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Calcitriol for Oral Mucositis Prevention in Patients With Fanconi Anemia Undergoing Hematopoietic SCT: A Double-Blind, Randomized, Placebo-Controlled Trial

Amir Ali Hamidieh, MD,[1] Mona Sherafatmand, PharmD,[2] Ava Mansouri, PharmD,[3] Molouk Hadjibabaie, PharmD,[2,3] Asieh Ashouri, PhD,[4] Zahra Jahangard-Rafsanjani, PharmD,[2,3] Kheirollah Gholami, PharmD,[2,3] Mohammad Reza Javadi, PharmD,[2,3] Ardeshir Ghavamzadeh, MD,[1] and Mania Radfar, PharmD[2,3]*

Fanconi anemia is a rare inherited aplastic anemia, which is cured only by hematopoietic stem-cell transplantation (HSCT). One of the most debilitating complications of high-dose chemotherapy regimen before HSCT is oral mucositis (OM), which occurs frequently in this population. Vitamin D has identified immunoregulatory, anti-inflammatory, and antioxidant role. This study was designed to examine the efficacy of vitamin D in the prevention of OM in patients with Fanconi anemia undergoing allogenic HSCT. Twenty-eight patients were enrolled in the study. They received either calcitriol (0.025 μg) or placebo capsule once daily, from the first day of chemotherapy schedule for 14 consecutive days. Incidence of OM was assessed as the primary outcome. Moreover, the association of baseline vitamin D level with OM was evaluated. In this study, calcitriol did not change OM incidence ($P = 1$) and severity ($P = 0.54$) significantly; however, a significant association of baseline vitamin D level with OM complete resolution was found ($P = 0.03$; hazard ratio, 1.01; 95% confidence interval, 1.00–1.01). In conclusion, we did not find considerable benefits of calcitriol in the prevention of OM. However, further studies with bigger sample size and different calcitriol supplementation schedules are needed to confirm these findings.

Keywords: Fanconi anemia, calcitriol, oral mucositis, hematopoietic stem-cell transplantation

[1]*Hematology-Oncology and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran;* [2]*Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran;* [3]*Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran; and* [4]*Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.*

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**Address for correspondence: Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Enqelab SQ, 16 Azar Avenue, PO Box 14155/6451, Tehran, Iran. E-mail: radfarma@tums.ac.ir*

INTRODUCTION

Fanconi anemia is a rare hereditary aplastic anemia.[1] The disease is associated with some leading features, such as bone marrow failure, congenital malformations, and predisposition to cancer.[2–4] Its prevalence in the world is 1–5:1,000,000 births.[5] The only effective modality to cure this disease is hematopoietic stem-cell transplantation (HSCT).[6]

Oral mucositis (OM) is a major complication of high-dose chemotherapy drugs received as conditioning regimen before HSCT. It develops within 14 days after conditioning regimen administration.[7] Prevalence of this excruciating side effect in patients with Fanconi anemia undergoing HSCT is relatively high.[8] It has been stated in studies that severe OM (>grade 2) is

one of the most frequent side effects of HSCT conditioning regimen (about 94%) in these patients.[9] OM is associated with hazardous outcomes, such as severe pain, dysphasia, impairment in nutrient intake (difficulty in swallowing), and increment in narcotic analgesic use. It can also increase the risk of bleeding, life-threatening infections, such as sepsis, and thus it prolongs the hospitalization length, and augments the treatment costs and mortality.[10] Chemotherapy agents form free radicals and successively cause DNA damage. In the first phase of OM, thus trigger a cascade of inflammatory reactions. In the subsequent phases, proinflammatory cytokines, such as TNF-α, IL1b, and IL6 are generated. They damage the mucosal tissue and subsequently, some lesions are formed. The mucosal damages will resolve eventually.[11]

Vitamin D, as a pleiotropic compound, plays a fundamental immunoregulatory role through its receptors expressed in diverse myeloid and lymphoid cells.[12–14] Experimental investigations have demonstrated that vitamin D is able to diminish the release of TNF-α and also to increase the synthesis of IL10 (anti-inflammatory cytokine).[15,16] In addition, it has been suggested that vitamin D induces the synthesis of antimicrobial peptides, such as defensin and cathelicidin, in immune cells.[17] Moreover, animal studies mention the anti-inflammatory effect of vitamin D against inflammatory bowel disease through modification of some cytokines, such as IL1b, IL10, and IL17.[18] It has been stated that vitamin D supplementation in patients with leg ulcers may lead to better lesion healing with a probable mechanism of inducing the synthesis of platelet-derived growth factor, a key growth factor in wound healing, and consequently stimulating collagen production by fibroblasts.[19] Studies have clarified antioxidant activity of vitamin D by indicating its capability to fight oxidative stress through upregulation of glutathione peroxidase and superoxide dismutase or modulating free radical formation.[20–22]

According to the aforementioned studies, we suggested that calcitriol, the active form of vitamin D, could be efficient in prevention of high-dose chemotherapy-induced OM.

Because we did not find any study regarding the effect of calcitriol on OM in patients with Fanconi anemia undergoing HSCT, this study was designed to assess the efficacy of calcitriol in prevention of OM in this population.

MATERIALS AND METHODS

We conducted a double-blind, randomized, placebo-controlled clinical trial from June 2012 to January 2014 in the Hematology-Oncology and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran University of Medical Sciences. The study was conducted in accordance with the Declaration of Helsinki and approved by institutional review board, and written informed consent was obtained from guardians of the study participants before study enrollment (Trial registration ID: IRCT201307141030N15).

Participants

Patients with Fanconi anemia aged 1–15 years, undergoing allogeneic HSCT, were eligible to participate in our study. Children were excluded from the study if they had a baseline serum 25-OH vitamin D level more than 100 ng/mL, serum calcium level more than 10 mg/dL, serum phosphorus level more than 4.6 mg/dL, or a history of taking supplements containing vitamin D within the past 3 months.

Twenty-eight patients fulfilling the above mentioned criteria, who were admitted in the Pediatric Bone Marrow Transplantation Ward, enrolled in this study.

Study design

A blocked randomization method was used to allocate 28 participants to either calcitriol or placebo group. We administered calcitriol (0.025 μg) or placebo capsules once daily, from the first day of conditioning regimen administration for 14 consecutive days. Calcitriol and placebo capsules both were identical in size and shape.

Conditioning regimen

The selective conditioning regimen and supportive care for the patients were according to the hospital protocol. Their conditioning schedule included busulfan 0.2 mg/kg daily orally for 4 days (total dose 0.8 mg/kg) followed by cyclophosphamide 15 mg/kg daily intravenously for 4 days (total dose 60 mg/kg), and antithymocyte globulin 2.5 mg/kg daily intravenously for 3 days (total dose 7.5 mg/kg).

The prophylaxis regimen of OM based on the hospital protocol included nystatin 15–20 drops every 3 hours, a chewable tablet of sucralfate 500 mg every 6 hours, and 10 mL diluted povidone–iodine every 3 hours. None of our patients received narcotics to palliate their pain.

Study outcomes

Primary outcome

The primary outcome of this study was to evaluate the incidence of OM. We also examined severity, time of onset, and recovery of OM using the World Health Organization oral toxicity scale. This scale uses the subjective and objective findings to grade the OM.[23]

Evaluation of OM was performed by the investigator once daily for each patient (excluding weekends and holidays) from the first day of conditioning till 21 days after transplantation or until OM resolution. The investigator and the ward physicians were blinded to patients' allocation.

Secondary outcomes

Hematologic indices

We assessed the hematologic indices, such as the duration of neutropenia [absolute neutrophil count (ANC) under 500 cells/mm^3], neutrophil engraftment time (ANC reaches the level of 500 cells/mm^3 for 3 consecutive days), and platelet engraftment time (platelet count reaches the level of at least 20,000/mm^3 for 3 consecutive days without transfusions of platelet).

Nonhematologic indices

Besides, we recorded serum creatinine (Cr) level and blood urea nitrogen test (as renal function indices) and liver enzymes, such as aspartate aminotransferase (AST) and alanine transaminase (ALT) (as liver function indices), on daily basis during hospitalization. Serum calcium and phosphorus levels were measured biweekly, whereas erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were recorded weekly.

Other recorded parameters were the duration of fever and length of hospitalization (defined as the interval between conditioning regimen administration and patient discharge).

We also documented incidence and severity of acute graft-versus-host disease (GVHD). Grading the severity of GVHD was based on Glucksberg scale.[24,25]

Laboratory measurement of plasma levels of 25-OH vitamin D

To determine baseline serum 25-OH vitamin D level, a blood specimen (5 mL) was collected from every patient of both calcitriol and placebo groups on the first day of conditioning regimen before calcitriol or placebo administration. The specimens were centrifuged for 5 minutes, and the serum was isolated and stored at −80°C until the analysis was performed. The measurement of 25-OH vitamin D level was based on EIA method. The diagnostic sensitivity of investigational kit (Immunodiagnostic Systems, Boldon, United Kingdom) was >2 ng/mL, ranging from 2.4 to 144 ng/mL.

Statistical analysis

Statistical analysis was performed using SPSS version 20. To report continuous variables, we used mean ± SD (for parametric variables) or median (for nonparametric variables). The categorical variables were reported as percentage. Comparison of continuous and categorical data between different study groups was done by performing Mann–Whitney U test and χ^2 test, respectively. The Cox-regression analysis was used to evaluate the mucositis recovery association with baseline serum vitamin D level. The statistically significant P values were defined as P values <0.05 in this study.

RESULTS

Patient characteristics

Twenty-eight patients participated in the study. Fourteen patients were enrolled in each calcitriol and placebo group. Follow-up was completed for all the patients. Patients' characteristics are listed in the Table 1. The demographic characteristics of the patients in calcitriol and placebo groups were comparable.

Based on baseline serum 25-OH vitamin D level, we divided the participants into deficient and nondeficient subgroups in every study arm, and we found that 2 groups were similar regarding baseline serum 25-OH vitamin D status.

Oral mucositis

One patient in each group did not develop mucositis. The difference in overall incidence of OM between calcitriol and placebo group was not statistically significant. This was the same for the onset and the duration of OM between 2 groups (Table 2).

Moreover, the occurrence of severe OM grades (grade 3–4) did not differ significantly between 2 groups (Figure 1).

The frequency of OM complete resolution (recovery to grades 0–1) had a statistically meaningful relationship with baseline vitamin D level (P = 0.03; hazard ratio, 1.01; 95% confidence interval, 1.00–1.01). Besides, recovery of grades 3–4 of OM to lower grades was significantly associated with baseline vitamin D status (nondeficient vs. deficient group) (P = 0.04; hazard ratio, 2.70; 95% confidence interval, 1.03–7.04).

Hematologic and nonhematologic indices

All the participants had successful engraftment. There was no significant difference in neutrophil and platelet engraftment time between study groups. Furthermore, comparison of the mean duration of neutropenia between 2 groups did not reveal a significant difference (Table 3).

All the patients developed at least 1 episode of fever above 38.3 in their hospitalization. Regarding the

Table 1. Baseline characteristics of participants.

Variable	Calcitriol group (n = 14)	Placebo group (n = 14)	*P*
Patient sex, n (%)			0.32
Female	4 (29)	1 (7)	
Male	10 (71)	13 (93)	
Patient age, mean ± SD (range)	9 ± 2.7 (3–13)	8 ± 2.5 (4–12)	0.32
Donor sex, n (%)			0.67
Female	7 (50)	5 (36)	
Male	7 (50)	9 (64)	
Donor age, mean ± SD (range)	32 ± 14.2 (3–49)	23 ± 20 (2–62)	0.16
Stem-cell source, n (%)			0.12
Bone marrow	7 (50)	2 (14)	
Peripheral blood	6 (43)	10 (71)	
Cord blood	1 (7)	2 (14)	
HLA type, n (%)			0.59
Full match	14 (100)	13 (93)	
5/6 (single antigen mismatch)	0 (0)	1 (7)	
Baseline serum vitamin D (ng/mL), median (range)	12.11 (6.41–32.05)	17.62 (8.41–38.46)	0.28
Baseline serum vitamin D status, n (%)			0.13
Deficient (<15 ng/mL)	9 (64)	5 (36)	
Insufficient (15–20 ng/mL)	0 (0)	3 (21)	
Sufficient (>20 ng/mL)	5 (36)	6 (43)	

frequency of fever episodes, both groups had statistically similar patterns ($P = 0.73$).

Median hospitalization length for both groups was 25 days, which did not show any significant difference between them ($P = 0.8$).

Calcitriol was well tolerated and none of our patients developed hypercalcemia, hyperphosphatemia, or other adverse drug reactions related to calcitriol. Serum levels of Cr, ALT, and AST had no significant differences between groups of study.

In assessment of GVHD, we did not encounter any significant differences in incidence of GVHD and its overall severity between study groups (Table 4).

The frequency of skin GVHD and gastrointestinal GVHD occurrence were 36% and 21% in calcitriol group versus 28% and 66% in placebo group, respectively. Neither patients in calcitriol group nor in placebo group developed liver GVHD.

The frequency of positive cultures (blood, stool, and urine) was 42.9% in calcitriol group versus 35.7% in placebo group ($P = 0.69$), which was not significantly different.

The mean ESR or CRP index did not show a significant difference between 2 study groups ($P = 0.9$ for ESR and $P = 0.46$ for CRP).

DISCUSSION

Up until now, the researchers have applied various agents, such as antimicrobials, growth factors, antioxidants, immunomodulators, and anti-inflammatory agents in prevention or treatment of OM in which a few have demonstrated promising results, whereas the majority failed to be efficacious.[10] Only palifermin, a keratinocyte growth factor, has FDA approval to be used in prevention of OM.[11]

In this regard, Moslehi et al conducted a randomized clinical trial to evaluate N-acetyl cysteine effectiveness in prevention of OM. N-acetyl cysteine has antioxidant activity and prevents inflammatory reactions. Although they observed no significant difference in the incidence of OM between 2 groups, there was a considerable difference regarding the incidence of severe grades and the mean duration of OM between study groups.[26]

Another investigation was performed on the efficacy of selenium, as an antioxidant and anti-inflammatory agent in OM prophylaxis. The incidence of OM and the mean duration of OM did not demonstrate a significant difference between study groups; however,

Table 2. Comparison of OM incidence, onset, and the duration between study groups.

Outcome	Calcitriol group (n = 14)	Placebo group (n = 14)	*P*
Mucositis, n (%)	13 (93)	13 (93)	1*
Maximum grades, n (%)			0.54†
0	1 (7)	1 (7)	
1	0 (0)	1 (7)	
2	2 (14)	0 (0)	
3	5 (36)	4 (29)	
4	6 (43)	8 (57)	
Median days to the onset of mucositis (range)	10 (6–13)	10 (5–16)	0.84†
Median days to recovery to grade 0–1 of mucositis (95% CI)	16 (6–26)	11 (9–13)	0.74‡
Median days to recovery of grades 3–4 of mucositis to lower grades (95% CI)	7 (5–9)	6 (4–8)	0.20‡
Recovery to grade 0–1 of mucositis, n (%)	5 (38)	7 (54)	0.45*
Recovery of grade 3–4 of mucositis to lower grades, n (%)	11 (100)	11 (92)	1*

*The *P* value was reported from χ^2 test or Fisher exact test.
†The *P* value was reported from Mann–Whitney *U* test.
‡The *P* value was reported from log-rank test.
CI, confidence interval.

occurrence of severe grades was considerably different between 2 groups.[27]

We administered calcitriol as a potent antioxidant agent, which holds anti-inflammatory characteristics similar with N-acetyl cysteine and selenium; however, none of the OM indices showed significant difference between our study groups. This may be as a result of shorter duration of intervention compared with the 2 aforementioned studies.

Fidler et al evaluated the efficacy of chamomile mouthwash for prevention of OM in patients receiving fluorouracil. The rationale for applying this plant was its known anti-inflammatory and antimicrobial functions. Studied groups received chamomile mouthwash or placebo 3 times a day from the first day of chemotherapy administration for 2 weeks. No significant difference was observed in the severity of mucositis between 2 groups.[28]

In this study, we used calcitriol, an agent with anti-inflammatory and antimicrobial properties, for 2 weeks starting on the first day of receiving conditioning regimen, and our results were in line with Fidler et al report. It did not change the severity of OM considerably. Because ulceration usually occurs within 14 days after chemotherapy and the main goal of the study was OM prevention, the duration of calcitriol administration seems reasonable.[29] Although, according to the palifermin administration schedule for prevention of OM,[30] it seems better to start calcitriol before chemotherapy administration. This could provide enough time for modification of proinflammatory and anti-inflammatory cytokines by calcitriol to conquer the triggered inflammatory cascade of mucositis.

Based on wound-healing properties of granulocyte–macrophage colony-stimulating factor (GM-CSF), the efficacy of GM-CSF mouthwash in OM prophylaxis was assessed in 90 patients with cancer undergoing HSCT. Patients received either GM-CSF mouthwash 150 μg daily or placebo. This schedule was started 1 day after the end of chemotherapy until neutrophil engraftment (ANC >500 cells/mm^3) or OM resolution. The incidence, severity, or the duration of OM was not significantly different between study groups.[31]

Lelie et al accomplished a trial in 36 patients undergoing HSCT. GM-CSF, 300 μg, with a base of methylcellulose gel or placebo was administered daily for study groups. They observed no significant difference in OM outcomes between 2 groups.[32]

Calcitriol with the same biologic feature as GM-CSF in wound healing in this study failed to show beneficial effects in OM prophylaxis.

In another study, the effectiveness of pentoxifylline in prevention of chemotherapy-induced OM in

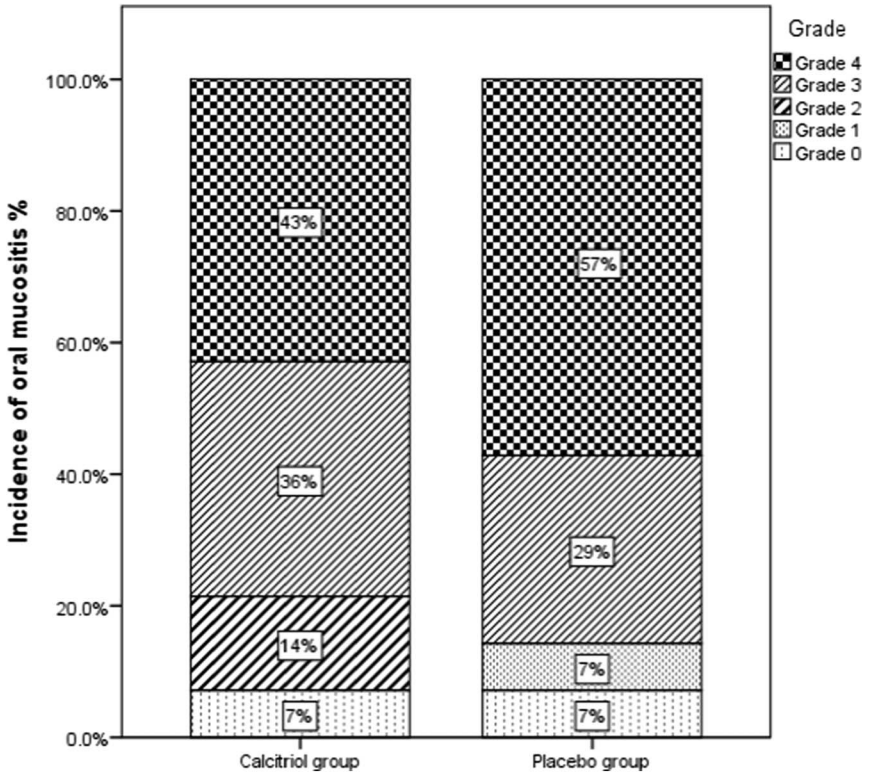

FIGURE 1. Incidence of different OM grades in study groups.

patients undergoing bone marrow transplantation was evaluated. Pentoxifylline plays an anti-inflammatory role through suppression of TNF-α synthesis. The patients were assigned to receive either pentoxifylline 400 mg 4 times daily from day 8 until +100 or receive no medication as control group. The incidence of OM, which needed to be palliated by morphine and the mean duration of morphine administration, did not show a significant difference between 2 groups.[33]

Mansouri et al explored the effects of zinc supplementation on OM prophylaxis in HSCT candidate patients. Zinc has established antioxidant and immunoregulatory functions, and it promotes wound healing. Sixty patients undergoing HSCT received either zinc sulfate 220 mg or placebo twice daily from the day before chemotherapy schedule for 21 consecutive days. There were no differences regarding incidence, severity, or the duration of OM between study groups.[34]

Table 3. Hematologic indices in study groups.

Variable	Calcitriol group (n = 14)	Placebo group (n = 14)	*P*
Duration of neutropenia (d), mean ± SD	13.64 ± 2.71	12.93 ± 2.86	0.50
ANC engraftment (d), median (95% CI)	13 (12–14)	13 (12–14)	0.80
Platelet engraftment (d), median (95% CI)	14 (13–15)	14 (13–15)	0.95

CI, confidence interval.

Table 4. Incidence of GVHD and its overall severity in study groups.

Outcome	Calcitriol group (n = 14)	Placebo group (n = 14)	*P**
GVHD, n (%)			0.44
No	7 (50)	5 (36)	
Yes	7 (50)	9 (64)	
Overall Glucksberg grade, n (%)			0.12
1	3 (21)	0 (0)	
2	3 (21)	4 (29)	
3	1 (7)	4 (29)	
4	0 (0)	1 (7)	

*The *P* value was reported from χ^2 test.

These studies indicate that agents with anti-inflammatory, antioxidant, and immunoregulatory characteristics, which might interfere with OM formation process, do not necessarily provide promising results in OM prophylaxis in clinical settings.

To the best of our knowledge, no data are available in the literature regarding the effect of calcitriol on OM. However, there is pile of evidence regarding immunoregulatory, anti-inflammatory, and antioxidant activities of vitamin D and its wound-healing effects.[12–22]

Based on the established effects of vitamin D on keratinocytes and fibroblasts, Burkiewiez et al explored the association of vitamin D and leg ulcers. Fifty-two participants enrolled in the study of which 26 had leg ulcers. Patients with leg ulcer and vitamin D deficiency were assigned to receive either vitamin D 50,000 IU or placebo weekly for 8 weeks. Although they found that ulcer frequency was inversely related to baseline serum vitamin D level, their intervention did not have a significant impact on ulcer size.[19]

In corroboration with this study, we observed that higher baseline serum vitamin D was associated with higher recovery rate but surprisingly, calcitriol supplementation did not show any beneficial effect on OM outcomes.

In a study, Ye et al[35] observed a reverse relationship between the level of hCAP18 (the precursor of antimicrobial peptide, cathelicidin) and the risk of OM occurrence.

In another study, a crucial defensive function for vitamin D against wounds was proved and the mechanism by which vitamin D induces cathelicidin synthesis was elucidated. After binding a pathogen to its responsive Toll-like receptor, 25-OH vitamin D undergoes 1 alfa-hydroxylation and becomes active. Subsequently, it stimulates cathelicidin gene to synthesize the protein.[36]

We administered calcitriol for 2 weeks starting before OM ulcerative phase, aimed to prevent OM than healing. While the function of vitamin D on antimicrobial peptide synthesis, prevention of bacterial overgrowth, and wound exacerbation is induced by pathogen entry during ulceration.[36] Therefore, it would be better to examine calcitriol as a healing agent in another study, that is, the clacitriol supplementation course should cover after ulceration period completely.

An investigation was designed based on the inflammatory pathogenesis of congestive heart failure and the anti-inflammatory function of vitamin D. One hundred twenty-three patients were enrolled in this study, of whom, 61 received vitamin D, 50 μg/d for 9 months and the remainder received placebo. Clinical variables such as left ventricular ejection fraction did not change meaningfully. They reasoned that the increase in vitamin D level after supplementation may be too low to maintain all the predicted functions of vitamin D.[37]

In accordance with this study, our findings might be the result of inadequate calcitriol administration. We administered calcitriol instead of colecalciferol, taking into account the lack of enough time needed for its activation in our study. Therefore, 25-hydroxy vitamin D, the standard marker of vitamin D status, was only helpful in interpretation of baseline status, and it was determined only before intervention. To assess the efficacy of calcitriol, measurement of 1,25-dihydroxy vitamin D level in blood, before and after calcitriol administration, is necessary. Unfortunately, this was not possible throughout the study in practical limitations.

CONCLUSIONS

In summary, although we did not find considerable benefits of calcitriol in the prevention of OM, the association between baseline vitamin D and mucositis recovery indicates that larger trials with different calcitriol administration schedules are needed to ensure sufficient levels of vitamin D and to ascertain the anticipated effects of vitamin D. Also, we recommend that longer studies be performed in future to evaluate healing and therapeutic effects of calcitriol on OM ulcers.

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