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Original article

Vitamin D supplementation in the critically ill: A systematic review and meta-analysis

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Summary

Introduction

Vitamin D insufficiency is reported in up to 50% of the critically ill patients and is associated with increased mortality, length of stay (LOS) in intensive care unit (ICU) and hospital, and respiratory disorders with prolonged ventilation. Benefits of vitamin D supplementation remain unclear. The aim of this systematic review was to evaluate the clinical benefits of vitamin D administration in critically ill patients.

Methods

We searched Medline, Embase, CINAHL and Cochrane database for randomized controlled trials (RCT) conducted on heterogeneous ICU patients comparing vitamin D administration to placebo. Evaluated outcomes included mortality, infectious complications, hospital/ICU LOS and length of mechanical ventilation. Two independent reviewers assessed eligibility, risk of bias and abstracted data. Data was pooled using a random effect model to estimate the relative risk (RR) or weighted mean difference. Pre-defined subgroup analysis included oral-enteral vs. parenteral administration, high vs. low dose, vitamin d deficient patient, high vs. low quality trials.

Results

Six RCTs (695 patients) met study inclusion. No reduction in mortality was found ($P = 0.14$). No differences in ICU and hospital LOS, infection rate and ventilation days existed. In the subgroup analysis, the oral-enteral group, there was no improvement in mortality ($P = 0.12$) or hospital LOS ($P = 0.16$). Daily doses >300,000 IU did not improve mortality ($P = 0.12$) and ICU LOS ($P = 0.12$).

Conclusions

In critically ill patients, Vitamin D administration does not improve clinical outcomes. The statistical imprecision could be explained by the sparse number of trials.

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Vitamin D; Critically ill; Cholecalciferol; Calcitriol; Meta-analysis

1. Introduction

Vitamin D is a fat-soluble vitamin that is synthesized in the skin in response to sunlight exposure and then converted in the liver to 25-hydroxyvitamin D3 or cholecalciferol, which is mainly transformed by the kidneys in 1, 25-dihydroxyvitamin D also known as calcitriol. Vitamin D participates in bone mineral metabolism through the modulation of calcium and phosphorous levels. Moreover, in recent years an increased body of research has shown the biological effect of vitamin D on cardiac function through reduced remodeling and fibrosis secondary to a negative regulation of renin by vitamin D receptor (VDR)-linked gene regulation and through reduced cardiac metalloproteinase activities [1]. VDR are also expressed on immune cells (T and B cells, monocytes/macrophages, mast cells and antigen-presenting cells). In murine models, VDR-deficient mice supplemented in calcium exhibited a grossly deficient immune system susceptible to infections and auto-immune diseases, a high renin hypertension, cardiac hypertrophy, increased thrombogenicity [1]. In human, similar findings exist but clear functional explanation and solid association is still missing. According to current literature, normal level of vitamin D is defined by serum cholecalciferol greater than 30 ng/mL 2 ; 3, whereas serum level lower than 30 ng/L define vitamin D insufficiency, whilst deficiency is generally described when it is under 20 ng/L [4].

So far, several observational studies have demonstrated that 50% of critically ill adult patients exhibit vitamin D deficiency, with undetectable levels in almost 17% [3]. These epidemiologic numbers are only slightly higher than general population in America, but are well higher than European statistics 5 ; 6. In the critical care setting, this deficiency has been associated with adverse outcomes such as infections, longer length of stay, acute kidney injury and higher mortality 7 ; 8. In 2014, in a systematic review and meta-analysis, Haan et al. [9] identified vitamin D deficiency as a risk factor for severe infections and mortality in the critically ill, whereas another meta-analysis [10] found an association between vitamin D deficiency and mortality in intensive care unit (ICU) patients. Nonetheless, in a recently published study of patients with severe sepsis and septic shock, vitamin D deficiency was not associated with 90-day mortality [11]. So far, the role of vitamin D in the critically ill has not yet been fully understood [12]. Moreover, it remains unknown whether vitamin D deficiency in ICU patients is an epiphenomenon, a marker of illness severity, or is a major contributor of mortality and morbidity with direct causative effects. A good mean of evaluating the presence of vitamin D in the causal pathway is to evaluate if administration improves the mortality/morbidity.

Over the past six years, few randomized controlled trials (RCT) have evaluated the effect of high-dose vitamin D3 therapy using different dose regimens provided by oral, enteral, and parenteral route in critically ill patients 7; 12; 13; 14; 15 ; 16. While the original rationale was to administrate Vitamin D in order to restore the normal body content, many trials also supplemented at supra-physiological level, supporting the concept of pharmaconutrition 12; 13; 14; 15 ; 16. So far, clinical results of these interventional studies have been inconclusive. With regard to current recommendations, in 2015 the Canadian Clinical Practice Guidelines (CPGs) concluded that there were insufficient data to make a recommendation about vitamin D therapy in the critically ill patient [17], whereas the most recent American Society for Parenteral and Enteral Nutrition (ASPEN)/Society of Critical Care Medicine (SCCM) guidelines, based on expert consensus suggest that fat soluble vitamins substitution, including vitamin D, should be considered in ICU patients with history of bariatric surgery accordingly to the recommended dietary allowance (RDA) due to their high risk of vitamin deficiencies but do not support administration in other patients [18]. No precision regarding high-dose supplementation of vitamin D was mentioned.

Putzu et al. [19] have recently published a systematic review and meta-analysis on vitamin D supplementation in the serious illness. However, the authors included one trial

that reported biochemical outcomes and another trial of non-critically ill patients. Moreover, in another meta-analysis of vitamin D therapy Weng et al. [20] after aggregating 4 trials found a significant reduction in hospital length of stay (LOS). Nonetheless, this meta-analysis did not include all the studies evaluating the overall efficacy of vitamin D supplementation on clinical important outcomes in critical care. Thus, we conducted an updated and comprehensive systematic review and meta-analysis of all RCT evaluating high dose vitamin D therapy on relevant clinical outcomes in adult critically ill patients.

2. Methods

2.1. Search strategy and study identification

A literature search was conducted in Embase, CINAHL, Medline, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews to identify all randomized controlled trials (RCTs) published between 2000 and September 2016. No language restrictions were applied and broad search terms were used to find references corresponding to the following words and MeSH headings: “randomized,” “clinical trial,” “critical care”, “critically ill”, “supplementation”, “therapy”, “cholecalciferol”, “calcitriol” and “vitamin D”. The reference lists of the relevant articles were also reviewed to ensure adequate study identification.

2.2. Eligibility criteria

Trials were eligible if they corresponded to the following characteristics:

1. Study design: randomized controlled trials (RCTs) with parallel groups. The trial had to report the primary outcome, hospital mortality, or any of the secondary outcomes, including ICU and hospital LOS, mechanical ventilation days and infection rates as defined by the authors. If hospital mortality was not reported, 30-day mortality was used to complete the meta-analysis.
2. Population: adult patients (≥18 years of age) hospitalized in the ICU, including medical, surgical and neurologic ICU. If ambiguous, a population was considered critically ill if the reported mortality rate was higher than 5% in the control group.
3. Intervention: oral, enteral or parenteral vitamin D administration as 1, 25-dihydroxyvitamin D (calcitriol) or 25-hydroxyvitamin D (cholecalciferol).
4. Comparator: either placebo or a vitamin D administration included in standard nutritional therapy.
5. Outcomes: the trial was required to report any clinical outcomes in ICU patients between mortality, infectious complications, length of ventilation including invasive and non-invasive MV, ICU and hospital length of stay (LOS). Trials reporting only biochemical outcomes were excluded.

2.3. Eligibility review and data abstraction

Two reviewers (PLL and CS) independently screened citation and evaluate the full text of potentially eligible studies in duplicate, then abstracted data onto customized, pre-tested forms. Disagreements between reviewers were resolved through discussion or third party adjudication.

2.4. Assessment of risk of bias

For every included RCT, the methodological quality was assessed in duplicate by two independent reviewers using a data abstraction form with a scoring system from 0 to 14 (see Supplementary material) according to the following criteria:

1. Concealed randomization
2. Extent of blinding
3. Intention-to-treat analysis (ITT)

4. Baseline group comparability
5. Loss to follow-up
6. Description of the studied intervention
7. Similarity of co-interventions between groups
8. Pre-specified and pre-defined clinical outcomes

Reviewers reached consensus for every methodological score obtained during data abstraction. When the trials were only available as abstract, when the published paper was in a language impossible for us to read or when data was missing for adequate data abstraction, trials' authors were contacted to obtain additional details. We designated a trial as a level 1 study if all of the following criteria are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis. A study was considered as level 2 study if any one of the above characteristics was unfulfilled.

2.5. Statistical analysis

Excepting the test for asymmetry, all analyses were conducted using RevMan 5.3 (Cochrane IMS, Oxford, UK) with a random effect model. This model was used due to the low number of included trials and the important difference of patient numbers between Amrein et al. [12] and the other trials. The random model allowed the smaller trials to contribute to the final conclusions of this trial instead of obtaining the same conclusions as our biggest trial. We aggregated data from all trials reporting the analyzed outcome in order to estimate the pooled risk ratio (RR) with 95% confidence intervals (CIs). Pooled RRs were calculated using the Mantel–Haenszel test for the incidence of mortality and infectious complications. When data was continuous as for ICU LOS, hospital LOS and ventilation days, overall weighted mean difference (WMD) with 95% confidence intervals were estimated by the inverse variance approach. The random effects model of DerSimonian and Laird was used to estimate variances for both the Mantel–Haenszel and the inverse variance estimators. We used weighted Mantel–Haenszel $\chi 2$ to test for heterogeneity and we quantified its importance by calculating the Cochrane I^2 value, as proposed in RevMan 5.3 [21]. When more than two groups existed, we combined the number of events, the mean value and standard deviation according to the recommendation in Cochrane handbook [22]. Pre-specified subgroup-analysis was conducted according to the test of subgroup differences described by Deeks et al., and the results expressed using the P values. For the subgroup analysis evaluating high vs low dose, the trials which compared two experimental groups were separated in group A (high dose) and group B (low dose) and were analyzed in their respective forest plot. To evaluate the risk of publication bias, we generated a funnel plot and tested for the asymmetry of the outcomes, as proposed by Egger et al. [23]. Throughout the statistical analysis, we considered a P value to be statistically significant if <0.05.

2.6. Subgroup analysis

Predefined subgroup analyses were conducted to assess the possible influence on the outcomes of the route of administration, the dose of supplemented vitamin D, as well as the vitamin D nutritional status of the patient. We first evaluated if the parenteral administration improved the outcomes when compared to an oral/enteral route of administration. Second, we compared the clinical outcomes when a high dose of Vitamin D was administered, compared to a lower one. The threshold was set to 300,000 IU daily according to Kearns et al. review on vitamin D supplementation in the adult [24]. We evaluated if clinical outcome were improved when supplementation was given in a group of patients with vitamin D deficiency, as defined by serum level <20 ng/mL of cholecalciferol. Finally, we conducted a subgroup analysis by opposing level 1 trials, as previously defined, with low risk of bias, to the level 2 trials with higher risk of bias.

3. Results

3.1. Study identification and selection

A total of 39 relevant citations were identified from the search of computerized bibliographic databases and a review of reference lists from related articles (see Fig. 1). Of these, we excluded 33 due to the following reasons: 6 trials did not include ICU patients 25; 26; 27; 28; 29 ; 30; 8 articles were reviews and meta-analysis 9; 31; 32; 33; 34; 35 ; 36; 18 were observational studies and one study evaluated only biochemical outcomes [37]. Finally, 6 RCTs were included, enrolling a total of 695 patients and a total studied population of 677 patients (see Table 1 ; Table 2 and Supplementary Table 1) 7; 12; 13; 14; 15 ; 16. The reviewers reached 100% agreement on the inclusion of the trials. The analyzed population presented a broad variety of admission diagnosis, including trauma (8,6%), sepsis (27%), cardiovascular (10,6%), neurologic (17,7%) and others. MV was used for 66,5% of the patients while RRT was used in 4,4% of the included patients. The reader is referred to the Supplementary Table 1 for any further details on patient characteristics.

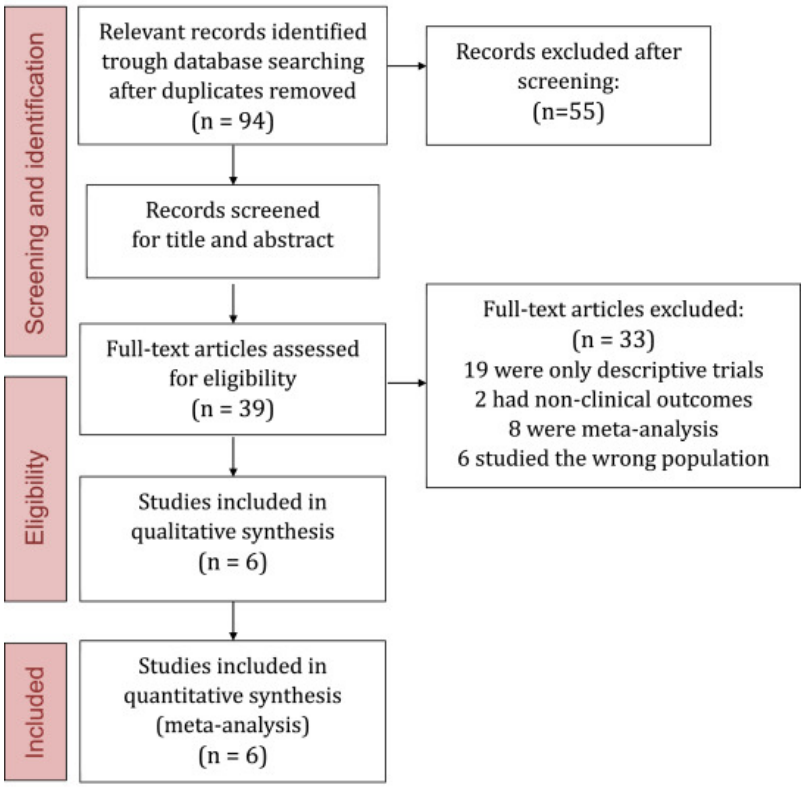


Fig. 1.
Study flow chart of literature search.

Figure options

Table 1.
Randomized clinical Trials Evaluating Vitamin D supplementation in critically ill patients.

Study	Population	Methods Score	Interventions
Amrein 2011	Patients with vitamin D deficiency [25-hydroxyvitamin D (25(OH)D) ≤20 ng/mL] and an expected stay in the ICU >48 h N = 25	C.Random: not sure ITT: no Blinding: double blind (7)	540,000 UI of vitamin D (cholecalciferol = 13, 5 mg) dissolved in 45 mL herbal oil vs. Placebo (herbal oil) both of them enterally or orally.

Study	Population	Methods Score	Interventions
Leaf 2014	Patients older than 18 years, severe sepsis or septic shock, and presence of an arterial or central venous catheter (for blood drawing). N = 67	C.Random: yes ITT: yes Blinding: double blind (12)	A single intravenous dose of calcitriol (2 ug) vs. Placebo (appearing equal volume of saline −2 mL)
Amrein 2014	Patients who were 18 years or older, expected to stay in the ICU for 48 h or more, and found to have a 25-hydroxyvitamin D level of 20 ng/mL (to convert to nmol/L, multiply by 2.496) or lower. N = 492 patients	C.Random: yes ITT: yes Blinding: double blind (12)	540,000 IU of vitamin D3 dissolved in 45 mL of oleum arachidis (Oleovit D3 [containing 180,000 IU of vitamin D3 in 15mLof oleum arachidis per bottle]), either orally or via feeding tube. Vs. Placebo (received 45 mL of oleum arachidis) either orally or via feeding tube.
Quraishi 2015	Patients ≥18 years of age, admitted to the medical or surgical ICU, and within 24 h of new-onset sepsis. N = 30	C.Random: yes ITT: yes Blinding: no (9)	High dose patients (N = 10) supplementation with 400,000 UI cholecalciferol (A) and Low dose patients (N = 10) supplementation with 200,000 UI cholecalciferol (B), both of them supplied in a clear liquid vs. Placebo (supplied in a clear liquid form by a commercial vendor. All interventions orally or enterally).
Nair 2015	Patients were those who developed three of four SIRS criteria within 24 h after admission and were expected to stay in ICU for at least 48 h after randomization. N = 50	C.Random: yes ITT: yes Blinding: single blind (10)	Two doses of 300.000 (0.3 mU) of intramuscular cholecalciferol vs. Standard Therapy received a single dose of 150.000 UI (0.15mU) of intramuscular cholecalciferol.
Han 2016	Patients to receiving care in an ICU with age greater than 18 years; expected to require MV for at least 72 h after study entry; expected to surviving remain in the ICU for at least 96 h after study entry; and enteral access in place to enable delivery of vitamin D3 or placebo. N = 31	C.Random: yes ITT: no Blinding: double blind (8)	High dose (N = 11): to received 2 pills of 50,000 IU of vitamin D3 daily for 5 days (500,000 IU total) (A) and Low dose (N = 10): to receive 1 pill for a total of 250,000 IU (B) vs. Placebo (received two inactive medication tablets daily for 5 days).

Abbreviations: C.Random: concealed randomization; ICU: intensive care unit; ITT: intention to treat; N: number of patients.

Table options

Table 2.
Reported outcomes of included RCTs evaluating vitamin D supplementation in critically ill patients.

Study	Mortality (%)		Infections (%)		LOS Days (n)		Ventilator d
	Experimental	Control	Experimental	Control	Experimental	Control	Experiment
Amrein 2011	**Hospital** 6/12 (50)	**Hospital** 6/13 (46)	NR	NR	**ICU** 13.4 ± 11.7 (12) **Hospital** 23.7 ± 24.7 (12)	**ICU** 14 ± 16.3 (13) **Hospital** 23.2 ± 21.2 (13)	10.57 ± 7.9 (10)
Leaf 2014	**ICU** 7/36 (19) **Hospital** 8/36 (22) **28 days** 6/36 (17)	**ICU** 6/31 (19) **Hospital** 7/31 (23) **28 days** 7/31 (23)	NR	NR	**ICU** 13.3 ± 14.7 (36) **Hospital** 25.9 ± 18.9 (36)	**ICU** 11.2 ± 9.1 (31) **Hospital** 22.2 ± 19 (31)	8.30 ± 11 (3

Study	Mortality (%)		Infections (%)		LOS Days (n)		Ventilator d
	Experimental	Control	Experimental	Control	Experimental	Control	Experiment
Amrein 2014	**ICU** 54/237 (22.8) **Hospital** 67/237 (28.5) **6 month** 83/237 (35)	**ICU** 63/238 (26.5) **Hospital** 84/238 (35.3) **6 month** 102/238 (42.9)	NR	NR	**ICU** 15.7 ± 20.9 (237) **Hospital** 26.7 ± 25.3 (237)	**ICU** 17.3 ± 22.3 (238) **Hospital** 26.7 ± 24.3 (238)	11.58 ± 14. (159)
Quraishi 2015 A	**30 days** 2/10 (20)	**30 days** 3/10 (30)	NR	NR	**ICU** 8 ± 8 (10) **Hospital** 16 ± 10 (10)	**ICU** 10 ± 5 (10) **Hospital** 37 ± 30 (10)	NR
Quraishi 2015 B	**30 days** 3/10 (30)		NR	NR	**ICU** 9 ± 8 (10) **Hospital** 13 ± 5 (10)		NR
Nair 2015	**ICU** 4/25 (16) **Hospital** 5/25 (20) **90 days** 5/25 (20)	**ICU** 5/25 (20) **Hospital** 5/25 (20) **90 days** 5/25 (20)	NR	NR	**ICU** 14.5 ± 16.7 (25) **Hospital** 45.5 ± 12 (25)	**ICU** 18.2 ± 8.91 (25) **Hospital** 40.5 ± 44.5 (25)	NR
Han 2016 A	**Hospital** 1/11 (10) **84 days** 4/11 (36)	**Hospital** 1/10 (10) **84 days** 2/10 (20)	2/11 (18)	3/10 (30)	**ICU** 15 ± 10 (11) **Hospital** 18 ± 11 (11)	**ICU** 23 ± 14 (10) **Hospital** 36 ± 19 (10)	14 ± 10 (11
Han 2016 B	**Hospital** 0/9 **84 days** 1/9 (11)		3/9 (33)	3/10 (30)	**ICU** 17 ± 14 (9) **Hospital** 25 ± 14 (9)		12 ± 10 (9)

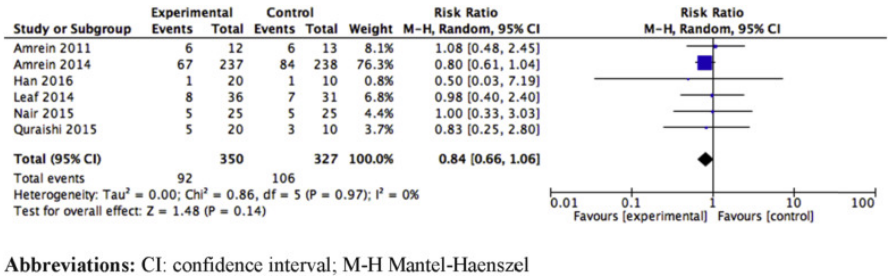
Abbreviations: A: high dose vitamin D supplementation; B: low dose vitamin D supplementation; ICU: intensive care unit; n: number of patients; NR: Not reported.

Table options

3.2. Meta-analysis of primary outcome

3.2.1. Overall hospital mortality

All six RCTs reported overall hospital mortality 7; 12; 13; 14; 15 ; 16. Five trials reported hospital mortality and only one study included 30 days mortality [13]. When statistically pooled, supplementation with vitamin D did not improve mortality (RR 0.84, 95% CI 0.66–1.06, P = 0.14, see Fig. 2). No heterogeneity existed in the data (I^2 = 0%, P = 0.97).



Abbreviations: CI: confidence interval; M-H Mantel-Haenszel

Fig. 2.
Effect of vitamin D on mortality.

Figure options

3.3. Meta-analysis of secondary outcomes

3.3.1. Overall effect on ICU length of stay

ICU LOS was reported in all clinical trials 7; 12; 13; 14; 15 ; 16. The meta-analysis of these data reported no change of ICU LOS when supplementation of vitamin D was administered (WMD −1.42; 95% CI −3.78–0.94, P = 0.24). Heterogeneity was not significant (I^2 = 0% P = 0.69).

3.3.2. Overall effect on hospital length of stay

All six clinical trials reported hospital LOS and, when aggregated, vitamin D supplementation did not change hospital LOS (WMD −3.21; 95% CI −10.27–3.85, P = 0.37) 7; 12; 13; 14; 15 ; 16. However, heterogeneity was on the limit for this analysis (I^2 = 54% P = 0.05).

3.3.3. Mechanical ventilators days

From the six clinical trials included, only four reported mechanical ventilators days 7; 12; 15 ; 16. When analyzed, vitamin D supplementation did not change mechanical ventilators days when compared to placebo (WMD −1.20; 95% CI −3.72–1.33, P = 0.35; I^2 = 0%).

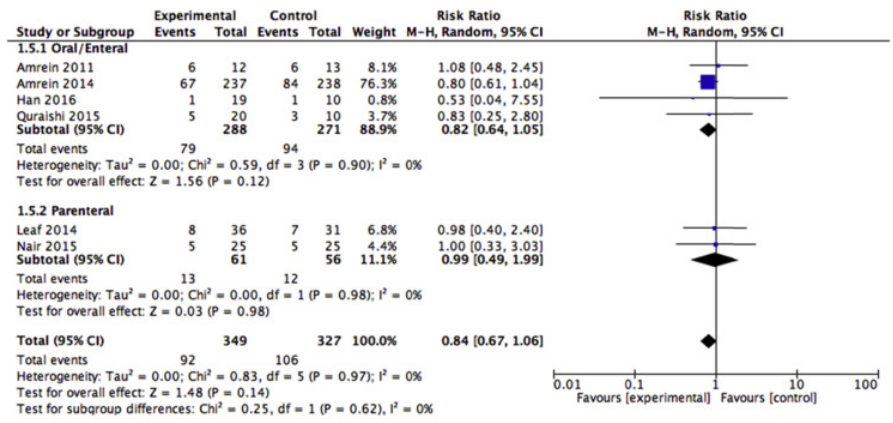
3.3.4. Infections

From all clinical trials, only one study comprising 31 patients reported on infections outcome [15]. No meta-analysis could thus be conducted. In this trial, infections occurred in 18% of the patients exposed to high dose vitamin D supplementation, in 33% of patients with low dose vitamin D, and in 30% of those not supplemented (P = 0.77).

3.4. Subgroup analysis

3.4.1. Oral-enteral vs. parenteral administration

In four of the included RCTs, vitamin D was administered by oral or enteral route 12; 13; 15 ; 16 while two of them were parenteral 7 ; 14. The oral-enteral group showed no improvement in mortality reduction (P = 0.12, see Fig. 3), in hospital LOS (P = 0.16, see Fig. 4) and in other clinical outcomes. Significant heterogeneity existed in these analyses.

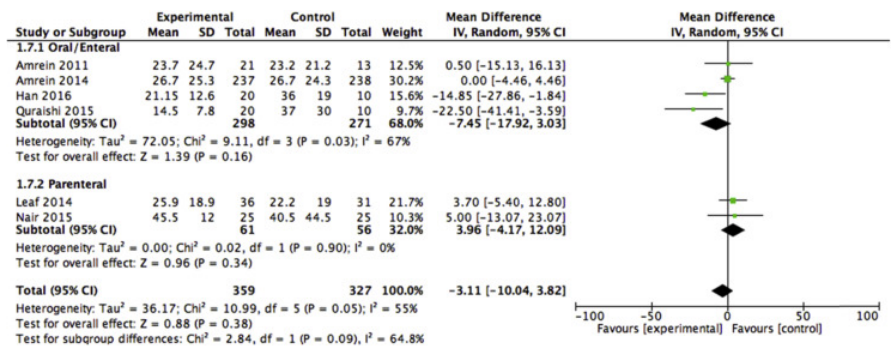


Abbreviations: CI: confidence interval; M-H Mantel-Haenszel

Fig. 3.

Effect on mortality, subgroup analysis oral/enteral vs. parenteral.

Figure options



Abbreviations: CI: confidence interval; M-H Mantel-Haenszel

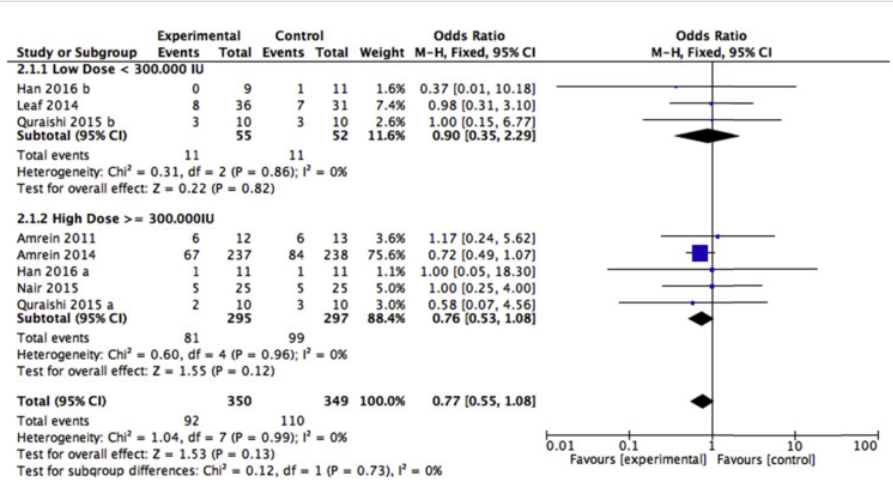
Fig. 4.

Effect on hospital LOS, subgroup analysis oral/enteral vs. parenteral.

Figure options

3.4.2. High vs. low dose vitamin D

Five of them received high dose vitamin D supplementation (higher than 300.000 IU) 12; 13; 14; 15 ; 16 and the three other groups received a low dose (equal or lower than 300.000 IU) 7; 13 ; 15. When statistically compared, there was no significant difference between the 2 dosing groups regarding mortality reduction (RR 0.76, 95% CI 0.53–1.08, P = 0.12, see Fig. 5) and ICU LOS (P = 0.12), No statistical difference existed between both groups regarding hospital LOS (P = 0.76).



Abbreviations: CI: confidence interval; M-H Mantel-Haenszel

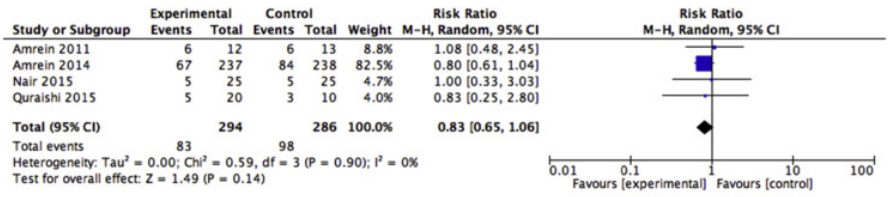
Fig. 5.

Effect on mortality, subgroup analysis high dose vs. low dose.

Figure options

3.4.3. Patients with vitamin D deficiency

We conducted a subgroup analysis with patients insufficient in vitamin D (serum value < 30 ng/mL) 12; 13; 14 ; 16. In this specific group, no reduction in mortality was found (P = 0.14, see Fig. 6). No changes existed regarding ICU LOS (P = 0.19) and hospital LOS (P = 0.56).



Abbreviations: CI: confidence interval; M-H Mantel-Haenszel

Fig. 6.
Effect on mortality, sensibility analysis with vitamin D deficiency.

Figure options

3.4.4. Level 1 vs. level 2 trials

Two trials were level 1 trials 7 ; 12 while the remaining four trials were level 2 trials 13; 14; 15 ; 16. In the high methodological level 1 trials, no improvement in mortality was found (P = 0.11), as well as in other outcomes. In the level 2 trials, no changes existed regarding hospital LOS (P = 0.18) and MV duration (P = 0,18) or other outcomes. Finally, in all analysis, no heterogeneity existed inside each subgroup and no significant differences existed between both subgroups.

3.5. Risk of bias and grading of evidence

Risk of bias regarding indirectness is very low as the results correspond to the research question that was initially asked. All trials included evaluated an intensive care population to whom vitamin D was administered and compared it to a placebo group regarding clinically important outcomes. The heterogeneous population of ICU patients included a broad variety of admission diagnosis, which allows generalization of the results to the different ICU patients.

There is a moderate risk of imprecision bias, because the confidence intervals of our meta-analysis are wide and cross the no-effect line. It must therefore be considered that vitamin D administration did not exhibit significant adverse effects and is not a costly treatment. For most outcomes, risk of inconsistency bias is very low with the heterogeneity analysis resulting in an non-significant value and a I^2 value of 0%. Only hospital LOS presented a substantial inconsistency with a borderline p value of 0,05 with I^2 of 55%.

Individual trials presented a mean and a median methodological score of 9.5 on a maximum of 14 (range 7–13). Randomization was concealed in 5/6 trials (84%) 7; 12; 13; 14 ; 15, ITT analysis was performed in 4/6 trials (67%) 7; 12; 13 ; 14, and double blinding was done in 4/6 of the studies (67%) 7; 12; 15 ; 16. The details of the methodological quality of the individual trials are shown in Table 1.

Publication bias is hard to evaluate but seem low throughout the analysis. A test of asymmetry on the funnel plots was generated for every outcome and they were not significant (mortality, P = 0.47; ICU LOS, P = 0.22, hospital LOS, P = 0.08, MV days, P = 0.34). However, assessing funnel plots asymmetry to investigate publication bias is recommended only if at least 10 trials are included. This data should therefore be interpreted with caution [23]. To further assess the risk of publication bias and according to Cochrane, we conducted a subgroup analysis by opposing high methodological quality to lower quality. We found no difference in subgroups (P = 0.54), orientating us towards the absence of publication bias, but the high quality group only included two trials. In conclusion, publication bias regarding vitamin D administration to critically ill patients is hard to assess, but no data is leading us towards a significant bias.

4. Discussion

Critical illness is associated with a vitamin D deficiency but its physiopathology remains poorly understood. The most accepted mechanism includes a decrease in the protein carrier of the vitamin, which reduces vitamin D reabsorption at the renal tubule [38]. This dramatic reduction of Vitamin D Binding Protein (VDBP) is explained by the same

mechanism responsible for albumin and other serum protein reduction during systemic inflammation, namely the decreased synthesis, the hemodilution during active resuscitation, and the interstitial extravasation in context of increased vascular permeability [39]. Although this reduction could only be a correlated marker to the severity of critical illness, vitamin D deficiency has been associated with increased ICU and hospital length of stay, multiple organ failure, mechanical ventilation and mortality 15 ; 34. In this context, the administration of vitamin D as a pharmaconutrient strategy to the critically ill represents an interesting therapeutic option but until recently, this theme remained scarcely investigated and the conclusions are still weak [40]. Therefore, we conducted a meta-analysis with the overall hypothesis that vitamin D supplementation, either orally, enterally or parenterally, could improve clinically important outcomes in critically ill patients. In our review of literature, we found six RCTs, five of which were published since 2014 7; 12; 13; 14 ; 15 and only one of them included more than 100 patients [12]. Unfortunately, throughout the analysis, no significant improvement in clinical outcomes was associated with vitamin d administration.

Even if these analyses did not reach statistical significance, the results are of notable interest. In the hypothesis, we defined a p value below 0.05 to be significant, which by definition, signifies that a result would have below 5% of chance to be coincidence. Theses results could be explained by an underpowered analysis and therefore looks interesting strictly on a research point of view. This analysis is speculative and the clinicians should remember that according to current knowledge high dose vitamin D supplementation did not improve clinical outcomes in the critically ill. Thus, in agreement with the recent position of the Canadian CPGs we can conclude that our results are still premature to warrant treatment recommendation [17]. Considering the high heterogeneity in the included population, the subgroup could have found a signal in a more specific population. Unfortunately, none were found in this meta-analysis.

With regard to the parenteral subgroup, only two trials totalizing 117 patients were included in the analysis, with the very small amount of 61 events (for mortality analysis), and thus, the results may be underpowered and are associated with a very high risk of imprecision bias 7 ; 14. For all subgroup analyses, we notice that those excluding Amrein et al. (2014) present a small number of aggregated patients and thus, present weak results [12]. These authors gathered in their RCT more patients and in all the others RCTs combined, it is responsible for the major signal of every analysis. To avoid this effect, we used a random effect analysis when conducting the statistical meta-analysis but Amrein et al. still explains up to 75% of the weight effect in certain analysis [12].

Our results differ from a recent meta-analysis published by Putzu et al. who found a significant reduction in mortality (OR = 0.70, 95% CI 0.50–0.98, P = 0.04) [19]. This difference can be explained by the inclusion of Han et al. in our analysis, as well as the inclusion of one trial in their analysis that did not correspond to our inclusion criteria 15 ; 41. This trial was conducted by Grossmann et al. on patients with exacerbated cystic fibrosis and did not correspond to our definition of ICU population [41]. In a meta-analysis recently published with trial sequential analysis, Weng et al. found similar results to this systematic review with no improvement in mortality in ICU, hospital, 30 days, 84 days and 6 months. The authors did not find reduction in hospital mortality (P = 0.10), 30 days mortality (P = 0.07) and 6 months mortality, but this last outcome was only evaluated by one trial [12]. However, the authors found a reduced hospital LOS (MD −6,70 days, 95% CI −13.05 to −0.35) [20] which might be explained by Nair et al. which was not included and by the authors who duplicated the control groups instead of aggregating the two experimental groups when the included RCT had three arms. Therefore, results must be interpreted with caution. Nonetheless, the trial sequential analysis (TSA) by Weng et al. showed that reduction of hospital LOS might be a false positive while the absence of reduction of ICU LOS might me a false negative [20]. These specific results support the idea that more research on vitamin D administration in ICU patients should be conducted.

The strength of our meta-analysis resides in the several methods we used to reduce bias, including a comprehensive literature search and an independent assessment of trials

eligibility, of risk of bias and of data abstraction using pretested form. Moreover, we focused on clinically relevant outcomes to further orientate the clinician on significant outcomes. Nevertheless, we remain aware of the several limitations of this meta-analysis. The first one is the absence of statistically significant data, which could be explained by an underpowered analysis secondary to the limited amount of RCTs yet conducted. Second, we analyzed only data from RCTs while excluding all the comprehensive data contained in the 18 observational trials found in the literature search. Nonetheless, RCTs are the strongest methodology and should guide future practice. Third, Amrein et al. counts for a more than significant part of this meta-analysis and drives the results by its weight [12]. Finally, the studied population was very broad and could therefore hide signal that we did not find in specific subgroups of patients. The pathophysiology of patients hospitalized in ICU can significantly differ, especially as surgical and medical ICU patients were included, and vitamin D could have different effects on subgroups of this broad population. Nonetheless, at the current state of literature, the results found through this meta-analysis are the highest level of evidence available and showed to be neutral.

Moreover, we did not address the type of vitamin D supplementation (calcitriol and cholecalciferol) but it might provide different results. Han et al. suggested, after comparing recent RCTs, that cholecalciferol may induce a more robust immune response 7; 12 ; 42. It could also be interesting to evaluate vitamin D in specific population, as sepsis, but more RCTs are required [43]. When speculating about the discrepancy between vitamin D deficiency and disappointing findings on vitamin D supplementation in ICU patents, we could say that clinical studies on vitamin D therapy in critical care have mostly been small trials with high risk of bias, and therefore inadequate to evaluate clinical efficacy of vitamin D supplementation in the critically ill. In addition, we need to know more about pharmacokinetics and pharmacodynamics of vitamin D therapy in insufficient/deficient ICU patients. From now on, we strongly believe that we should go back to basics and obtain more pharmacokinetic data using specific dosing strategies. We certainly believe that, without this unavoidable first step exploring pharmacokinetic data, no further research on vitamin D therapy in the critically ill is warranted.

5. Conclusion

Vitamin D deficiency seems to be a common condition in critically ill patients. The physiopathological explanation underlying this finding is still scarcely understood, but vitamin D deficiency is associated with poorer outcome. Nonetheless, after aggregating data from the most recent RCTs on vitamin D supplementation in the critically ill, we did not find any statistically significant benefits on clinical outcomes. With these results, it is not possible to include vitamin D in a causal pathway of increased mortality/morbidity as it could still be related to a simple epiphenomenon. The statistical imprecision observed could be explained by the sparse number of trials included in this meta-analysis as well as the heterogeneous population included in this meta-analysis. Considering this, data is currently insufficient to allow any strong conclusion and more research is needed, notably to explore the pharmacokinetic profile of vitamin D administration.

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Disclosures

None.

Conflict of interest

None.

Appendix A. Supplementary data

The following is the supplementary data related to this article:

Help with DOCX files

Options

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