



## THE EFFECTS OF VITAMIN D SUPPLEMENTATION IN RESPIRATORY INDEX OF SEVERITY IN CHILDREN (RISC) OF HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA: A DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL

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### TYPE OF ARTICLE: ORIGINAL

#### ABSTRACT

**Background:** Many children are affected by pneumonia and its complications annually, despite the fact that there are several known risk factors; vitamin D deficiency may play a role in this disease.

**Objective:** The aim of this study was to determine the efficacy of vitamin D supplementation in Respiratory Index of Severity in Children (RISC) hospitalized clinical outcomes of hospitalized patients with community-acquired pneumonia.

**Methods:** This randomized double-blind clinical trial was conducted on children from 2 months to 6 years old with pneumonia, hospitalized at Bandar Abbas Pediatric Hospital of Iran between January 2015 and 2016. Children were randomly divided into two groups of A: received vitamin D (at a dose of 50,000 IU per day for 2 days) in addition to routine treatment of pneumonia, and B: received placebo instead of vitamin D. The primary outcome was RISC alterations before and after interventions. The statistical software SPSS 16 and Chi-square and Independent Samples T tests were used for analysis.

**Results:** One hundred patients were studied. The demographic variables were similar in two groups ( $P > 0.05$ ). There was no significant difference between the vitamin D group and control group in percentage of patients with wheezing ( $P = 0.408$ ), fever ( $P = 0.393$ ), retraction ( $P = 0.146$ ), crackles ( $P = 0.753$ ), tachypnea ( $P = 0.105$ ), and poor feeding ( $P = 0.157$ ). The duration of antibiotic use was significantly lower in vitamin D group ( $4.18 \pm 1.40$  versus  $3.22 \pm 1.32$  days;  $P = 0.001$ ).

**Conclusion:** According to the results, it seems that vitamin D supplementation may reduce the duration of antibiotic therapy in children with pneumonia.

**Clinical Trial Registration:** The trial was registered at the Registry of Clinical Trials (<http://www.clinicaltrials.gov>) with the ID: NCT02936895.

**KEYWORDS:** Pneumonia, vitamin D, children

### 1. INTRODUCTION

Pneumonia is the leading cause of hospitalization of children in the United States, with medical costs of almost one billion dollars in 2009 (1). It is estimated that about 120 million children under 5 years old had pneumonia in 2010-2011, and more than 10% of them had severe episodes of the disease (2). It is estimated that 0.22 episodes of pneumonia occurs per child in developing countries worldwide (3). Some studies have shown that supplementing with vitamin D reduces disease of the respiratory tract infection (4-6). Other studies have shown anti-inflammatory effect of vitamin D in cell lines (7). Studies regarding the role of vitamin D supplementation in pneumonia in children are inadequate, thus inconclusive about its role. Epidemiological studies show the role of vitamin D

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deficiency in autoimmune diseases, cancer, cardiovascular disease, depression, dementia, infectious diseases, and muscle loss (8). In developing countries, such as Iran, knowledge about the role of vitamin D supplementation in pneumonia may be helpful for decreasing the rate of pneumonia in children. However, more studies in this field are needed. The aim of this study was to determine the efficacy of vitamin D supplementation in Respiratory Index of Severity in Children (RISC) hospitalized clinical outcomes of hospitalized patients with community-acquired pneumonia.

## **2. MATERIAL AND METHODS**

### **2.1. Research design and setting**

This randomized, double blind clinical trial study was conducted on children aged 2 months to 6 years old, hospitalized with pneumonia at Children's Hospital of Bandar Abbas, Iran between January 2015 and 2016.

### **2.2. Sampling**

Considering the confidence interval of 95%, power of 80%, and standard deviation of 1.5 days in each group for duration of hospitalization a sample size of 72 was calculated to detect one day difference in duration of hospitalization in two groups.

### **2.3. Selection criteria**

The inclusion criteria were 1) aged between 2 months to 6 years (A- less than 2 years, B- 2 to 4 years, C- 4 to 6 years); 2) fever, cough, audible findings in lungs (rale), respiratory distress symptoms (increased respiratory rate based on age: infants more than 50 minutes, 1 to 5 years more than 40 per minute, over 5 years more than 30 per minute); 3) chest x-ray changes revealing pneumonia diagnosis. Exclusion criteria were the following: 1) immunocompromised patients or receiving immunosuppressive drugs; 2) description of air ways hyperactivity and asthma or audible wheezing in lungs; 3) allergies, nasal polyps, nasal inhaled medications up to one month prior to the study (corticosteroids or cromolyn); 4) hospitalized more than 24 hours (in case of hospitalization longer than 24 hours, the patient will not be enrolled in the study); 5) receiving high doses of vitamin D; 6) the ban on vitamin D as Hypercalcemia and hypervitaminosis D; 7) parents unwillingness to participate in the study, after explanation.

### **2.4. Blinding, allocation and Interventions**

Patients were randomly assigned into two groups using a computerized system. Patients and outcome assessors were unaware of the patients' allocation. In this study, subjects were divided randomly into two groups of 50 children. Treatment groups in addition to standard treatment (standard treatment for ceftriaxone is injection), vitamin D (at a dose of 50,000 IU per day for 2 days) and the control group in addition to the standard treatment (standard treatment for ceftriaxone is injection), olive oil (as a placebo) were administered respectively.

### **2.5. Outcomes**

Then the subjects, according to the criteria for discharge, including fever, cough, and chest pain, decres in respiratory rate and duration of hospital stay, were studied. Given that some patients were accepted at night, the number of hospitalization days up to 4 hours (16/0 day) were added or subtracted. Also, to assess the clinical symptoms (including cough, fever, respiratory rate, etc.) a check list was prepared of the patients during hospitalization, by the physician. A checklist of relevant information including age, sex and clinical findings and treatment was completed by the doctor, recorded and then encoded using statistical software. For determining severity of pneumonia, RISC (Respiratory Index of Severity in Children) scoring system was used, including oxygen saturation, chest retraction, wheezing and refusal to feed, together with growth standards (weight for age). According to the scoring system, patients are divided into 2 groups of severe pneumonia ( $Z \geq 6$ ) and non-severe (9). The research tools included testimonial by parents to participate in the investigation, as well as the check lists made by the physician based on symptoms in the patient list, and 100,000 units of eatable vitamin D (at a dose of 50,000 units for 2 days) as adjuvant therapy (as a placebo) was administered to hospitalized patients with pneumonia.

### **2.6. Research ethics**

A written informed consent was obtained from all parents of children. Patients' information was kept confidential. Also, patients were able to exit the study whenever they decided. The study was approved by the Ethics Committee of Hormozgan University of Medical Sciences. The trial was registered at the Registry of Clinical Trials (<http://www.clinicaltrials.gov>) with the ID: NCT02936895.

**2.7. Statistical analyses**

Also, data were analyzed by SPSS for Windows, Version 16.0 (Chicago, SPSS Inc, Released 2007) by means of independent samples t-test and Chi-square tests.

**3. RESULTS**

This study was conducted on 100 children with pneumonia. There were 30 males in the control group (61.2 percent) and 20 females (38.8 percent) and in the vitamin D group, 27 males (54%) and 23 females (46 percent). The average age of participants in the vitamin D group was 17.6 months and in the control group it was 16.8 months. According to the RISC scoring system, all patients entered in the study, placed into not severe acquired pneumonia ( $Z < 6$ ).

**Table 1.** Clinical symptoms and physical exam in hospitalized patients with pneumonia in pediatric hospital

Parameter	Vitamin D group, n (%)	Control group, n (%)	p-value
Fever	41 (82 %)	43(86 %)	0.393
Cough	50 (100%)	50 (100 %)	-
Retraction	20 (40 %)	14 (28 %)	0.146
Wheeze	11 (22 %)	13 (26 %)	0.408
Rale	49 (98 %)	49 (98 %)	0.753
Tachypnea	30 (60 %)	22 (44 %)	0.105
O2 sat $\leq$ 90	0 (0 %)	0 (0 %)	-
Poor feeding	25 (50 %)	19 (38 %)	0.157

**Table 2.** Clinical symptoms and physical exam in hospitalized patients with pneumonia in pediatric hospital

Parameters	Groups	Mean $\pm$ SD	p-value
Duration of fever (days)	Control	3.82 $\pm$ 2.62	0.702
	Vitamin D	3.62 $\pm$ 2.58	
Respiration rate (per min)	Control	46.04 $\pm$ 15.21	0.480
	Vitamin D	48.08 $\pm$ 13.5	
Pulse rate (per min)	Control	122.78 $\pm$ 14.44	0.150
	Vitamin D	118.520 $\pm$ 14.88	
Age (months)	Control	16.86 $\pm$ 16.85	0.809
	Vitamin D	17.68 $\pm$ 17.03	
Duration of antibiotic therapy (days)	Control	4.18 $\pm$ 1.40	0.001
	Vitamin D	3.22 $\pm$ 1.32	

**4. DISCUSSION**

Today, there are many studies about the relationship between vitamin D and pneumonia around the world. Numbers of studies have shown that some of the vitamin D receptor gene polymorphisms can be effective in community-acquired pneumonia among children (10). The aim of this study was to compare the efficacy of vitamin D supplementation in patients with community-acquired pneumonia that were admitted to the Pediatric Hospital of Bandar Abbas in 2016. The results indicated that vitamin D supplementation in combination with antibiotics for treating pneumonia in patients, reduces the duration of patient admission (22.3 days in the control group vs. 18.4 days in the control group,  $P < 0.05$ ), which indicates the positive effect of vitamin D in improving the CAP. This was similar to findings in studies from Holter et al (11), Jovanovich et al (12), Remmelts and colleagues (13), Larkin and colleagues (14), Roth and colleagues (15), Leis and colleagues (16), Monlezun and colleagues (17) and Zeghoud and colleagues (18). However, they were not consistent with studies by Kim and colleagues (19), Manaseki-Holland and colleagues (20), Choudhary et al (9) or Ranjan Das and colleagues (21). In Manaseki-Holland and colleagues(20) studies, 100,000 units of eatable vitamin D, as a starting dose for treatment in children aged 1 to 26 months, and also in the Choudhary et al (9) study, short-term supplementation of 2000 IU of vitamin D orally for 5 days in pneumonia in children under five years, had no beneficial effect. However, in the Ranjan Das and colleagues (21) study and the Zeghoud and colleagues (18) study, usage of a single dose of 100,000 units has a significant beneficial effect in the treatment of pneumonia, but the Leis and colleagues (16) study demonstrated that the consumption of vitamin D, less than 80 IU/kg/day, is at four times higher risk of pneumonia than children who consumed more than 80 IU/kg/day. The argument made in some of the studies indicates that the use of a single dose of vitamin D is less effective (9) this could be one of the reasons of the mismatch in studies of other researchers.

Also in Choudhary and colleagues' study, due to concerns about the complications of vitamin D and the widespread prevalence of vitamin D deficiency in the population under study, low dosage of vitamin D was prescribed, this is another reason for the incompatibility of the current study and that with Goubet and colleagues. Despite close monitoring by the author, no side effects were observed, although theoretically, increase in level of vitamin D in the body is possible, it's possible to provide the best protection from the lack of this vitamin without an increase in the level of it in high risk children with clear instructions about supplements and 100,000 units of vitamin D, even with normal range from vitamin D base line, and no known side effect is reported (18). So the evidence indicates that the recommended dose in this study is harmless and effective. Also due to lack of determining the basic level of vitamin D in patients with various foundations and causes of pneumonia, according to geographic area, age, time/season and the social and economic level of the population under study, results are different. One of the limits of this study is to provide the consent of the parents and discharge to complete the course of treatment and recovery.

## 5. CONCLUSIONS

The study found that the use of vitamin D supplementation with dosage of 50,000 daily for 2 days with antibiotics in hospitalized patients with a primary diagnosis of pneumonia, has been associated with reduced hospitalization time.

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## CONFLICT OF INTEREST:

There is no conflict of interest to be declared.

## AUTHORS' CONTRIBUTIONS:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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