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Critical Care 2011, **15**:R104 doi:10.1186/cc10120

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ISSN 1364-8535

Article type Research

Submission date 3 November 2010

Acceptance date 28 March 2011

Publication date 28 March 2011

Article URL <http://ccforum.com/content/15/2/R104>

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Short-term effects of high-dose oral vitamin D3 in critically ill vitamin D deficient patients: a randomized, double-blind, placebo-controlled pilot study

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ABSTRACT

Introduction

Vitamin D deficiency is encountered frequently in critically ill patients and might be harmful. Current nutrition guidelines recommend very low vitamin D doses. The objective of this trial was to evaluate the safety and efficacy of a single oral high-dose vitamin D3 supplementation in an intensive care setting over a one-week observation period.

Methods

This was a randomized, double-blind, placebo-controlled pilot study in a medical ICU at a tertiary care university center in Graz, Austria. Twenty-five patients (mean age 62 ± 16 yrs) with vitamin D deficiency [25-hydroxyvitamin D (25(OH)D) ≤ 20 ng/ml] and an expected stay in the ICU >48 hours were included and randomly received either 540,000 IU (corresponding to 13.5 mg) of cholecalciferol (VITD) dissolved in 45 ml herbal oil or matched placebo (PBO) orally or via feeding tube.

Results

The mean serum 25(OH)D increase in the intervention group was 25 ng/ml (range 1-47 ng/ml). The highest 25(OH)D level reached was 64 ng/ml, while two patients showed a small (7 ng/ml) or no response (1 ng/ml). Hypercalcemia or hypercalciuria did not occur in any patient. From day 0 to day 7, total serum calcium levels increased by 0.10 (PBO) and 0.15 mmol/L (VITD; $P < 0.05$ for both), while ionized calcium levels increased by 0.11 (PBO) and 0.05 mmol/L (VITD; $P < 0.05$ for both).

Parathyroid hormone levels decreased by 19 and 28 pg/ml (PBO and VITD, ns) over the seven days, while 1,25(OH)D showed a transient significant increase in the VITD group only.

Conclusions

This pilot study shows that a single oral ultra-high dose of cholecalciferol corrects vitamin D deficiency within 2 days in most patients without causing adverse effects like hypercalcemia or hypercalciuria. Further research is needed to confirm our results and establish whether 25(OH)D supplementation can affect the clinical outcome of vitamin D deficient critically ill patients.

EudraCT Number: 2009-012080-34

German Clinical Trials Register (DRKS): DRKS00000750

Introduction

Hypocalcemia is frequent in critical illness and has been related to adverse clinical outcomes including increased mortality [1-3]. Underlying reasons remain largely unknown but vitamin D deficiency and accompanying secondary hyperparathyroidism may be one of them. However, there is currently no proven intervention which corrects and sustains calcium levels safely and effectively in critical illness. Various forms of calcium and calcitriol supplementation were unable to demonstrate sustained effects and in some cases resulted in hypercalcemia and increased mortality [2]. Several case reports have suggested vitamin D deficiency as a cause of hypocalcemia with adverse outcome, which can be corrected effectively and safely by vitamin D supplementation [4-5].

Published data [6-9] as well as our own observations suggest that most critically ill patients are vitamin D deficient, although there are concerns in this special group of patients that acute fluid shifts and inflammatory states may influence the assessment and interpretation of vitamin status [10-13]. There is now extensive literature on adverse health outcomes in patients with vitamin D deficiency reporting increased mortality, cardiovascular events and impaired function of the immune and musculoskeletal system [14-15]. Many tissues, including cardiomyocytes and immune cells have a nuclear vitamin D receptor and respond to 1,25-dihydroxyvitamin D [1,25(OH)₂D] [16-17]. This active form of vitamin D is either derived from the kidney where it is secreted into the circulation or is formed within the target cell by hydroxylation of 25(OH)D to 1,25(OH)₂D. A large potential for beneficial clinical effects of a normalized vitamin D status in the setting of critically ill patients has recently been brought forward and attracted attention [18]. The beneficial effects of vitamin D on muscle, heart and immune function could be of particular interest in

critical care, especially in patients with respiratory failure or those who are on mechanical ventilation for other reasons.

The current recommendation for parenteral vitamin D₃ is 200 IU per day [19], a dose that is too low to have an effect on serum vitamin D levels in patients with established vitamin D deficiency. European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines do not specifically address vitamin D supplementation [20-21].

Insecurity exists on the dosage of vitamin D supplementation that should be used. Vitamin D intoxication can potentially be life-threatening but the majority of officially recorded cases could be related to prolonged intakes of >40,000 IU per day [22]. Two study groups have recently shown safety and efficacy of a single high-dose cholecalciferol administration in rheumatologic and elderly patients [23-24], and here mean increases of 26 ng/ml at a dose of 300,000 IU (von Restorff) and 28 ng/ml at 500,000 IU (Bacon) one to three months after administration were reported. The feasibility of 60,000 IU cholecalciferol given twice a week to critically ill patients has been studied by a Spanish group but in this report safety issues were not addressed [25]. Except for dosing problems further main limitations of vitamin D administration include the contraindication for intramuscular injections in most ICU patients, the unavailability of parenteral high-dose vitamin D formulations and finally unreliable gastrointestinal absorption after oral dosing due to multifactorial gastrointestinal dysfunction, changes in gastrointestinal blood supply and motility, as well as the presence of sepsis and multiorgan failure.

Our hypothesis was that a single ultra-high dose may overcome some of these limitations and is able to restore normal 25(OH)D levels without causing adverse effects. The results obtained from this study should provide a basis of an easy-to-administer dosing regimen for other prospective intervention trials in an ICU setting.

Materials and methods

The trial was started in August 2009 and terminated in January 2010. In a single-center setting of a tertiary care university hospital, 25 vitamin D deficient adult patients [25(OH)D levels \leq 20 ng/ml] with an expected stay in the medical ICU of >48 hours were randomly assigned to receive either 540,000 IU of vitamin D₃ (which equalled 3 bottles of a commercially available vitamin D preparation in Austria: Oleovit D₃[®] solution; 400 IU vitamin D₃/drop) dissolved in 45 ml of herbal oil ("VITD" group) or herbal oil only (placebo group, "PBO"). The study medication was prepared, labelled and randomized by a pharmacist and physician not involved in the trial. The randomization was performed with sealed envelopes and all aspects of the trial were performed in a double-blind fashion. Exclusion criteria included moribund patients expected to die within 24 hours, hypercalcemia, ileus, pregnancy and a history of kidney stones, sarcoidosis or tuberculosis. Most patients received the study medication via a nasogastric feeding tube, while 2 patients in each group were able to take it orally.

The institutional ethical committee approved the trial before commencement (protocol number: 20-366 ex 08/09; EudraCT 2009-012080-34, DRKS00000750). Patients able to follow study protocol gave informed consent in written form while mechanically ventilated patients were asked for their approval after regaining consciousness. 25-hydroxyvitamin D was measured by enzyme immunoassay (IDS, Boldon, United Kingdom). On weekdays, 25(OH)D analyses in our institution were performed on a daily basis. 1,25-dihydroxyvitamin D was analysed with ELISA (Immunodiagnostic Systems, Boldon, UK). Serum electrolytes as well as urinary creatinine and electrolytes were measured on a Roche Modular (Roche Diagnostics, Mannheim, Germany). Parathyroid hormone was analyzed by

electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany). Serum triglycerides were determined enzymatically with the GPO-PAP method (Roche Diagnostics, Mannheim, Germany). N-terminal prohormone brain natriuretic peptide (NT-proBNP) was measured by electrochemiluminescence (Elecsys 2010, Roche Diagnostics, Mannheim, Germany). The active study participation for each patient lasted 7 days with an optional follow-up at 28 days in case patients were still residing within the hospital. The primary endpoint was the percentage of patients who reached 25(OH)D levels ≥ 30 ng/ml on day 7. Secondary endpoints included various biochemical and clinical parameters related to vitamin D and mineral metabolism [i.e. 1,25(OH)₂D, serum parathyroid hormone (PTH) levels, serum electrolytes, urinary calcium/creatinine ratio, and NT-proBNP levels], length of hospital and ICU stay, duration of mechanical ventilation and catecholamine support as well as hospital mortality.

Statistical Analysis

Data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA) and are expressed as mean \pm standard deviation or median (interquartile range) as appropriate. Between-group comparisons were carried out using Mann-Whitney-U test and χ^2 -test where appropriate. Unifactorial repeated measures ANOVA was used to analyze changes in blood and urinary parameters.

Results

Out of 25 patients enrolled we could obtain results from 20 at day 7 (10 in each group). The 25(OH)D level in the VITD group was 13.1 ± 2.0 ng/ml (mean \pm standard deviation) on day 0, 35.1 ± 15.2 ng/ml on day 3 and 38.2 ± 16.5 ng/ml on day 7

(respective interquartile ranges [IQR] 3.5, 18.5 and 21.5), while in the PBO group it was 14.1 ± 3.7 ng/ml on day 0, 14.5 ± 4.6 ng/ml on day 3 and 13.7 ± 4.2 ng/ml on day 7 (IQR 7.2, 6.2 and 7.5).

Clinical characteristics of the participants are given in Table 1. Biochemical changes during the follow-up period are shown in Table 2. Already on day 1, 25(OH)D was significantly higher in the intervention group (Figure 1). Eight out of 10 patients showed a normalization of 25(OH)D levels (≥ 30 ng/ml), and the highest level achieved was 64 ng/ml on day 3.

Two patients in the VITD group demonstrated either a small (7 ng/ml) or no (1 ng/ml) increase in 25(OH)D levels. This may in one patient be attributable to gastrointestinal dysfunction after hypoxia related to near-drowning and resuscitation, and in the other to a history of sclerodermiform gastrointestinal graft-versus-host disease after allogeneic stem cell transplantation. Individual patient data are given in Table 3.

Total serum calcium and ionized calcium increased significantly in both groups, whereas 1,25(OH)₂D levels did so in the VITD group only. The proportion of patients with normocalcemia on day 3 and 7 (ionized calcium ≥ 1.15 mmol/l) was not significantly different between both groups. Serum PTH levels had declined although not significantly in both groups at day 7. In this pilot study there were no differences in clinical outcome variables like duration of mechanical ventilation, vasopressor dependency or mortality between the two groups (Table 1). Interestingly, hospital mortality in patients who became normocalcemic on day 3 (ionized calcium ≥ 1.15 mmol/l) compared to those who remained in the hypocalcemic range was lower (20% versus 55%) although this difference did not reach statistical significance.

Discussion

In this pilot study an enteral ultra-high dose of 540,000 IU of vitamin D₃ given once to vitamin D deficient patients was able to rapidly normalize 25(OH)D levels in most patients in a medical ICU setting. Conversely, routine replacement with daily doses of 200 IU of cholecalciferol in the PBO group did not have any effect on 25(OH)D levels. The highest achieved 25(OH)D level in the VITD group was 64 ng/ml and far away from levels thought to be indicative of toxicity (>200 ng/ml) [22]. However, the individual maximal rise following application of this single dose of vitamin D₃ was variable, ranging from 1 to 47 ng/ml. In other (non-critically ill) populations the effect of a large dose of vitamin D yielded somewhat comparable or slightly higher 25(OH)D levels one week following administration [24, 26].

The progressive increase in 25(OH)D levels may not only be explained by initial differences in intestinal absorption of vitamin D₃, but also by limited capacity of the vitamin D binding protein transport system, or that of the liver to hydroxylate the precursor. Moreover, there may be interindividual differences applying to storage effects, whereby cholecalciferol is taken up or released by adipose and muscle tissues. Most of the vitamin D, however, that enters the body is catabolized and excreted without ever being stored in tissues, and without ever becoming 25(OH)D [27]. We thus cannot exclude that either a change towards smaller dosages or more frequent dosing intervals may also have yielded the desired effects and normalized 25(OH)D levels.

Our study provides novel information on how vitamin D replacement may correct vitamin D deficiency. Of interest in this study is also the plasma kinetics of 1,25(OH)₂D that in this small patient sample indicated an progressive and at day 3 almost 3-fold increase above baseline levels that seemed to rapidly decline thereafter. Since serum PTH and total calcium levels which both modulate CYP27B1

activity remained unchanged during that period it seems that this transient rise in 1,25(OH)₂D was mainly attributable to the boost of suddenly available 25(OH)D substrate. A plausible reason for the subsequent decrease in 1,25(OH)₂D levels following day 3 may be the induction of CYP24 hydroxylase gene that shifts 25(OH)D more towards production of inactive 24,25(OH)₂D thus limiting the rise of 1,25(OH)₂D levels. Serum calcium levels increased in both groups over the one-week observation period (without a respective change in serum protein) and likely represent the consequence of acute immobilization on bone turnover dynamics. It is of note that despite the marked increases in serum 25(OH)D and 1,25(OH)₂D as well as serum calcium levels there was no clear-cut suppression of PTH secretion in the VITD group and only a tendency for lower levels. We speculate that these data may be indicative of a change in calcium responsiveness of the parathyroid gland in critically ill patients. Hypercalcemia was not encountered at any time-point in this patient setting. Despite the high fat content of the study medication, triglyceride levels did not change significantly in either group, neither did NTproBNP serum levels, as opposed to recent results in older patients with heart failure [28].

The most important limitation of this pilot study is its size. The results may not be applicable to every patient group encountered in the ICU. Not surprisingly, we did not find any differences in clinical outcome parameters, however, the sample size and its statistical power did not allow for such analysis. A larger trial addressing these issues is currently being performed at our institution.

Conclusions

High-dose vitamin D continues to be a promising and inexpensive intervention in vitamin D deficient critically ill patients that has a low risk profile and a broad

therapeutic window. Further trials are needed to confirm that the dosing scheme proposed by the results of this study is indeed reasonable and most importantly, that normalization of 25(OH)D status is also related to improvement in clinical outcome parameters.

Key messages

- Vitamin D deficiency is highly prevalent and is linked to increased morbidity and mortality in the general population.
- Vitamin D plays a crucial role in calcium homeostasis besides other skeletal and non-skeletal effects; it has an excellent safety profile and likely a broad therapeutic window.
- The scarce available data suggests that vitamin D deficiency affects the majority of patients in the ICU despite vitamin D supplementation in enteral and parenteral nutrition.
- This pilot study is the first randomized controlled trial that investigates short-term effects of high-dose vitamin D in a limited number of critically ill patients.
- Further research is needed to study whether vitamin D deficiency is an independent risk factor for the critically ill and if correction leads to clinical benefits.

Abbreviations

25(OH)D, 25-hydroxyvitamin D; 1,25(OH)₂D, 1,25-hydroxyvitamin D; CPR, cardiopulmonary resuscitation; CYP, cytochrome P450 enzyme; FT, feeding tube; MV, mechanical ventilation; NTproBNP, N-terminal prohormone brain natriuretic peptide; O, oral; PBO, placebo; PTH, parathyroid hormone; VITD, vitamin D; VP, vasopressor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The authors' responsibilities were as follows—KA and HD designed the study, performed the statistical analysis and drafted the manuscript; AH, HS and CS participated in data collection, analysis and preparation of the manuscript; GW participated in data collection and analysis; TP, KS and TS revised the manuscript.

Acknowledgements

The authors would like to thank Harald Lothaller for support with the statistical analyses, James Cody for language editing and the laboratory teams, especially Barbara Obermayer-Pietsch, for performing the analyses in addition to their routine workload.

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TABLES

Table 1. Clinical characteristics at baseline and secondary clinical outcomes of the two groups

	Placebo (n=13)	Vitamin D (n= 12)	P- Value
<i>Baseline characteristics</i>			
Male – no. (%)	10 (77)	9 (75)	.91
Age (yrs)	64.1±16.4	61.1±16.7	.65
Body Mass Index (kg/m ²)	29.3±8.5	28.7±9.7	.87
SAPS II (ICU admission)	38.3±22.3	33.2±12.2	.47
TISS (study start)	38.0±7.2	30.2±7.1	.08
Renal replacement therapy – no. (%)	3 (23)	1 (8)	.31
Diagnostic category	infectious (4) cardiovascular (4) neurologic (4) gastrointestinal (1) other (0)	infectious (6) cardiovascular (3) neurologic (1) gastrointestinal (0) other (2)	-
Mechanical ventilation - no.(%)	11 (85)	10 (83)	.93
Vasopressor therapy - no.(%)	12 (92)	8 (67)	.10
<i>Outcome variables</i>			
Mechanical ventilation – duration (hrs)	163 (91-541)	229 (82-366)	.88
Vasopressor therapy - duration (hrs)	146 (48-351)	65 (42-299)	.56
Hospital stay, days (from study start)	15 (8-38)	16 (8-32)	.97
ICU stay, days (from study start)	6 (3-23)	10 (5-21)	.54
Hospital mortality - no.(%)	6 (46)	6 (50)	.84

Continuous data are presented as means (SD) or median (IQR), categorical data are shown in total numbers (percentages).

SAPS, simplified acute physiology score; TISS 28, Therapeutic Intervention Scoring System

Table 2. Biochemical changes during the 7-day observational period

	Day 0	Day 1	Day 2	Day 3	Day 7
25(OH)D (ng/ml)					
<i>Placebo group</i>	14.1	15.3*	15.0*	14.5*	13.7*
<i>Vitamin D group</i>	13.1	20.5*§	33.1*§	35.1*§	38.2*§
1,25(OH) ₂ D (pmol/l)					
<i>Placebo group</i>	50.6	36.3*	36.6	47.1	67.0
<i>Vitamin D group</i>	68.6	89.5*§	175.2*§	170.8*§	114.2
PTH (pg/ml)					
<i>Placebo group</i>	91.3	72.0	79.0	75.7	71.7
<i>Vitamin D group</i>	73.7	65.1	77.3	100.4	52.0
Ionized serum calcium (mmol/l)					
<i>Placebo group</i>	1.03	-	-	1.05	1.14§
<i>Vitamin D group</i>	1.09	-	-	1.11	1.14§
Total serum calcium (mmol/l)					
<i>Placebo group</i>	2.03	2.02	1.98	2.02	2.13§
<i>Vitamin D group</i>	2.05	2.05	2.09	2.12	2.20§
Serum phosphorus (mmol/l)					
<i>Placebo group</i>	1.57*	1.34	1.49*	1.51*	1.22
<i>Vitamin D group</i>	1.01*	1.20	1.08*	1.07*	1.17
Triglycerides (mg/dl)					
<i>Placebo group</i>	111	126	-	-	116
<i>Vitamin D group</i>	180	175	-	-	178
NTproBNP (pg/ml)					
<i>Placebo group</i>	2100	-	-	-	2120
<i>Vitamin D group</i>	3089	-	-	-	3117
Urinary calcium/creatinine ratio (mmol/mmol)					
<i>Placebo group</i>	0.38	0.24	0.14	0.15	0.41
<i>Vitamin D group</i>	0.38	0.19	0.27	0.28	0.27

NTproBNP, N-terminal prohormone brain natriuretic peptide; PTH, parathyroid hormone. §= P < 0.05 for intra-group comparisons (calculated in relation to baseline values) and * =P< 0.05 for between-group comparisons.

Table 3. Clinical characteristics of individuals in the VITD group

	Gender	Age	BMI	Diagnosis	Gastrointestinal function	Application	VP	MV	25(OH)D levels		
									Day 0	Day 3	Day 7
02	female	83	33,2	Pneumonia	normal	FT	yes	yes	13,7	64,2	59,4
05	male	72	30,1	Heart failure, renal transplant	normal	FT	yes	yes	12,2	33,1	34,8
06	male	77	21,1	Myelodysplastic syndrome, sepsis	normal	O	no	no	10,1	36,5	-
08	male	84	23,1	Pneumonia	normal	FT	yes	yes	16,0	50,6	63,4
11	male	55	36,6	Wegener's granulomatosis, renal failure	normal	FT	no	yes	10,8	26,9	29,8
14	female	45	21,7	CPR (near-drowning)	hypoxic gastrointestinal dysfunction	FT	yes	yes	9,7	8,3	10,3
15	male	78	27,0	Seizures	normal	FT	no	yes	10,1	63,5	-
16	male	58	27,4	H1N1 influenza, renal transplant	normal	O	no	no	13,7	30,5	50,3
18	male	47	27,5	H1N1 influenza, renal transplant	normal	FT	yes	yes	15,1	42,9	29,3
22	female	51	24,8	CPR (ventricular fibrillation)	normal	FT	yes	yes	12,8	36,6	43,6
25	male	46	17,3	Allogeneic stem cell transplantation for chronic	sclerodermiform gastrointestinal graft-versus-host disease	FT	yes	yes	15,4	24,5	22,1
26	male	37	54,6	Pneumonia	normal	FT	yes	yes	12,0	33,0	38,8

CPR, cardiopulmonary resuscitation; FT, feeding tube; MV, mechanical ventilation; O, oral; VP, vasopressor.

Figure legends

Figure 1: Mean 25-hydroxyvitamin D levels (\pm SEM) after a single enteral dose of 540,000 IU vitamin D3 or placebo in vitamin D deficient patients at a medical ICU. The numbers given below the study days refer to the number of patients per group

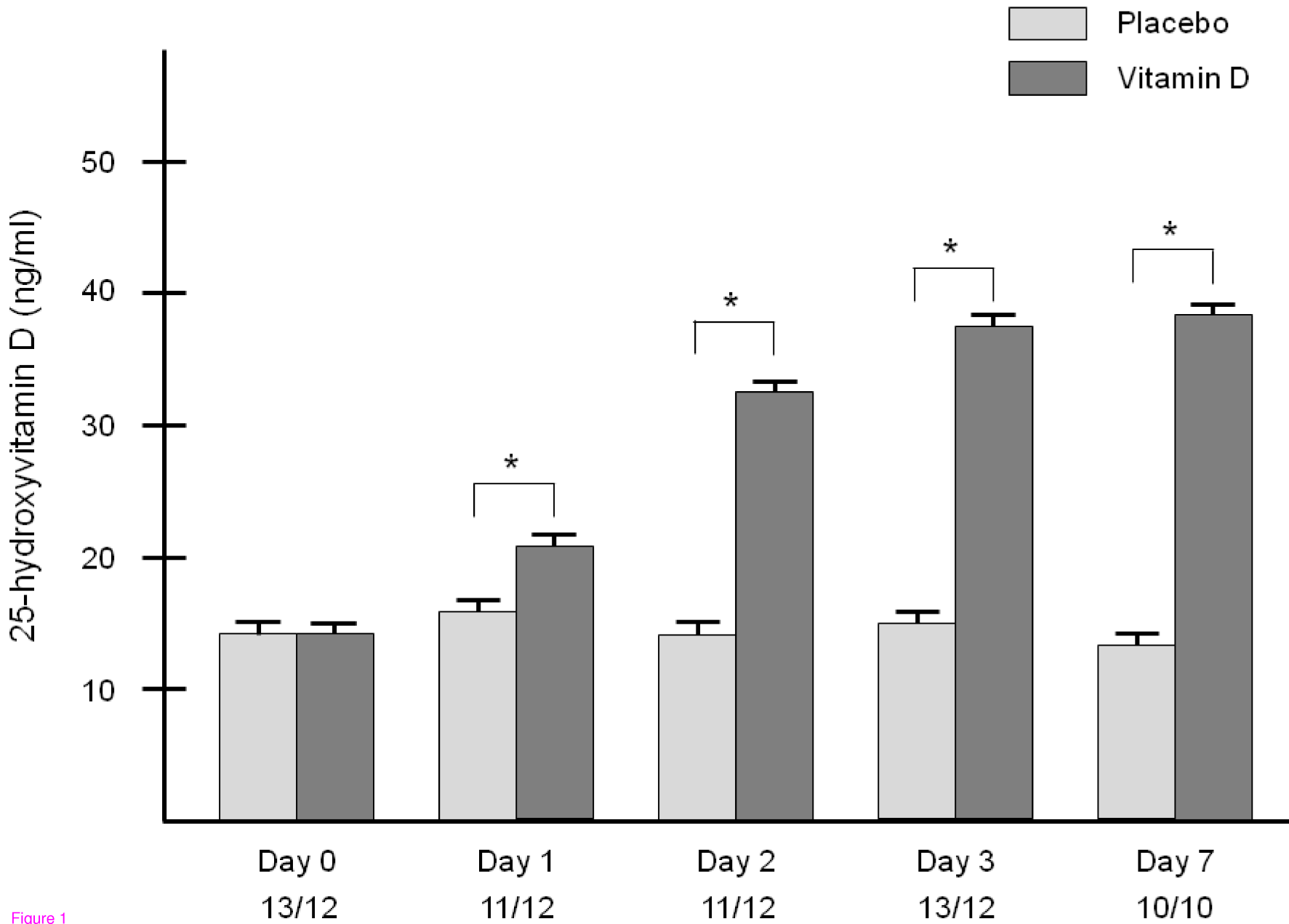


Figure 1