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The Effect of Vitamin-D Supplementation in Severe Pneumonia Among Infants

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Abstract

Background: Worldwide, acute lower respiratory tract infection (ALRTI) is a leading cause of mortality in children less than 5 years old, more than 90% are in developing countries. Pneumonia is the leading infectious cause of death in children, accounting for 18.3% of all deaths in children less than 5 years of age. Vitamin D is thought to have roles in the improvement of immune function and the reduction of inflammation and may reduce respiratory tract infection susceptibility in children. Vitamin D has an important influence on the host's immune system, modulating both innate and adaptive immunity and regulating the inflammatory cascade.

Aim of Study: We aimed to compare the duration and outcome of severe pneumonia of children in the two study groups receiving the standard therapy (appropriate antibiotic and other supportive therapy) with those receiving vitamin D3 supplementation in addition to the standard therapy. Our hypothesis is that vitamin D supplementation decreases the duration of resolution of severe pneumonia in children less than two years of age.

Patients and Methods: This was a double-blinded, randomized, placebo-controlled trial undertaken in the Children University Hospital, Assiut University during winter. Infants with severe pneumonia between the ages of 3 and 23 months are studied. Patients were randomized to receive vitamin D3 treatment (intervention group) or placebo (control group) to assess the clinical benefit of oral supplementation of vitamin D3, in addition to standard antibiotic and other supportive therapy, to hospitalized infants less than two years of either sex with severe pneumonia.

Results: The results of this small randomized controlled clinical trial indicate that short-term supplementation with vitamin D along with antibiotic treatment, significantly reduces the mean time taken for resolution of severe pneumonia (p<0.001) and the mean time taken for the improvement of oral feeding (p<0.05), in the intervention group receiving vitamin D 100IU/kg for at least 5 days from the first day of admission. Vitamin D supplementation was well tolerated in all patients without showing any side effects.

Key Words: *Pneumonia – Respiratory distress – Vitamin D3.*

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Introduction

WORLDWIDE, acute lower respiratory tract infection (ALRTI) is a leading cause of mortality in children less than 5 years old, more than 90% are in developing countries. Pneumonia is the leading infectious cause of death in children, accounting for 18.3% of all deaths in children less than 5 years of age [1,2].

Vitamin D is thought to have roles in the improvement of immune function and the reduction of inflammation [3] and may reduce respiratory tract infection susceptibility in children [4]. The immune enhancing actions of vitamin D include induction of monocyte differentiation, inhibition of lymphocyte proliferation, stimulation of phagocytosis dependent and antibody-dependent macrophages, and modulation of T and B lymphocytes that produce cytokines and antibodies [5].

The Vitamin D Receptors and (CYP27B 1) One alpha hydroxylase cytochrome P450 enzyme gene are present in immune cells and bronchial and pulmonary epithelial cells, and are upregulated after the ligation of specific toll-like receptors by extracellular pathogens, implicating vitamin D in innate immunity [6]. 1,25-Dihydroxy vitamin D3, acts through the vitamin D receptor (VDR), a polymorphic nuclear receptor that modulates the expression of genes involved in immune function and cytokine production [7].

So, We hypothesize that in the management of hospitalized severe pneumonia in infants, vitamin D3 supplementation, as an adjunct to the standard antibiotic and other supportive therapy, will hasten recovery from severe pneumonia, may shorten duration of severe pneumonia and also reduce the risk of new episode of pneumonia.

Patients and Methods

This was a double-blinded, randomized, placebo-controlled trial undertaken in the Children University Hospital, Assiut University from December 2015 to March 2016.

During winter, infants with severe pneumonia who presented to the pediatric pulmonology clinic within 7 days of the onset of symptoms of pneumonia were recruited into the study.

In a double-blind, randomized clinical trial, the study included 80 infants (45 boys and 35 girls) between the ages of 3 and 23 months. Patients were randomized to receive vitamin D3 treatment (intervention group) or placebo (control group). Both vitamin D3 and placebo were in drop form and were identical in shape and nearly the same taste and color.

Inclusion criteria:

- Infants of either sex from one to 23 months (less than 2 years).
- Patients attending Assiut university children hospital with clinically diagnosed severe pneumonia.
- Children with fever, cough, tachypnea and crepitations whom were diagnosed with pneumonia. Tachypnea was defined as a respiratory rate ›_50/min in children between 2-12 months and ›_40/min in 1-2 year age group. Those with pneumonia and either chest indrawing or at least one other danger signs (inability to feed, lethargy, and cyanosis) were diagnosed as having severe pneumonia.
- Radiological diagnosis of pneumonia was based on lobar or bronchopneumonic infiltration demonstrated by X-ray [8].

Exclusion criteria:

- Known cases of hypercalcemia or allergy to vitamin D, as determined by history or previous medical records.
- Congenital Heart disease, evidenced by clinical examination or past medical records.
- Renal or hepatic insufficiency, evidenced by clinical examination or past medical records.
- Known case of tuberculosis, evidenced by medical records.
- Critically ill children requiring ICU care, such as those with septic shock or cardiac arrest or apnea.
- Known case of brochiolitis, evidenced by history and clinical examination findings.
- Received vitamin D or calcium supplementation within the last 4 weeks before current admission, as evidenced by history or medical records.
- Any children diagnosed as hypernatremia during the main phase of the study.
- Any children diagnosed with rickets clinically and/or radiologically.
- Patients with gastrointestinal disease associated with malabsorption were excluded.

Collection of demographic data and baseline assessment: Baseline data were collected from all patients, including age, sex, detailed clinical history and chest examination, vital data (temperature, heart rate, respiratory rate, and blood pressure), assessment of signs of respiratory distress (tachypnea, chest retractions, grunting, and cyanosis), mental status, and anthropometric measurements (weight, length, and head circumference). The oxygen status of all patients was assessed by using a pulse oximeter in room air.

All patients were hospitalized and received treatment as in the standard protocol for treatment of pneumonia, according to the guidelines of Children University Hospital, Assiut University. The treatment included intravenous antibiotics, oxygenation, and antipyretics. Inhalation of bronchodilator was administered according to the decision of a senior pediatrician. All patients were assessed at the beginning for assessment of patient eligibility and after that the researcher followed up all patients every 6h once the medication was started. All patients were followed-up for at least 5 days in hospital; some patients had an additional hospital stay for 2-4 days. Side effects were recorded throughout the study.

The measures for the outcome of the therapy included the following:

- The child's general condition for respiratory distress:
  - Tachypnea.
  - Chest retractions.
  - Grunting.
  - Cyanosis.
- Oxygen saturation.
- Feeding status.
- Conscious level.

Primary outcome variable: The primary outcome of interest was the time to resolution of severe pneumonia. Resolution of severe pneumonia was considered when lower chest retraction and

the danger signs (inability to feed, lethargy, cyanosis or hypoxia) were no longer present.

Secondary outcome variables: The secondary outcome variables included:

1- Durations of oxygenation.

2- The time to resolution of tachypnea (respiratory rate cut off for severe pneumonia as per age), chest retractions, and other signs of respiratory distress.

3- Durations of IV therapy and inability to feed.

4- The duration of hospitalization was defined as the time (in hours) between study enrollment and discharge. The patient was considered fit for discharge when he/she was afebrile (axillary temperature <37.5ºC), tachypnea had subsided, there were no chest indrawings and oral feeding had resumed, for a minimum period of 24 hours.

Results

Table (1) and Figs. (1-3) show the clinical and demographic parameters of intervention and placebo groups before treatment. Group 1 consisted of forty children, 23 males and 17 females, aged from 2 to 22 months with mean age ± SD; 8.8±2.6. Group 2 consisted of forty children, 22 males and 18 females, aged from 3 to 23 months with mean age ± SD; 9.1 ±4.

This table shows the anthropometric data, including the weight and length of both groups. In addition, Table (1) shows some clinical parameters of both groups including; fever, dyspnea, cough, respiratory rate, oxygen saturation status, feeding status i.e. percentage of inability to feed, conscious level and lethargy. There were no significant differences between either group regarding anthropometric data, age, or other clinical parameter at the beginning of the study.

Table (2) and Fig. (4) demonstrate the proportion of patients with positive physical findings as detected by the researcher, in both groups. The most frequent abnormal findings in all patients examined were the presence of rales in 100% of patients of both groups. Rales were unilateral in 12.5% and 17.5% in group 1 and group 2 respectively. Bronchial breath sounds were present in 42.5% and 37.5% in group 1 and group 2 respectively. Tactile vocal fremitus abnormalities were present in 37.5% and 35% in group 1 and group 2 respectively. Other abnormal chest findings, including, rhonchi and abnormal percussion note, were uncommon in both groups, ranged from 5% to 17.5% (Table 2).

Table (3) and Fig. (5) show the Findings on the chest radiographs in both groups, including bilateral patchy areas of consolidation in 59 patients, and lobar consolidation in 21 patients. Upper lobes were the most common site for abnormal radiographic abnormalities, then lower and middle lobes. Air bronchograms were bilateral in 65 patients and unilateral in the remaining 15 cases. Complications of pneumonia were present in 17 patients, parapneumonic effusion was present in 12 patients and atelectasis was present in 5 patients.

Table (4) and Fig. (6) show the outcome parameters of intervention and placebo groups after treatment. The intervention group with vitamin D therapy had better outcomes in two parameters. The mean time taken for resolution of the disease was considered when lower chest retraction and the danger signs (inability to feed, lethargy, cyanosis or hypoxia) were no longer present and improvement of oral feeding, in the intervention group significantly shorter than in the placebo group, with $p<0.001$ and $p<0.05$ respectively. The other parameters were comparable between both groups (Table 4). The side effects noted by the research team during the study period included diarrhea in 2 patients in group 1 with vitamin D supplementation. Diarrhea was mild and transient, and the patients continued the study.

Table (1): Clinical and demographic parameters of intervention and placebo groups before treatment.

Findings	Intervention group (N=40)	Placebo group (N=40)	*p*-value
Age (months) Mean ± SD	8.8±2.6	9.1±4	NS
Sex:			
Males (number, %)	23 (57.5)	22 (55)	NS
Females (number, %)	17 (42.5)	18 (45)	NS
Weight (kg) Mean ± SD	9.8±1.8	10.1±2.1	NS
Length (cm) Mean ± SD	74.9±8	72.1±6	NS
Cough (number, %)	40 (100)	40 (100)	NS
Fever ≥38,5 (number, %)	39 (97.5)	40 (100)	NS
Dyspnea	40 (100)	40 (100)	NS
Respiratory rate (breath/minute) Mean ± SD	63.7±6.9	64.1±3.3	NS
Oxygen saturation (%) Mean ± SD	91.4±2.5	90.8±3.1	NS
Feeding status (% of inability to feed)	13 (32.5)	15 (37.5)	NS
Conscious level (% of lethargy)	5 (12.5)	6 (15)	NS

NS: Non Significant.

Table (2): Findings of physical chest examination of intervention and placebo groups at admission.

Findings	Intervention group	Placebo group
Rales:		
Unilateral	5 (12.5%)	7 (17.5%)
Bilateral	35 (87.5%)	33 (82.5%)
Bronchial breath sounds:		
Unilateral	5 (12.5%)	7 (17.5%)
Bilateral	12 (30%)	8 (20%)
Vocal fremitus	15 (37.5%)	14 (35%)
Rhonchi	3 (7.5%)	2 (5%)
Abnormal percussion	5 (12.5%)	7 (17.5%)

Table (3): Radiological findings of intervention and placebo groups at admission.

Findings	Intervention group (N and %)	Placebo group (N and %)
Consolidation:		
Unilateral (lobar)	10 (25%)	11 (27.5%)
Bilateral	30 (75%)	29 (72.5%)
Air bronchogram:		
Unilateral	6 (15%)	9 (22.5%)
Bilateral	34 (85%)	31 (77.5%)
Parapneumonic effusion	5 (12.5%)	7 (17.5%)
Atelectasis	3 (7.5%)	2 (5%)

Table (4): Outcome parameters of intervention and placebo groups after treatment.

Parameter	Intervention group (N=40) Mean ± SD	Placebo group (N=40) Mean ± SD	*p*-value
Duration of resolution of pneumonia	108± 12	156± 18	<0.001 *
Duration of resolution of tachypnea	90± 12	96± 18	NS
Duration of resolution of chest retractions	78± 12	84±6	NS
Duration of resolution of inability to feed	24±6	36± 12	<0.05*
Duration of O2 therapy	60± 12	66±6	NS
Duration of intravenous fluids	52± 12	52±6	NS
Duration of hospitalization	144±24	156±26	NS

*Significant, NS: Non-significant.

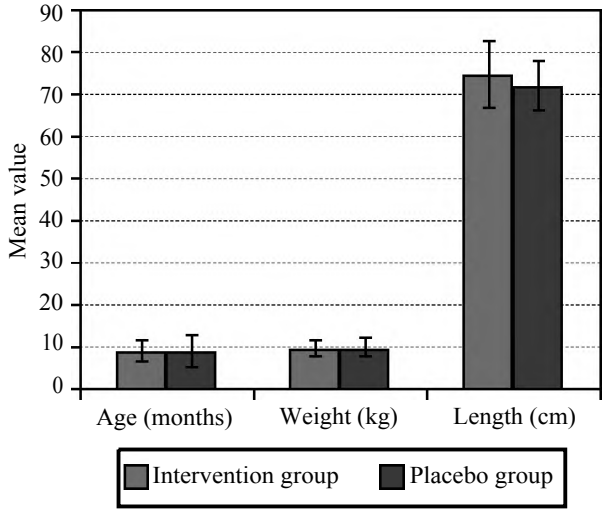

Fig. (1): Demographic parameters of intervention and placebo groups before treatment.

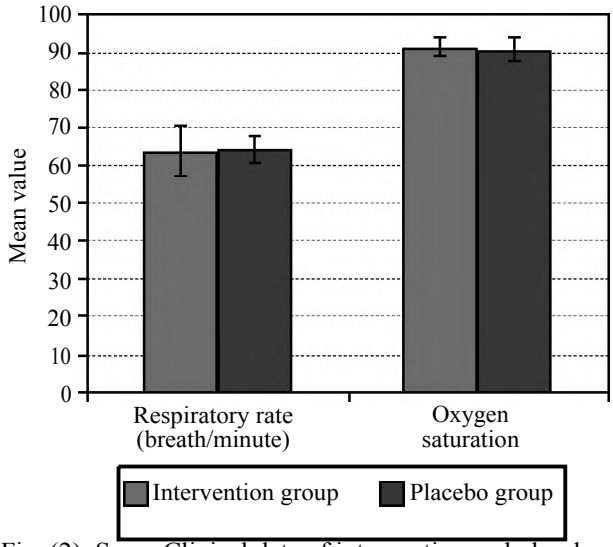

Fig. (2): Some Clinical data of intervention and placebo groups.

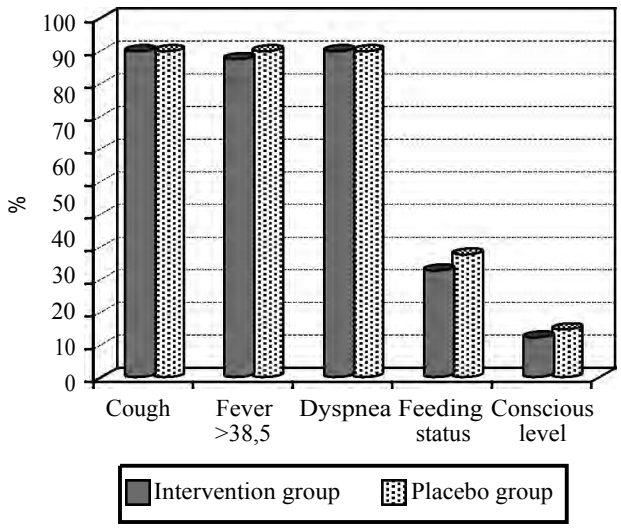

Fig. (3): Some Clinical data of intervention and placebo groups.

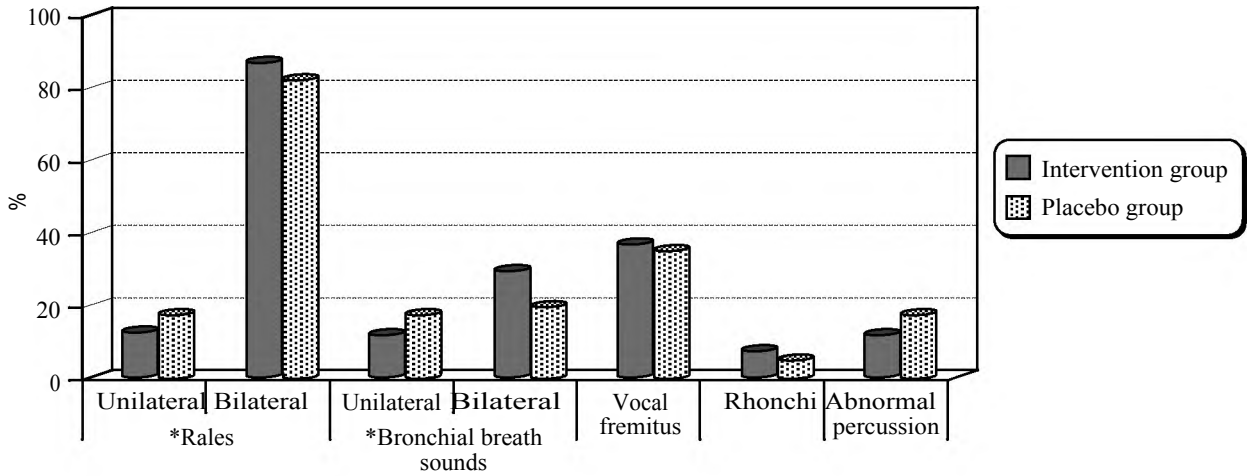

Fig. (4): Findings of chest examination of intervention and placebo groups.

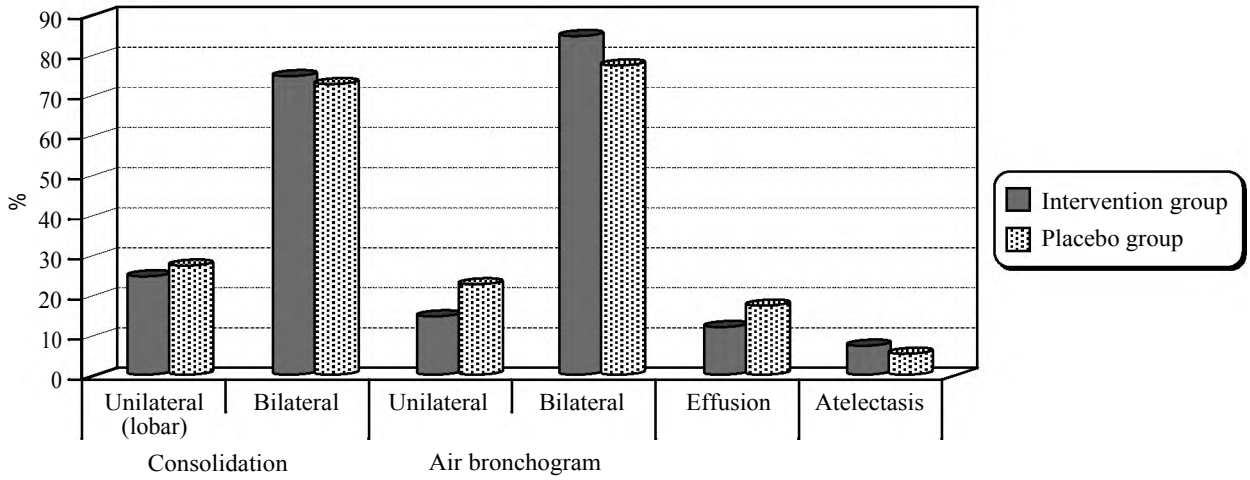

Fig. (5): Radiological findings of intervention and placebo groups.

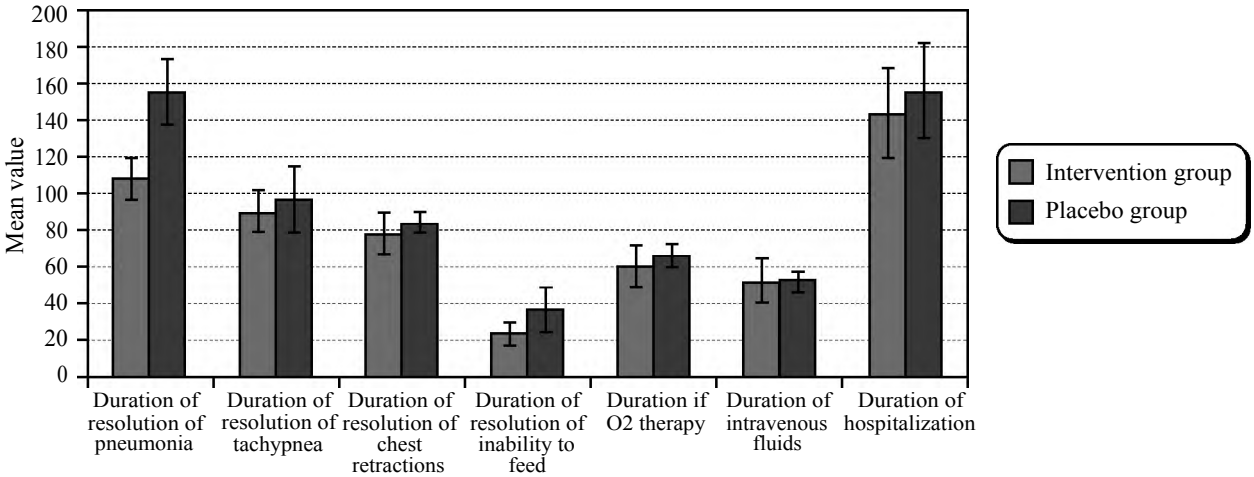

Fig. (6): Outcome parameters of intervention and placebo groups after treatment.

Discussion

In a double-blind, randomized clinical trial, the study included 80 infants (45 boys and 35 girls) between the ages of 3 and 23 months. Patients were randomized to receive vitamin D3 treatment (intervention group) or placebo (control group).

In addition to the important role of vitamin D in skeletal development and maintenance, there is

increasing evidence that it has a beneficial effect on extraskeletal tissues. In these tissues, vitamin D is thought to have roles in the improvement of immune function and the reduction of inflammation [3]. Accordingly, there is accumulating evidence that consumption of vitamin D may reduce respiratory tract infection susceptibility in children. Vitamin D has an important influence on the host's immune system, modulating both innate and adaptive immunity and regulating the inflammatory cascade [9]. The hypothesis of the immunoregulatory role of vitamin D derives from the discovery that there are several interactions between vitamin D and the immune system. The majority of immune cells express VDRs, mainly after they themselves have been stimulated [10]. The mechanism by which vitamin D regulates inflammation and immunity appears to be pleiotropic; it controls macrophage and dendritic cell activities and various Toll-like receptor mediated events in neutrophils and it diminishes the function of human dendritic cells by decreasing maturation, antigen presentation and the production of cytokines such as interleukin (IL)-12 and IL-23.

The results of this small randomized controlled clinical trial indicate that short-term supplementation with vitamin D along with antibiotic treatment, significantly reduces the mean time taken for resolution of severe pneumonia ($p<0.001$) and the mean time taken for the improvement of oral feeding ($p<0.05$), in the intervention group receiving vitamin D 100IU/kg for at least 5 days from the first day of admission. Vitamin D supplementation was well tolerated in all patients without showing any side effects.

Conclusion and Recommendation:

Vitamin D is currently one of the most widely researched vitamins, and this can be attributed to its proposed wide range of beneficial effects on the human body. There is a large body of research demonstrating the beneficial roles of vitamin D in various aspects of the immune system, including both innate and adaptive immunity. The vitamin D receptor is expressed by most cells of the immune system, and some cells of the immune system are also capable of producing the enzyme responsible for the conversion of 25-OHD to 1,25-(OH)2D, further pointing towards the essential role of vitamin D in preparing an immune response [11].

So, We concluded that short-term supplementation with 100IU/kg of vitamin D3 given orally for five to seven days in severe pneumonia to under-two years children may have beneficial effect especially on the resolution of severe pneumonia. Vitamin D is inexpensive, readily available and safe.

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