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ORIGINAL ARTICLE

Randomized Controlled Trial

Efficacy of vitamin D supplementation for children with acute bronchiolitis: A randomized controlled trial

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Abstract

BACKGROUND

Previous studies have suggested an association between vitamin D deficiency and bronchiolitis, but the therapeutic benefits of vitamin D supplementation remain uncertain.

AIM

To investigate the efficacy of vitamin D supplementation for hospitalized children with acute bronchiolitis.

METHODS

This two-arm randomized controlled trial included 146 children aged 3-24 months who were hospitalized with bronchiolitis at an Egyptian tertiary care center. Participants were equally randomized to receive a single intramuscular dose of 200000 IU (study group) or a daily oral dose of 400 IU (comparison group) of vitamin D_3. The primary outcome was the time to hospital discharge. Secondary outcomes included time to oxygen weaning, discontinuation of intravenous fluids, and discharge readiness as well as serum 25-hydroxyvitamin D [25(OH)D] levels on day 3 post-randomization. Both the study and comparison groups were compared in the whole cohort (primary analysis) and within the subgroup of participants with baseline serum 25(OH)D levels < 30 ng/mL (prespecified subgroup analysis).

RESULTS

In the overall analysis, the study and comparison groups showed no significant differences in median time to discharge (130 hours *vs* 140 hours, $P = 0.149$) or in

secondary outcomes, except for a higher serum 25(OH)D level in the study group (51 ± 12.8 *vs* 32 ± 13.2 ng/mL, P < 0.001). However, among the subgroup of participants with baseline serum 25(OH)D levels < 30 ng/mL, the study group demonstrated significantly shorter median times to hospital discharge (120 hours *vs* 170 hours, P < 0.001), oxygen weaning (56 hours *vs* 79 hours, P = 0.012), discontinuation of intravenous fluids (55 hours *vs* 73 hours, P = 0.017), and discharge readiness (118 hours *vs* 165 hours, P = 0.001) as well as a greater increase in serum 25(OH)D levels (40 ± 6.6 ng/mL *vs* 20 ± 6.1 ng/mL, P < 0.001) than the comparison group.

CONCLUSION

Vitamin D supplementation may improve clinical outcomes in hospitalized children with bronchiolitis who have vitamin D deficiency or insufficiency, supporting a test-and-treat approach.

Key Words: Bronchiolitis; Cholecalciferol; Length of hospital stay; Respiratory tract infections; Vitamin D deficiency

Core Tip: Vitamin D deficiency has been linked to bronchiolitis, yet the therapeutic benefit of supplementation remains uncertain. In this randomized controlled trial, a single intramuscular dose of 200000 IU vitamin D_3 significantly shortened hospital stay and reduced oxygen and intravenous fluid requirements in children with bronchiolitis who were vitamin D deficient, but not in those with sufficient levels. These results suggest that targeted supplementation may improve outcomes in deficient children, supporting a test-and-treat strategy.

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INTRODUCTION

Acute bronchiolitis is the most frequent lower respiratory tract infection in children under two years of age and represents a major cause of medical visits, hospital admissions, and mortality[1,2]. Respiratory syncytial virus (RSV) is the most common causative agent (accounting for 50%-80% of cases), followed by other viruses, such as rhinovirus, human bocavirus, adenovirus, metapneumovirus, parainfluenza, influenza, coronavirus, and enterovirus. However, the epidemiological pattern may have been influenced by the coronavirus disease 2019 pandemic[3,4].

Bronchiolitis is typically diagnosed based on a constellation of clinical manifestations, including respiratory distress and wheezing, preceded by a viral upper respiratory tract prodrome in children younger than two years[5]. Management is mainly supportive, focusing on maintaining adequate oxygenation and hydration[5,6]. Although a monoclonal antibody (nirsevimab) has shown promising results in preventing severe RSV infection in infants, its availability remains limited, particularly in low- and middle-income countries[2]. Given the sizable burden of bronchiolitis and the lack of specific treatment, there is a pressing need to explore potential therapeutic options, such as vitamin D[7].

Accumulating evidence indicates that vitamin D plays an important role in bronchiolitis through its antiviral and immunomodulatory effects[8-11]. Numerous observational studies have linked low vitamin D levels to an increased risk and severity of bronchiolitis[12-16], although this association has not been consistently observed in all studies[17,18]. However, the value of vitamin D supplementation in bronchiolitis has been investigated in only three randomized controlled trials (RCTs) with inconsistent findings[7,19,20]. Importantly, these studies had small sample sizes and did not account for baseline vitamin D status[7,19,20].

Against this background, the authors conducted an RCT to investigate the efficacy of vitamin D supplementation for children with severe bronchiolitis. We hypothesized that in hospitalized children with bronchiolitis, a single intramuscular bolus of 200000 IU vitamin D_3, compared with the standard daily oral dose of 400 IU, would be more effective in reducing the length of hospital stay.

MATERIALS AND METHODS

Study design and setting

This study was an open-label, randomized, two-arm, parallel, 1:1, superiority trial conducted between April 2023 and July 2024 at the Department of Pediatrics, Sohag University Hospital (southern Egypt). The primary analysis compared the randomized study group (received a single intramuscular 200000 IU vitamin D_3 bolus) and comparison group (received the standard oral dose of 400 IU/day vitamin D_3) in the overall population. Besides the primary overall comparison, we performed a priori, pre-specified stratified (subgroup) analysis, comparing between the randomized study and comparison groups within the subgroup of participants with baseline serum 25-hydroxyvitamin D [25(OH)D] levels < 30 ng/mL (pre-specified vitamin D deficiency/insufficiency subgroup).

The study was approved by the Research Ethics Committee of Faculty of Medicine, Sohag University (Approval no: Soh-Med-23-03-11MS; dated March 8, 2023). Written informed consent was obtained from parents or legally authorized representatives of all participants. All conducted procedures were in accordance with the 1954 Helsinki Declaration and its subsequent revisions. The trial was prospectively registered on www.clinicaltrials.gov (identifier: NCT05795933) on March 21, 2023 (https://clinicaltrials.gov/study/NCT05795933). The manuscript follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines for parallel-group RCTs.

Participants

Eligibility criteria were children aged 3-24 months with the first episode of bronchiolitis, enrolled during the first 24 hours of hospital admission. Bronchiolitis was clinically defined following the American Academy of Pediatrics (AAP) guidelines (Supplementary material)[5]. We included only children with stable or decreasing oxygen requirements, confirmed by two measurements taken two hours apart, along with a pulse rate < 180 beat/minute, respiratory rate < 80 breath/minute, oxygen supplementation < 40% fraction of inspired oxygen or < 2 L/minute *via* nasal prong, and who were not on high flow nasal cannula, continuous positive airway pressure, or mechanical ventilation at enrollment. Exclusion criteria were a history of previous wheezing episodes, history of apnea, chronic lung disease requiring home oxygen or associated with pulmonary hypertension, cardiac disease (*e.g.*, cyanotic, hemodynamically significant, or associated with pulmonary hypertension), neuromuscular disorder, metabolic disease, immunodeficiency, chromosomal abnormality, craniofacial malformation, hemoglobinopathy, hypercalcemia, and vitamin D intake > 400 IU/day in the past month.

Sample size calculation

The required sample size of this superiority RCT was calculated using Stata/BE 17 (StataCorp, College Station, TX, United States). Assuming that the study group would have a 12-hour shorter time from randomization to hospital discharge than the comparison group (84 hours *vs* 96 hours), with a two-sided α of 0.05 and β of 0.2, the estimated sample size was 62 participants per group. This number was increased to 73 per group to account for a possible 15% attrition rate.

Randomization

Participants were randomly assigned in a 1:1 ratio to either the study or comparison group using permuted blocks of four, generated by Research Randomizer software (www.randomizer.org). An independent individual concealed these random numbers in successively ordered opaque envelopes. For each enrolled participant, the corresponding envelope was opened, and the allocated medication was administered. Blinding was not implemented.

Intervention

Participants in the study group received a single intramuscular dose of 200000 IU vitamin D_3 (Devarol-S-200000 IU in 2 mL ampoule, Memphis Company for Pharmaceutical and Chemical Industries, Cairo, Egypt) within 24 hours of hospitalization. Participants in the comparison group were given the standard oral dose of 400 IU/day vitamin D_3 (Vidrop 2800 IU/mL, Medical Union Pharmaceuticals, Cairo, Egypt).

Assessment and standard of care

All enrolled children received standard management for bronchiolitis following the institutional protocol and AAP guidelines, emphasizing adequate oxygenation and hydration, regular evaluation, and parental education[5]. All medical decisions were made independently by the treating physicians. Bronchiolitis severity was assessed using the Wang respiratory score, and feeding adequacy was evaluated using the parent-rated feeding adequacy scale (FAS). Oxygen therapy was adjusted to maintain an oxygen saturation above 92%, and intravenous fluids were provided to children with dehydration, poor feeding, or severe respiratory distress that impaired oral intake. We measured serum levels of total 25(OH)D and ionized calcium at baseline and on day 3 post-randomization. Vitamin D deficiency and insufficiency were defined according to endocrine society clinical practice guidelines as < 20 ng/mL and 20-29.9 ng/mL, respectively [21]. Children with progressive respiratory distress were transferred to the pediatric intensive care unit (PICU) for further evaluation and advanced respiratory support. Criteria for hospital discharge were body temperature < 38 °C, oxygen saturation > 92% on room air, age-appropriate respiratory rate, FAS score ≥ 7, and adequate parent education and social support. Additional methodological details are provided in Supplementary material.

Outcomes

The study timeframe was limited to the in-hospital phase. The primary outcome was the time from randomization to hospital discharge (in hours). Secondary outcomes included times from randomization to discontinuation of oxygen therapy, discontinuation of intravenous fluids, and fulfillment of hospital discharge criteria; time from hospital admission to discharge, serum levels of 25(OH)D and ionized calcium on day 3 post-randomization; use of bronchodilator therapy; use of systemic steroids; PICU admission; endotracheal intubation; and in-hospital mortality.

Statistical analysis

Data were analyzed on an intention-to-treat basis using Stata/BE 17. Results were presented as mean ± SD, median (interquartile range), and *n* (%), as appropriate. Two-group comparisons were conducted using independent *t*-test for normally distributed quantitative data, Wilcoxon rank sum test for non-normally distributed quantitative data, and χ^2/Fisher exact test for categorical data. In addition to the primary overall comparison, we conducted a pre-specified stratified analysis, comparing between the randomized study and comparison groups within the subgroup of participants

with baseline serum 25(OH)D levels < 30 ng/mL (pre-specified vitamin D deficiency/insufficiency subgroup). This stratified analysis was planned a priori. Moreover, we investigated the homogeneity of the intervention effect on primary outcome over several factors, including age, sex, body mass index, use of nebulized β2 agonists, use of systemic corticosteroids, oxygen saturation, Wang respiratory score, FAS, and baseline serum 25(OH)D levels, using linear regression models that contained terms for intervention, selected factor, and intervention-factor interaction. A two-tailed *P* value < 0.05 was deemed statistically significant.

RESULTS

Among 227 children assessed for eligibility, 146 were randomized equally into the study and comparison groups, and all completed the study (Figure 1). The participants (97 males and 49 females) had a median age of six months. The median time from bronchiolitis onset to hospital admission was 45.5 hours. Nearly two-thirds of participants had been receiving regular oral supplementation with 400 IU/day of vitamin D_3. About one-third had vitamin D deficiency, 16.4% had vitamin D insufficiency, and half had normal serum 25(OH)D levels. Importantly, baseline participants' features were comparable between the study and comparison groups (Table 1).

Baseline characteristics of study participants in the whole cohort stratified by vitamin D status are provided in the Supplementary material. Compared to those with normal 25(OH)D levels, participants with vitamin D deficiency/insufficiency exhibited significantly more frequent allergies (12.3% *vs* 1.4%, *P* = 0.017) and a higher respiratory rate (55 ± 7 *vs* 53 ± 6, *P* = 0.010). No statistically significant differences were observed in other parameters.

In the overall outcome analysis, the study group had a shorter median time from randomization to discharge than the comparison group, but this difference did not reach statistical significance (130 hours *vs* 140 hours, *P* = 0.149). Similarly, there were no significant differences in other outcomes between both groups, except for serum 25(OH)D levels on day 3, which were significantly higher in the study than in the comparison group (51 ± 12.8 ng/mL *vs* 32 ± 13.2 ng/mL, *P* < 0.001) (Table 2).

In the pre-specified subgroup of participants with baseline serum 25(OH)D levels < 30 ng/mL (vitamin D deficiency/insufficiency), no statistically significant differences in baseline features were observed between those randomized into the study and comparison group (Supplementary material). Table 3 shows the comparison of outcomes within this subgroup. In contrast to the comparison group, children in the study group had significantly shorter median times from randomization to hospital discharge (120 hours *vs* 170 hours, *P* < 0.001), discontinuation of oxygen therapy (56 hours *vs* 79 hours, *P* = 0.012) and intravenous fluids (55 hours *vs* 73 hours, *P* = 0.017), and meeting discharge criteria (118 hours *vs* 165 hours, *P* = 0.001). Additionally, the study group had a shorter median time from hospital admission to discharge (126 hours *vs* 178 hours, *P* < 0.001) and higher serum 25(OH)D levels (40 ± 6.6 ng/mL *vs* 20 ± 6.1 ng/mL, *P* < 0.001).

Among the investigated factors, linear regression analyses showed significant interactions of the intervention effect on the primary outcome with only baseline serum 25(OH)D levels (*P* = 0.004) and Wang respiratory score (*P* = 0.011) (Supplementary material).

DISCUSSION

We found that a single intramuscular dose of 200000 IU vitamin D_3 significantly improves multiple clinical outcomes in hospitalized children with bronchiolitis who have vitamin D deficiency/insufficiency but not in those with normal vitamin D levels. This supports a test-and-treat approach to identify children with bronchiolitis who have suboptimal vitamin D levels and may benefit from bolus vitamin D supplementation. However, additional confirmatory studies are warranted before clinical application.

Supporting our findings, Saad *et al*[19] conducted an RCT study on 89 Egyptian infants hospitalized with bronchiolitis, showing that oral vitamin D_3 supplementation at 100 IU/kg/day, compared to placebo, shortens the time to recovery, oral feeding, and hospital discharge. Nevertheless, this study did not measure serum vitamin D levels. Likewise, Osman *et al*[20] performed an RCT on 60 hospitalized infants with bronchiolitis in Egypt, demonstrating that oral vitamin D_3 100 IU/kg/day reduces the time to resolution of respiratory distress, weaning from oxygen therapy, and hospital discharge. Notably, 78.1% of participants in Osman *et al*[20] study had serum 25(OH) D levels < 30 ng/mL, compared to 50% in our study. This higher prevalence of vitamin D deficiency/insufficiency may explain the significant efficacy of vitamin D supplementation in the overall analysis in Osman *et al*[20] study.

In contrast, Khoshnevisasl *et al*[7] compared oral vitamin D_3 (100 IU/kg/day), oral zinc (20 mg/day), and nebulized hypertonic saline for bronchiolitis in an Iranian hospital, showing no significant differences in the length of hospital stay or improvement in respiratory distress, wheezing, cyanosis, or oxygen saturation. However, this lack of significant efficacy of vitamin D may be attributed to several reasons. First, the small sample size (30-33 subjects per arm) may have limited the study power. Indeed, children who received vitamin D showed a trend toward a greater improvement in respiratory distress by day 3 and shorter hospitalization than the other two groups. Furthermore, the study population was older (mean 10 months) compared with those in Saad *et al*[19] (mean 7 months), Osman *et al*[20] (median 4 months), and our study (median 6 months). This age difference may have contributed to the discrepancy, as RSV is more prevalent among younger infants and is associated with greater clinical severity[22,23]. In addition, Khoshnevisasl *et al*[7] did not measure baseline vitamin D levels, making it unclear whether children with vitamin D deficiency/insufficiency would have benefited more. Finally, genetic differences between the Iranian and Egyptian populations may influence the therapeutic response to vitamin D. For instance, the *VDR* FokI (rs2228570) polymorphism has been demonstrated to

Table 1 Baseline characteristics of study participants, median (interquartile range)/*n* (%)

Characteristics	Total (*n* = 146)	Study group (*n* = 73)	Comparison group (*n* = 73)	*P* value
Age (month)	6 (4-9)	6 (4-9)	6 (4-8)	0.664
Male sex	97 (66.4)	50 (68.5)	47 (64.4)	0.599
Body mass index (kg/m^2), mean (SD)	17.2 (2.85)	17.1 (2.70)	17.4 (3.00)	0.515
Breastfeeding	103 (70.6)	51 (69.9)	52 (71.2)	0.856
Parental smoking	85 (58.2)	41 (56.2)	44 (60.3)	0.615
Family history of allergy	27 (18.5)	15 (20.6)	12 (16.4)	0.522
Allergies	10 (6.9)	5 (6.9)	5 (6.9)	1.000
Regular vitamin D intake	94 (64.4)	45 (61.6)	49 (67.1)	0.489
Time from disease onset to admission (hour)	45.5 (24-72)	47 (27-72)	45 (24-70)	0.566
Time from admission to randomization (hour)	8 (4-12)	9 (5-12)	8 (4-13)	0.672
Respiratory rate (breath/minute), mean (SD)	53.9 (6.37)	54.3 (5.37)	53.5 (7.26)	0.485
Oxygen saturation (%), mean (SD)	89.2 (0.94)	89.2 (0.92)	89.2 (0.95)	0.792
Wang respiratory score, mean (SD)	8.5 (1.01)	8.5 (0.87)	8.4 (1.13)	0.512
Feeding adequacy scale, mean (SD)	5.8 (1.12)	5.7 (1.26)	5.9 (0.98)	0.510
Oxygen supplementation (L/minute), mean (SD)	1.8 (0.45)	1.8 (0.47)	1.8 (0.43)	1.000
Parenteral fluids	146 (100)	73 (100)	73 (100)	1.000
Tube feeding	82 (56.2)	43 (58.9)	39 (53.4)	0.505
Serum ionized calcium (mmol/L), mean (SD)	1.15 (0.12)	1.16 (0.11)	1.15 (0.12)	0.505
Serum 25 hydroxy vitamin D (ng/mL), mean (SD)	30.5 (13.30)	31.40 (13.12)	30.0 (13.43)	0.415
Serum 25 hydroxy vitamin D categories				0.670
Normal (≥ 30 ng/mL)	73 (50)	38 (52.1)	35 (48.0)	
Insufficiency (20-29 ng/mL)	24 (16.4)	13 (17.8)	11 (15.1)	
Deficiency (< 20 ng/mL)	49 (33.7)	22 (30.1)	27 (37.0)	

hinder the ability of vitamin D to reduce the signal transducer and activator of transcription 1 (STAT1)-mediated immunopathologic response to RSV infection *in vitro*[24].

Observational studies indicate that low vitamin D levels are associated with increased risk and severity of bronchiolitis [12-16], although findings have been inconsistent[17,18]. Establishing a causal relationship between low vitamin D levels and bronchiolitis based on observational research is challenging due to bias and confounding factors, including variations in baseline vitamin D status and its assessment methods, nutritional status, viral etiology, bronchiolitis severity measures, and genetic factors[9,10,14]. Regarding other lower respiratory tract diseases in children, recent systematic reviews highlight uncertainty about the efficacy of supra-physiological doses of vitamin D for acute pneumonia[25] or asthma control[26]. However, potential benefits for vitamin D-deficient subgroups remain underexplored.

The mechanisms underlying the efficacy of vitamin D for bronchiolitis are not fully understood but may involve enhanced antiviral immunity and suppressed exaggerated inflammatory response[8-10,27,28]. Respiratory infections induce macrophages, dendritic cells, and epithelial cells to increase the expression of vitamin D receptors and 1α-hydroxylase enzyme[10,11]. Locally synthesized 1,25-dihydroxy vitamin D promotes innate immunity against respiratory viral infections (*e.g.*, RSV, rhinovirus, influenza) through upregulating the expression of host defense proteins, such as cathelicidin and β-defensin 2[29], enhancing macrophage autophagy for viral clearance[10,11], and stabilizing pulmonary epithelial barriers *via* protein kinase A signaling[30]. Conversely, active vitamin D can suppress the hyperinflammatory response to lower respiratory viral infections, which largely contribute to disease severity, by downregulating excessive expression of certain toll-like receptors (*e.g.*, toll like receptor 2 and 4) and shifting the cytokine balance from proinflammatory type-1 [*e.g.*, interferon-gamma, interleukin (IL)-12, IL-6, IL-8, TNF-α] to anti-inflammatory type-2 (IL-10, IL-4, IL-5) phenotypes[8,11,29]. Notably, *in vitro* experimental data indicate that active vitamin D inhibits nuclear factor kappaB - and STAT1-mediated immunopathology following RSV infection[24,31].

A novel finding in the current study is that vitamin D benefited only the subgroup of children with bronchiolitis who had vitamin D deficiency/insufficiency. A plausible explanation is that lower 25(OH)D levels contribute to greater disease severity, which vitamin D supplementation mitigates. In the same vein, Bhan *et al*[32] described that vitamin D therapy significantly increases cathelicidin levels only in individuals with 25(OH)D < 32 ng/mL. Other studies have shown that vitamin D supplementation confers extra-skeletal health benefits (*e.g.*, improved lung functions, decreased

Table 2 Outcomes between randomized study groups in the overall population (*n* = 146), median (interquartile range)/*n* (%)

Outcomes	Study group (*n* = 73)	Comparison group (*n* = 73)	*P* value
Time from randomization to hospital discharge (hour)	130 (107-150)	140 (105-190)	0.149
Time from randomization to discontinuation of oxygen supplementation (hour)	70 (50-90)	70 (45-90)	0.916
Time from randomization to discontinuation of parenteral fluids (hour)	70 (50-80)	66 (40-90)	0.944
Time from randomization to meeting discharge criteria (hour)	128 (100-145)	138 (100-181)	0.138
Time from hospital admission to discharge (hour)	143 (110-163)	154 (109-200)	0.141
Serum 25 hydroxy vitamin D on day 3 after randomization (ng/mL), mean (SD)	51.1 (12.80)	30.9 (13.15)	< 0.001[a]
Serum ionized calcium on day 3 after randomization (mmol/L), mean (SD)	1.19 (0.11)	1.16 (0.11)	0.051
PICU admission	1 (1.4)	6 (8.2)	0.116
Intubation	0	0	NA
Death	0	0	NA
Nebulized salbutamol therapy	69 (94.5)	68 (93.2)	1.000
Systemic corticosteroids	15 (20.6)	15 (20.6)	0.840

[a]*P* <0.05.
PICU: Pediatric intensive care unit; NA: Not available.

Table 3 Outcomes between randomized study groups within the subgroup of participants with baseline serum 25-hydroxyvitamin D levels < 30 ng/mL (pre-specified vitamin D deficiency/insufficiency subgroup, *n* = 73), median (interquartile range)/*n* (%)

Outcomes	Study group (*n* = 35)	Comparison group (*n* = 38)	*P* value
Time from randomization to hospital discharge (hour)	120 (100-144)	170 (120-190)	< 0.001[a]
Time from randomization to discontinuation of oxygen supplementation (hour)	56 (40-68)	79 (49-90)	0.012[a]
Time from randomization to discontinuation of parenteral fluids (hour)	55 (40-75)	72.5 (48-95)	0.017[a]
Time from randomization to meeting discharge criteria (hour)	118 (92-136)	165 (118-181)	0.001[a]
Time from hospital admission to discharge (hour)	126 (106-157)	177.5 (124-200)	< 0.001[a]
Serum 25 hydroxy vitamin D on day 3 after randomization (ng/mL), mean (SD)	39.9 (6.56)	19.8 (6.05)	< 0.001[a]
Serum ionized calcium on day 3 after randomization (mmol/L), mean (SD)	1.21 (0.12)	1.16 (0.13)	0.123
PICU admission	0	5 (13.2)	0.055
Intubation	0	0	NA
Death	0	0	NA
Nebulized salbutamol therapy	32 (91.4)	36 (94.7)	1.000
Systemic corticosteroids	9 (25.7)	6 (15.8)	0.294

[a]*P* <0.05.
PICU: Pediatric intensive care unit; NA: Not available.

progression to type-2 diabetes mellitus, and lower central blood pressure) in deficient but not vitamin D-replete individuals[33]. Accordingly, a test-and-treat approach is recommended, targeting only children with suboptimal 25(OH)D levels for vitamin D supplementation.

In the present study, serum levels of 25(OH)D and ionized calcium remained within safe ranges three days after a 200000 IU intramuscular vitamin D_3 dose (51 ng/mL and 1.2 mmol/L, respectively). A recent systematic review concluded that single bolus doses of vitamin D_3 up to 600000 IU are well tolerated and safe in children under six years, without an increased risk of hypercalcemia or other remarkable adverse effects[34]. However, since serum 25(OH)D levels may continue to rise for up to four weeks post-intramuscular injection, longer monitoring is warranted[35].

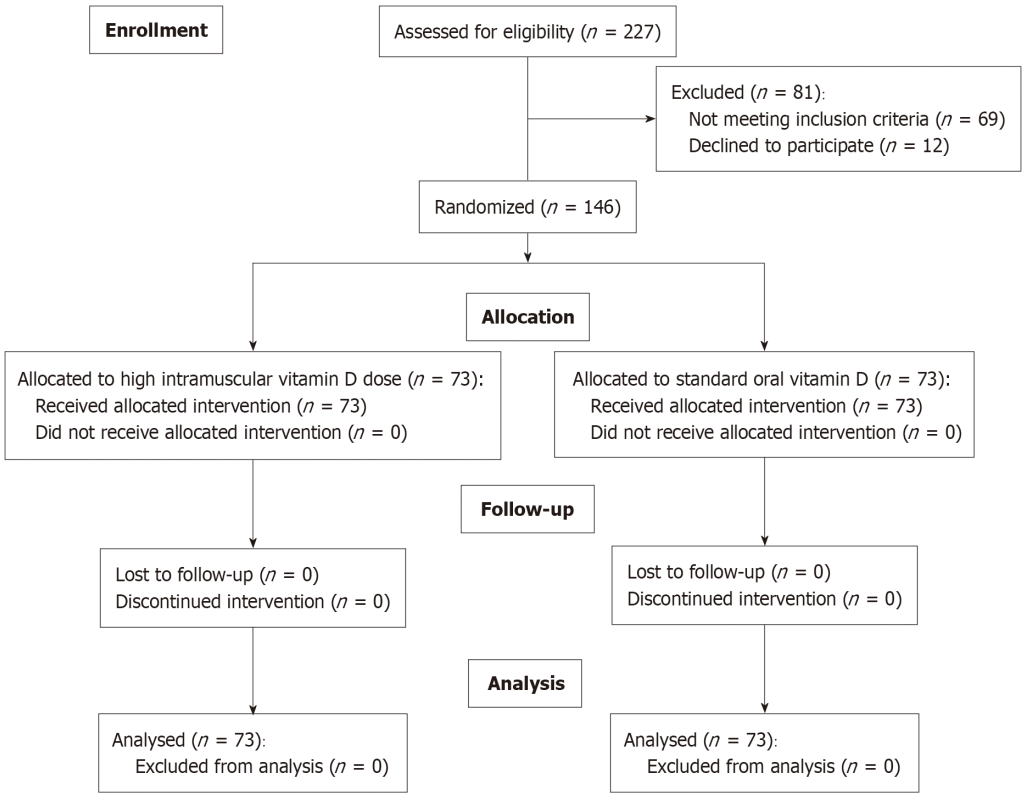

Figure 1 Study participants flow diagram.

Importantly, some studies suggest that daily vitamin D supplementation may be more effective than bolus therapy for childhood pneumonia[25], which requires future investigations into bronchiolitis.

Strengths of the present study include its randomized controlled design and stratified analysis by baseline serum 25(OH)D levels. However, we acknowledge some limitations. First, the study included only children with severe bronchiolitis requiring hospitalization, which may limit the generalizability of the findings to milder cases. Moreover, while outcomes were objectively assessed, the open-label design may have introduced some bias. Additionally, bronchiolitis was diagnosed clinically based on practice guidelines, without imaging or viral testing[5,6]. Nevertheless, clinical and immunological responses to vitamin D supplementation may vary by the causative virus[23]. Compared with RSV, bronchiolitis due to rhinovirus tends to be less severe[22], exhibits a higher Th2/Th1 profile[36], and may respond more favorably to systemic corticosteroids[37]. Accordingly, future research should explore the efficacy of vitamin D supplementation for bronchiolitis across different viral etiologies.

Another limitation is the lack of molecular investigation into genetic variations affecting vitamin D metabolism, transport, and signaling, which may influence bronchiolitis severity [*e.g.*, *VDR* FokI (rs2228570), *VDBP* GC1s (rs7041_C)] [38,39] and response to vitamin D supplementation [*e.g.*, *VDR* FokI (rs2228570)][24]. Likewise, our study did not include advanced tests to unravel the mechanisms by which vitamin D supplementation improves clinical outcomes in infants with bronchiolitis, such as cytokine profiles, flow cytometry, or antiviral marker analysis. Furthermore, 95% and 21% of participants received nebulized salbutamol and systemic corticosteroids, respectively, at the discretion of treating physicians, independent of study enrollment, which deviates from guideline recommendations[5,6]. However, it is unlikely that this significantly affected the main study findings since bronchodilator and corticosteroid use were comparable between groups and did not modify vitamin D efficacy for the primary outcome. Notably, prior studies have similarly described overuse of non-recommended medications for bronchiolitis, which underscores the need for improved adherence to guidelines[40]. In addition, the limited study timeframe did not allow for investigating potential long-term effects of vitamin D supplementation, such as prevention of bronchiolitis recurrence or subsequent asthma development[2,41]. Finally, although the pre-specified subgroup analysis was planned a priori within the randomized cohort, future trials restricted to participants with vitamin D deficiency or insufficiency could further minimize potential bias and strengthen causal inference.

CONCLUSION

A single intramuscular 200000 IU vitamin D_3 bolus may reduce the duration of hospital stay, oxygen therapy, and parenteral fluid use in children with bronchiolitis who have vitamin D deficiency/insufficiency, but not among those with adequate vitamin D levels. Future studies should explore optimal dosing and administration routes, underlying immunological mechanisms, specific viral etiologies, genetic factors affecting therapeutic response, and long-term

outcomes of vitamin D supplementation.

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FOOTNOTES

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