotes immune response of the body.[3,4]

Prevention of recurrence of infections in children improves overall body state and reduces the disease burden. In this clinical trial, all variables were closely accessed by trained doctors and pneumonia was diagnosed by using both the IMCI criterion and reporting of chest x-rays from radiologists. Previous clinical trials either took clinical or the radiographic changes in the diagnosis of pneumonia.[8,10,11,3] This clinical trial was one of the very first controlled trials carried

out in our country to prove the protective role of vitamin D in young patients of lower respiratory tract infection.

LIMITATIONS

Complete follow-up after every two weeks was not possible for all the patients at the hospital, so we had to rely on monthly follow-up of the patients. Patients belonged to different socioeconomic background which affects the heath care and follow-up.

CONCLUSION

Our randomized clinical trial proved the preventive role of vitamin D supplementation (100,000 IU) in the recurrence of lower respiratory tract infections among patients of childhood category. Vitamin D can help a child for a little early recovery (although not statistically significant). As significant number of Pakistani children are vitamin D deficient, and develop frequent episodes of pneumonia, administering vitamin D may help to decrease the morbidity and mortality. However, clinical trials on a much larger scale are required for more evidence.

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4	Rahman Ahmad	Data collection	