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Original Article

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The Effect of Vitamin D Supplementation on Erythropoietin Utilization in Hemodialysis Patients: A Semi-experimental Study

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ABSTRACT

Background: This study aimed to evaluate the effect of vitamin D (cholecalciferol) supplementation on erythropoietin doses in hemodialysis patients.

Methods: In this semi-experimental study, we enrolled chronic kidney disease patients undergoing hemodialysis, referred to Shahid Beheshti hospital in Babol, Iran in 2018. All patients with concomitant serum levels of 25-hydroxyvitamin D less than 30 ng/mL and hemoglobin below 10 g/dL were enrolled. These patients were treated with the oral pearl of vitamin D for 12 weeks. Monthly levels of serum vitamin D and hemoglobin were measured. Also, erythropoietin doses were examined at baseline and each month after receiving cholecalciferol supplementation. A *P*-value <.05 was considered significant.

Results: In total, 38 patients (22 females and 16 males) with a mean age of 48.34 ± 14.62 years were enrolled. The mean erythropoietin dose was 59 684.21 ± 27 404.08 U/month at baseline and decreased to 51 157.89 ± 27 503.83 U/month after treatment in all patients ($P = .019$). The mean erythropoietin dose in the responders' group (25-D ≥30 ng/mL) was reduced ($P = .032$). Also, hemoglobin level increased ($P < .001$) after treatment compared to the baseline. There was no significant difference in the non-responders group (25-D <30 ng/mL) to erythropoietin dose and the hemoglobin level after treatment. Additionally, in all patients, the serum level of 25-D ($P < .001$ (and hemoglobin level ($P = .028$) were significantly different before and after treatment.

Conclusion: Our findings indicated that cholecalciferol administration might reduce the need for erythropoietin doses in end-stage renal disease patients undergoing hemodialysis.

Keywords: Chronic renal disease, anemia, vitamin D, erythropoietin, hemodialysis, cholecalciferol

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INTRODUCTION

According to international guidelines, chronic kidney disease (CKD) is defined as reduced glomerular filtration rate <60 mL/min/1.73 m^2 or increased urinary albumin excretion accompanied by other structural and functional abnormalities at least for a 3-month duration.[1-3] In 2017, the global prevalence of CKD was 9.1% (697.5 million cases), and 1.2 million people died from CKD worldwide.[4] In a meta-analysis study of 70 605 population in Iran, the prevalence of CKD was 15.1%.[5] Patients with CKD usually suffer from several complications such as cardiovascular disease, bone and mineral disorders, hypertension, diabetes, dyslipidemia, and anemia.[6]

Anemia, hemoglobin (Hb) levels <13.5 g/L in males and <12.0 g/L in females, is among the most common complications in CKD patients.[7] Generally, anemia is observed in the third stage of CKD, and the severity increases with the progress in CKD stages.[8] It is estimated that the likelihood of anemia occurrence in CKD patients is almost

2 times more than the general population.[9] Anemia can be associated with poor prognosis, decreased quality of life, increased incidences of cardiopulmonary diseases, and a higher mortality rate in CKD patients.[10-12] According to the Kidney Disease: Improving Global Outcomes guideline, to avoid repeated blood transfusion, anemia must be treated by erythrocyte stimulation agents (ESA) and iron supplements if associated with iron deficiency.[13] Another complication among CKD patients is vitamin D deficiency.[14] Some studies reported that patients' anemia improves with increment in serum vitamin D levels.[15]

Vitamin D (25-OH vitamin D) is converted to active form (1,25-dihydroxy vitamin D) by 1α-hydroxylase in renal parenchymal tissues.[16] There are renal damages and functional tissues loss in patients with CKD[16] leading to low levels of renal 1α-hydroxylase and 1,25-dihydroxy vitamin D.[16] Thus, the serum level of vitamin D may be low in CKD patients.[17] More than 60% of patients with CKD and glomerular filtration rate <30 mL/min/1.73 m^2 have a low vitamin D level.[18] Therefore, the treatment by active vitamin D (1,25-dihydrocholychalciferol) is necessary for patients with end-stage renal disease (ESRD). Although bone metabolism is a major effect of vitamin D, most body tissues have vitamin D receptors. Vitamin D has other functions such as erythroid precursor proliferation, angiogenesis, production and stimulation of cellular maturation, and regulation of the immune response.[19,20] Recent studies have shown that vitamin D deficiency is associated with low Hb levels and increased resistance response to ESA. The serum hepcidin level significantly decreased after treatment by ergocalciferol (ERGO) and was raised as a response to ESA.[20-22]

Most CKD patients undergoing hemodialysis require erythropoietin (EPO) supplementation (an expensive drug) to maintain their serum Hb between 11 and 12 g/L.[23] Previous studies have evaluated the impact of vitamin D administration on EPO utilization in CKD patients. Some of these studies have shown that such intervention reduces EPO utilization,[23,24] while others have not confirmed the reduction.[25] Due to discrepancies in the findings of the studies and the paucity of clinical data in this field, the present study was designed to examine the effect of vitamin D supplementation on EPO doses in hemodialysis patients.

MAIN POINT

- Hemodialysis patients have usually vitamin D deficiency and anemia.
- Vitamin D supplementation and increased serum level of vitamin D by cholecalciferol to more than 30gr/mL can increase the hemoglobin level.
- So the need for erythropoietin for the correctional of anemia decreased and the cost of drugs for an increase of hemoglobin decreased.

METHODS

Study Design and Participant

This semi-experimental (without control group) study was carried out on 38 hemodialysis patients (57.8% male and 42.2% female), with a mean age of 48.3 ± 14.6 years, referred to the hemodialysis ward of Shahid Beheshti hospital in Babol, Iran in 2018. Demographic and clinical information was collected using the medical records and file reviews. The following information was extracted: age, sex, vitamin D level, iron, ferritin, transferrin and iron-binding capacity (TIBC), calcium, alkaline phosphorus and phosphatase, and the doses of consumption drugs (EPO and iron).

Sampling and Eligibility Criteria

Method sampling was census and according to eligibility criteria. Inclusion criteria were: all ESRD patients with regular (2-3 times a week) hemodialysis, EPO administration at least during the past 6 months, Hb level less than 10 g/dL, serum vitamin D level below 30 ng/mL, serum phosphorus level less than 6.5 mg/dL, modified serum calcium level less than 10.5 mg/dL, and patients without liver diseases. Samples were excluded if they underwent a kidney transplant or their treatment was incomplete within 12 weeks.

Intervention

In this study, participants were adults more than 20 years old. They were followed every 4 weeks for a period of 12 weeks. Patients with serum vitamin D levels less than 10 ng/mL were prescribed pearl of vitamin D 50 000 IU/week for 6 weeks and 1000 IU daily for another 6 weeks. Also, patients with serum vitamin D levels between 10 and 30 ng/mL were treated with the pearl of vitamin D 1000 IU daily doses for 12 weeks. This treatment protocol was obtained from previous studies.[26,27] According to the Hb level, all patients were treated with EPO at doses of 2000, 4000, or 10000 IU 2-3 times per week at the beginning of the study. If Hb level surpassed 11 g/L, EPO dosage was reduced to 25% of the previous dose to prevent polycythemia or hypertension. Erythropoietin was produced by Pooyesh Darou Pharmaceutical Company, Tehran, Iran.

Evolution of Laboratory Parameters

Serum vitamin D and Hb levels were monitored every 4 weeks to 12 weeks. Vitamin D (25-OH-Vitamin D) level was assessed by the enzyme-linked immunosorbent assay (ELISA) method from 2 cc blood by Ideal Tashkhis kit. Additionally, serum levels of iron, ferritin, TIBC, calcium, phosphorus, alkaline phosphatase, and albumin were monitored monthly. Ferritin level was checked by the ELISA method (Pishtaz Teb, Iran). Transferrin and iron-binding capacity, phosphorus, and albumin levels were measured using an auto-analyzer and Pars Azmun kit. Alkaline phosphatase and calcium levels were checked by using an auto analyzer and Man kit. All tests were done in Shahid Beheshti Hospital laboratories.

Statistical Analysis

Data were statistically analyzed by SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Categorical (sex) and continuous variables (age and laboratory parameters) were assessed by frequency (percentages) and mean ± standard deviation, respectively. The doses of drug consumption (i.e., vitamins D, EPO, and iron) and laboratory results before and after treatment were compared using the paired sample *t*-test. A *P*-value <.05 was considered a statistically significant test.

Ethics Approval

The Ethics Committee of Babol University of Medical Sciences, Babol, Iran approved this study (approval no. MUBABOL HRI. REC. 1397. 244). The objectives of the study were explained to all patients and their informed consent was obtained.

RESULTS

Preliminary results indicated that after initial inspections, 55 patients met inclusion criteria (initially there were 180 patients). During the follow-up, 16 patients were excluded for reasons such as transferring to another center and kidney transplantation. Finally, 38 patients were enrolled in this study (Figure 1).

Among the selected patients, the most common causes of renal failure were hypertension (49%) and diabetes (28%), respectively. The finding of this study demonstrated that serum vitamin D levels of 23 (~59%), 9 (~23%), and 7 (~18%) patients were 20-30 mL/ng, 10-20 mL/ng, and <10 mL/ng, respectively. The mean baseline level of 25-OH-vitamin D was 19.25 ± 8 ng/mL compared with a mean of 36.60 ± 9.58 ng/mL after 3 months of ERGO supplementation (Mean Deviation (MD): 16.52, 95% CI: 12.92, 20.12; *P* < .001). This increase was seen in men and women; however, the difference was not significant. The mean Hb level for baseline was 8.6 ± 0.9 g/L compared with a mean of 9.47 ± 1.3 g/L after 3 months of treatment (MD: 0.48, 95% CI: 0.05, 0.91; *P* = .028). This increase was seen in men and women; however, the difference was not significant. The mean EPO dose was 59 684.21 ± 27 404.08 U/month at baseline and decreased to 51 157.89 ± 27 503.83 U/month after treatment in all patients (MD: −8526.31, 95%CI: −15 549.71, 1502.91; *P* = .019). This reduction was seen in men and women, but no significant difference was found between them. Additionally, the serum level of TIBC (MD: 17.10, 95%CI: −30.11, −4.09; *P* = .011), calcium (MD: 0.97, 95% CI: 0.55, 1.39; *P* < .001), alkaline phosphatase (MD: −56.88, 95% CI: −96.67, −17.05; *P* = .006), and albumin (MD: −0.54, 95% CI: −0.75, 0.34; *P* < .001) changed significantly after treatments. But the serum level of ferritin, phosphorus, and iron was not significantly changed after follow-up compared with baseline (Table 1).

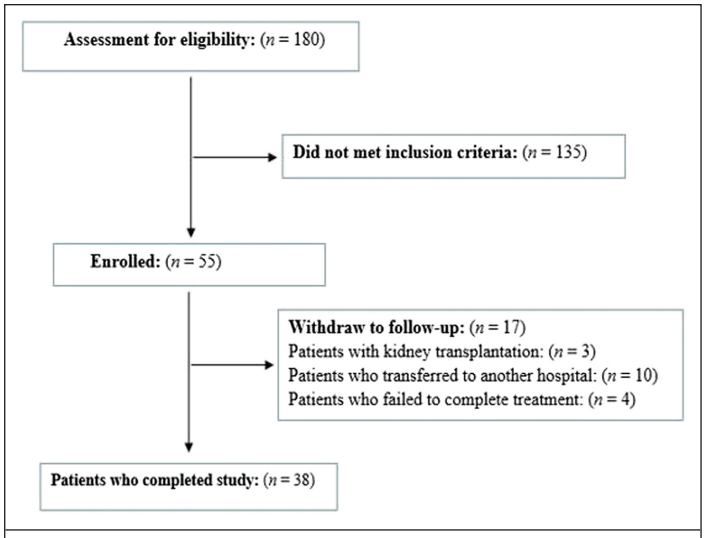

Figure 1. Flow diagram of study participants.

The result of laboratory parameters and EPO dose in responders (25-OH-vitamin D ≥30 ng/mL) and non-responders (25-OH-vitamin D <30 ng/mL) groups before and after 3 months of ERGO supplementation are presented in Table 2. In the responders group, the mean EPO dose (57 555.55 ± 28 302.39 vs. 48 222.22 ± 26 125.92) significantly reduced (*P* = .032), while the Hb level (8.92 ± 0.90 vs. 9.64 ± 1.26) significantly increased (*P* < .001). In the non-responders group, the need for EPO dose (64 909.0909 ± 25 571.29 vs. 58 363.63 ± 28 3072) decreased, and the serum Hb (9.06 ± 1.26 vs. 9.14 ± 0.78) increased after treatment compared to the baseline; however, there were no significant differences (*P* > .05).

Overall, the results of the study illustrated that the need for EPO after vitamin D consumption decreased in 23% of patients and increased in 10% of patients. Also, in 67% of patients, the need for EPO after vitamin D consumption did not change. However, the serum Hb levels in all patients increased.

DISCUSSION

Our findings indicated that after treatment with cholecalciferol in ESRD patients, almost all studied patients experienced an increase in vitamin D and Hb levels, and the need for EPO was significantly reduced in almost 23% of patients. Moreover, the dose of EPO was considerably reduced in patients whose serum vitamin D levels reached 30 ng/mL or above after treatment with cholecalciferol. Consistent with our findings, Kumar et al[24] found that after 4 months of treatment with ERGO, the serum vitamin D level increased in 94% of patients, and 44% of them reached more than 30 ng/mL. In addition, they showed that in 57% of patients, the need for EPO doses was significantly reduced compared to baseline doses. Rianthavorn et al[23] conducted a case–control study with 20 patients under 18 years of age with a mean age of 9.3 ± 5.3. They found that after 12 weeks of treatment with vitamin D (ERGO, 120-240 thousand units), the dose of EPO was significantly reduced in 10 patients. Moreover, the serum vitamin D level reached 30 ng/mL in 30% of patients.[23] Agarwal et al[25] showed that in 186 CKD patients who had received ERGO for 12 months (750-300 thousand units), the

Table 1. Mean and Standard Deviation of Laboratory Parameters in Before and After 3 Months of Ergocalciferol Supplementation in Study Patient

Parameters	After Treatment Mean ± SD	Before Treatment Mean ± SD	Mean Difference	95% CI	*P*
Mean Hb (g/L)	9.47 ± 1.3	8.9 ± 0.8	0.48	0.05, 0.91	.028
Mean Vitamin D (ng/mL)	35.78 ± 9.58	19.25 ± 8.12	16.52	12.92, 20.12	<.001
Mean EPO dose (U/month)	51 157.89 ± 27 503.83	59 684.21 ± 27 404.08	−8526.31	−15 549.71, −1502.91	.019
Mean iron (mg/dL)	109.4 ± 88.3	97.8 ± 76.5	10.52	−20, 34.55	.48
Serum ferritin (ng/mL)	139.66 ± 143	142.55 ± 153.5	−2.88	−40.25, 34.48	.85
TIBC (µg/dL)	243.36 ± 41.89	260.47 ± 48.41	−17.10	−30.11, −4.09	.011
Calcium (mg/dL)	8.65 ± 1.13	7.68 ± 0.72	0.97	0.55, 1.39	<.001
Phosphate (mg/dL)	5.33 ± 1.5	5.28 ± 1.05	0.076	0.38, −0.43	.76
ALP (unit/L)	352.84 ± 232.9	409.71 ± 227.5	56.88-	−96.67, −17.05	.006
Albumin (g/dL)	3.34±0.5	3.89±0.3	−0.54	−0.75, −0.34	<.001

SD, standard deviation; Hb, hemoglobin; EPO, erythropoietin; TIBG, transferrin and iron-binding capacity; ALP, alkaline phosphatase.

Table 2. Erythropoietin Dose and Laboratory Parameter in Responders and Non-responders Groups Before and After 3 Months of Ergocalciferol Supplementation in Study Patients

Parameters	Group	After Treatment Mean ± SD	Before Treatment Mean ± SD	Mean Diff	95% CI	*P*
Mean Hb (g/L)	25-D <30 ng/mL	9.14 ± 0.78	9.06 ± 1.26	0.081	−1.06, 0.89	.85
	25-D ≥30 ng/mL	9.64 ±1.26	8.92 ± 0.91	0.71	0.24, 1.18	.005
Mean EPO dose (U/month)	25-D <30 ng/mL	58 363.63 ± 283072.	64 909.0909 ± 25 571.29	-6545.45	−2082.16, −8369.20	.35
	25-D ≥30 ng/mL	48 222.22 ± 26 125.92	57 555.55 ± 28 302.39	-9333.33	-17 797.83, −868.82	.032
Mean iron (mg/dL)	25-D <30 ng/mL	111.45 ± 93.84	91.54 ± 88.13	19.90	−51.20, 96.67	.61
	25-D ≥30 ng/mL	105.07 ± 87.43	98.37 ± 73.74	6.70	20.75, 39.12	.65
Serum ferritin (ng/mL)	25-D <30 ng/mL	118.82 ± 91.26	132.0 ± 95.94	−13.18	−94.81, 76.68	.76
	25-D ≥30 ng/mL	148.16 ± 160.66	146.99 ± 171.24	1.17	−40.76. −41.19	.95
TIBC (µg/dL)	25-D <30 ng/mL	239.81 ± 45.07	259.63 ± 55.11	−16.81	−0.9, 34.27	.11
	25-D ≥30 ng/mL	244.81 ± 41.33	262.03 ± 46.46	−17.22	−34.27, −0.17	.048

SD, standard deviation; Hb, hemoglobin; EPO, erythropoietin; TIBG, transferrin and iron-binding capacity; ALP, alkaline phosphatase.

serum vitamin D level had increased, while EPO dose did not decrease significantly.

In our study, 80% of CKD patients had low serum levels of vitamin D. Vitamin D supplementation depends on the amount of vitamin D prescribed, the type of vitamin D, and duration of the prescription.[23-28] Thus, the serum vitamin D level over 30 ng/mL (normal serum level) is considered appropriate as normal.[28] Vitamin D and bone mineral hemostasis have essential functions in various human body organs such as bone marrow and kidneys.[29] Active vitamin D (1,25-di-hydrox ycholycalcipherol) stimulates the production of red blood cells in the bone marrow. In dialysis patients, a decrease or absence of 1α-hydroxylase enzyme activity is observed; however, this enzyme's activity may remain normal in extrarenal tissues.[23,25,28,29] Dusso et al[30] showed that the conversion of 25-hydroxy-vitamin D to 1,25-di-hydroxycholycalcipherol could also occur in the bone marrow. Thus, 25-hydroxyvitamin D can be used as a substrate for hydroxylase enzymes.[30] These findings indicate that patients with vitamin D deficiency consume only active vitamin D (1,25-di-hydroxycholycalcipherol) to treat mineral abnormality in CKD patients. The level of 1,25-dihydroxycholycalcipherol in bone marrow is insufficient to stimulate red blood cell production. Therefore, the administration of cholecalciferol to increase the storage of vitamin D in patients' body can improve erythropoiesis. Another mechanism of resistance to EPO is chronic inflammation in these patients, as vitamin D reduces resistance to EPO by its anti-inflammatory effect.[23]

Our findings indicated that the mean monthly dose of EPO significantly decreased after cholecalciferol administration,

especially when the serum vitamin D level reached 30 ng/mL. If the study duration was longer and serum vitamin D level had reached 30 ng/mL, it could have been expected to observe a decrease in the dose of EPO and an increase in serum Hb. Nand et al[31] indicated that after 4-month treatment with cholecalciferol, Hb level significantly increased in 50 adult patients. Moreover, serum vitamin D level raised in most patients to over 30 ng/mL with oral therapy. However, the result of EPO dose was different due to different durations of treatment and the type of oral vitamin D. Therefore, more studies are needed in the future.

The vitamin D and Hb levels were higher in men than women at the beginning of the study and after treatment. Although both genders had increments in serum levels of vitamin D and decrements in EPO doses, the changes were not significant. Rianthavorn et al[23] suggested that the gender of patients had no impact on the response to vitamin D supplementation. Other studies with more populations of patients are recommended to determine differences in both genders.

There were some limitations in this study. First, the number of patients was small that may reduce the reliability of findings. Follow-up of patients in this study was 12 weeks, and long-term administration of cholecalciferol probably can have a better effect on patients by increasing serum level of vitamin D to more than 30 ng/mL. Also, we could not measure the serum level of 1,25-dihydroxycholecalciferol during the study.

CONCLUSION

Many patients with CKD and ESRD have anemia. These patients are usually treated with EPO that is an expensive drug. Our findings indicated that when anemia is accompanied by vitamin D deficiency, the correction of serum level of vitamin D by cholecalciferol can increase serum Hb level leading to lower demands for EPO.

Ethics Committee Approval: Ethics committee approval was received for this study from the Babol University of Medical Sciences, Babol, Iran (Approval No: MUBABOL, HRI.REC. 1397. 244).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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