

Trial of Vitamin D Supplementation in Infants with Bronchiolitis: A Randomized, Double-Blind, Placebo-Controlled Study

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Background: There is interesting growing evidence for a relationship between bronchiolitis and vitamin D. This suggests a possible benefit from vitamin D therapy to children with bronchiolitis.

Methods: A double-blind, randomized clinical trial was performed on 89 infants with bronchiolitis. Patients were randomized to receive vitamin D or placebo.

Results: The intervention group, which received vitamin D therapy, had significant improvement in three parameters: the mean time taken for resolution of the disease, the mean time taken for the improvement of oral feeding, and the duration of hospitalization. All these outcomes in the intervention group (vitamin D) were significantly better than the control (placebo) group with $p < 0.001$, $p < 0.05$, and $p < 0.01$ respectively. The study supported the efficacy of vitamin D therapy in bronchiolitis.

Conclusion: This double-blinded, randomized placebo controlled trial of 100 IU/kg vitamin D supplementation daily in Egyptian children with bronchiolitis found a clinically and statistically significant reduction in hospitalization with rapid recovery of the disease. The study suggests that short-term supplementation with vitamin D given daily during the course of illness, starting from day 1, may help in resolution of bronchiolitis.

Introduction

BRONCHIOLITIS IS THE most common cause of lower respiratory tract infection and the leading cause for hospital admission in infants younger than 2 years age.¹ The majority of bronchiolitis cases is attributed to respiratory syncytial virus (RSV).² The hallmark pathological changes are acute inflammation of the bronchiolar airways with edema, necrosis, and mucous plugging causing airflow obstruction.² This result in tachypnea, chest wall retractions, tachycardia, cough, wheezes, and/or crackles; fever and apnea may also occur in neonates and young infants.^{1,2}

Bronchiolitis causes considerable morbidity and financial burden. Population-based studies in developed countries show an incidence rate of approximately 33% within the first year of life.² In developing countries, the impact of RSV disease (the major causative agent of bronchiolitis) may be greater.³ About 3% of hospitalized patients have symptoms severe enough to require admission to the intensive care unit. Over the previous decades, the number of

hospitalizations for bronchiolitis has risen at an alarming rate by 240%, from 12.9 per 1,000 in 1980 to 31.2 per 1,000 in 1996, whereas rates for other lower respiratory diseases have remained stable.^{4,5}

There is interesting and growing evidence for a relationship between bronchiolitis—as one of the respiratory viral infections—and vitamin D.⁶ Also, evidence shows that vitamin D has potent immunomodulatory properties and is closely related to host reactions against different infections complicated by vitamin D deficiency.⁷ In addition, the active form of vitamin D is involved via both the innate and the adaptive immune systems.^{6,7}

Vitamin D deficiency has been shown to increase the risk of viral respiratory tract infections and RSV-associated bronchiolitis. Also, serum vitamin D levels decrease in children with bronchiolitis, suggesting that vitamin D may play a role in the pathogenesis of bronchiolitis.^{6,8,9} Belderbos et al.¹⁰ performed a prospective birth cohort study and reported that children who are vitamin D deficient at birth have a sixfold risk of developing RSV bronchiolitis in the

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first year of life. Previous data suggest that action to change the vitamin D status of mothers during pregnancy and/or vitamin D supplementation of infants could reduce the risk of RSV-associated bronchiolitis.⁷ The aim of this study was to evaluate the efficacy of vitamin D in an Egyptian cohort of children with bronchiolitis.

Materials and Methods

The Ethical Committee of Assiut University (Assiut, Egypt) approved the study. Informed written consent in accordance with Assiut University Ethical Committee guidelines was taken from guardians of all cases and controls. This was a double-blinded, randomized, placebo-controlled trial undertaken in the Children University Hospital, Assiut University.

Patients

During winter, infants with bronchiolitis who presented to the emergency room within 7 days of the onset of symptoms were recruited into the study. Patients included 89 infants (45 boys) between the ages of 3 and 23 months. Bronchiolitis was diagnosed by two senior pediatricians and defined as acute-onset lower respiratory tract symptoms for <2 weeks with: (a) evidence of a viral infection (rhinorrhea, coryza, cough, or fever); (b) abnormal auscultatory findings (wheeze and/or crackles); and (c) increased respiratory effort (tachypnea and intercostal retractions).^{11,12}

Children were excluded if they exhibited severe respiratory distress, were admitted to the intensive care unit, or presented evidence of bacterial pneumonia (diagnosis of pneumonia was based on cough, chest wall in-drawing and/

or difficult breathing and tachypnea, fever and lobar, or bronchopneumonic infiltration demonstrated by X-ray).¹³ Children presenting with a history of atopic disorders such as asthma or known chronic cardiopulmonary disease, or immunodeficiency were also excluded from the study.

In addition, patients were excluded if they had a clinically significant chronic medical condition, including anemia, severe malnutrition, meningitis, neurological disease, or metabolic diseases. Also, patients with gastrointestinal disease associated with malabsorption were excluded. Finally, all patients should not have been taking any micro-nutrient supplementation or therapies containing vitamin D for 4 weeks prior to the study period.

Methodology

In a double-blind, randomized clinical trial, patients were randomized to receive vitamin D3 treatment (intervention group) or placebo (control group) by using a computerized random number generator. Both vitamin D3 and placebo were in drop form and were identical in shape and nearly the same taste and color. The assignments were kept in sealed envelopes until data analysis. The randomization and allocation process was done by a physician blinded to the study. The intervention group consisted of 44 patients (24 boys) who were randomly allocated to receive vitamin D3 treatment drops (100 IU/kg/day). The control group consisted of 45 patients (21 boys) who received a placebo drop solution with an identical outer cover and size of bottles as the intervention group. Throughout the study, the parents of children who administered the medications to their children were blind to assignments. The methodology is summarized in Figure 1.

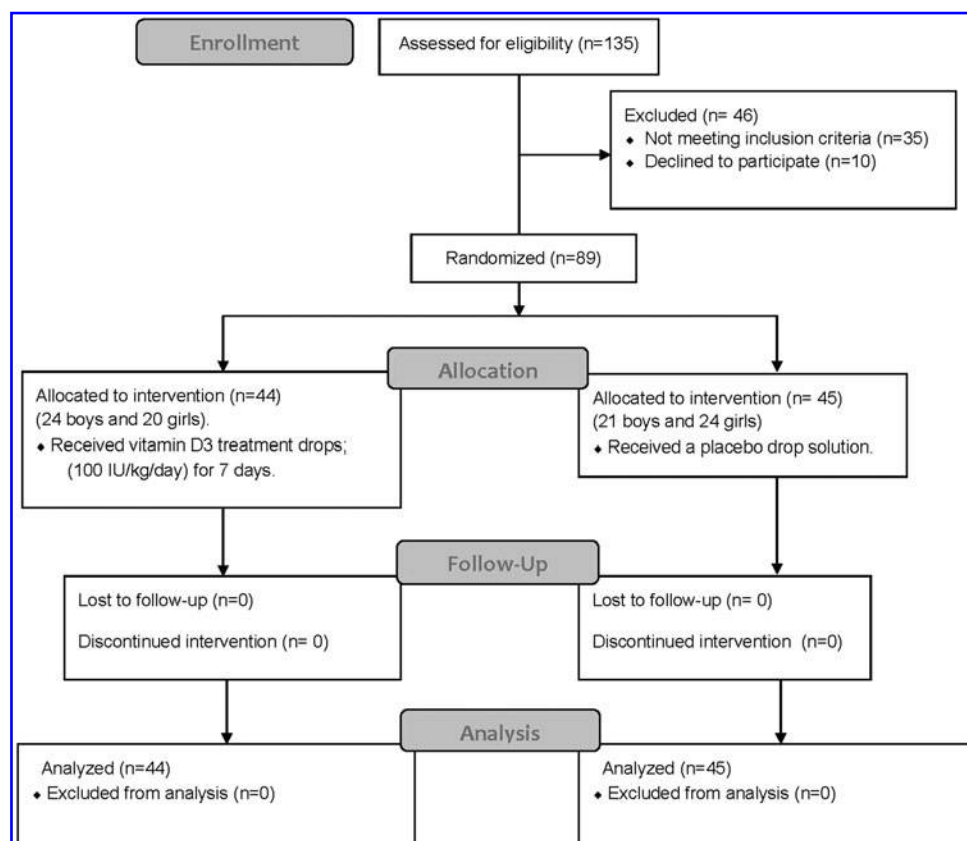


FIG. 1. Consort flow diagram.

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 bronchiolitis, according to the guidelines of Children University Hospital, Assiut University. The treatment included intravenous (i.v.) fluids, oxygenation, and antipyretics. Inhalation of epinephrine was administered according to the decision of a senior pediatrician. All patients were assessed by two pediatricians at the beginning and every 6 h 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:

1. Assessing the child's general condition for respiratory distress (tachypnea, chest retractions, grunting, and cyanosis), oxygen saturation, feeding status, and conscious level.
2. Time to resolution of bronchiolitis, defined by the absence of respiratory distress and other dangerous signs (inability to feed, lethargy, cyanosis, or hypoxia).
3. Other outcome measures, including durations of hospitalization, i.v. therapy, and oxygenation.

Statistical analysis

SPSS for Windows v16 (SPSS, Inc., Chicago, IL) was used for data analysis. Descriptive statistics as means were compared by Student's *t*-test. A *p*-value of <0.05 denoted a statistically significant difference.

Results

Table 1 shows the clinical and demographic criteria of the two groups. There were no significant differences between either group regarding anthropometric data, age, or other clinical parameter at the beginning of the study. Upon completion of the study, the mean values of clinical outcome are summarized in Table 2. The intervention group with vitamin D therapy had better outcomes in multiple parameters. The mean time taken for resolution of the disease, improvement of oral feeding, and duration of hospitalization in the intervention group were all significantly shorter than in the placebo group, with $p < 0.001$, $p < 0.05$, and $p < 0.01$ respectively. The other parameters were comparable between both groups (Table 2).

The side effects noted by the research team during the study period included diarrhea in four patients, two from each group. All were mild and transient, and all patients continued with the study.

Discussion

A growing number of epidemiologic studies have reported that children with lower vitamin D levels are at

TABLE 1. CLINICAL AND DEMOGRAPHIC PARAMETERS OF INTERVENTION AND CONTROL GROUPS BEFORE TREATMENT

Parameter	Intervention group (N=44) M (SD)	Control group (N=45) M (SD)	p-Value
Age	7.2 (2.6)	7(4)	NS
Sex			
Males	24	21	NS
Females	20	24	NS
Weight (kg)	6.0 (1.8)	5.8 (1.3)	NS
Length (cm)	62 (8)	64 (6)	NS
Respiratory rate (breath/minute)	73 (6)	73 (3.3)	NS
Oxygen saturation (%)	90 (0.9)	91 (1)	NS
Feeding status (% of inability to feed)	23 (52)	25 (56)	NS
Conscious level (% of lethargy)	7 (16)	6 (13)	NS

NS, not significant.

higher risk of acute respiratory infections (ARIs). Randomized controlled trials are needed to determine if vitamin D supplementation would decrease this risk.¹⁴ To the best of the authors' knowledge, this is the first randomized, double-blind, placebo-controlled trial of vitamin D therapy for bronchiolitis. Overall, there was a significant clinically important improvement with shorter duration of hospitalization, resolution of disease symptoms, and improvement of oral feeding.

Patients received 500–1,300 IU of vitamin D daily, which is higher than the recommended daily dose of 400 IU. Vitamin D doses of 100 IU/kg/day in our patients were adjusted in relation to kilograms of body weight, which was the recommendation of a prospective cohort observational study.¹⁵ Despite reported recommendations for vitamin D dose of 400 IU/day, vitamin D status in infants is still not fully recognized. It is unclear how far and to what extent the

TABLE 2. OUTCOME PARAMETERS OF INTERVENTION AND CONTROL GROUPS AFTER TREATMENT

Parameter	Intervention group (N=44) M (SD)	Control group (N=45) M (SD)	p-Value
Duration of resolution of bronchiolitis (h)	96 (12)	145 (8)	<0.001*
Duration of resolution of tachypnea (h)	70 (7)	72 (6)	NS
Duration of resolution of chest retractions (h)	69 (7)	70 (7)	NS
Duration of resolution of inability to feed (h)	20 (3)	36 (4)	<0.05*
Duration of O2 therapy (h)	51 (3)	52 (6)	NS
Duration of intravenous fluids (h)	26 (10)	28 (3)	NS
Duration of hospitalization (h)	139 (13)	198 (9)	<0.01*

*Significant.

recommended dose of 400 IU/day covers the needs of the growing organism, expressed as the proposed adequate 25-OHD serum concentration.^{15,16}

Camargo et al.¹⁴ performed a randomized, double-blind, placebo-controlled trial of Mongolian school children in winter, where vitamin D supplementation of milk with 300 IU/day produced a clinically and statistically significant decrease in risk of ARI. The ARI decrease was seen in children, both above and below the median baseline 25-hydroxyvitamin D level of 7 ng/mL. There was no evidence of a difference in benefit in this vitamin D-deficient population (with vitamin D deficiency defined as 20 ng/mL). Bergman et al.¹⁷ performed a meta-analysis of 11 placebo-controlled studies of 5,660 patients. They reported a protective effect of vitamin D supplementation against respiratory tract infections with a combined odds ratio of 0.64 [95% CI 0.49–0.84]. Although the overall results were in favor of a vitamin D effect, there was significant heterogeneity among the 11 studies. Inamo et al.¹⁸ found more children with acute lower respiratory infections who needed supplementary oxygen and ventilator management to be vitamin D deficient. These findings suggest that the immunomodulatory properties of vitamin D may influence the severity of acute lower respiratory infections.

Recent studies^{8,9} found low serum 25-hydroxyvitamin D levels in children with bronchiolitis. Other researchers^{10,19} have shown that cord blood levels of 25-hydroxyvitamin D have a strong inverse association with ARIs during the first 3 months of life and with ARIs due to RSV during the first year of life. Two large studies^{20,21} identified single nucleotide polymorphisms (SNPs) located in the vitamin D receptor (VDR Thr1Met; rs10735810) and JUN (c.750G/A; rs11688) genes. They concluded that children carrying the minor T allele of the VDR (Thr1Meth) SNPs may be predisposed to RSV disease, as this SNP was identified as a risk factor for severe RSV disease.^{20,21} Randolph et al.²² found a GC1s haplotype carriage, which may increase the risk of RSV bronchiolitis in infancy. The GC1s haplotype is associated with higher vitamin D-binding protein (VDBP) levels, resulting in less freely available vitamin D.

The mechanism by which vitamin D enhances immunity is complex. It acts through the innate immune system by inducing antimicrobial peptides in epithelial cells, neutrophils, and macrophages.²³ An important new mechanism explains the role of vitamin D is formation of human cathelicidin antimicrobial peptide 18 (hCAP-18) through hydroxylation of 25(OH)D creates 1,25-dihydroxyvitamin D, which *in vitro* increases the transcription of the innate immune protein (hCAP-18), which is capable of killing a wide variety of viral and bacterial pathogens.²⁴

Study limitations and recommendation

As Egypt is a developing country, pre- and post-serum vitamin D levels could not be obtained, so it is not known if deficient infants were helped more than sufficient infants. Larger randomized controlled trials are recommended using pre- and post-serum vitamin D levels in infants with bronchiolitis.

Conclusion

This double-blinded randomized controlled trial of Egyptian children with bronchiolitis found that 100 IU/kg

vitamin D supplementation daily led to a clinically and statistically significant reduction in hospitalization with rapid recovery from the disease. The study suggests that short-term supplementation with vitamin D given daily during the course of illness, starting from day 1, improves resolution of bronchiolitis.

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Author Disclosure Statement

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