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Comparison of relative frequency of treatment response and complications incidence in two therapeutic groups of patients with hypoparathyroidism treated with 1,25-dihydroxycholecalciferol and 25-hydroxycholecalciferol referred to clinics of Ahwaz educational hospitals in the years 2010–2020

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Cholecalciferol is used in a minority of patients due to fear of prolonged hypercalcemia and renal toxicity, given its long half-life and more patient compliance.
Objectives. The aim of this study was to compare the efficacy of 1,25-dihydroxycholecalciferol (calcitriol) versus 25-hydroxycholecalciferol (cholecalciferol) therapy in addition to oral calcium in the treatment of hypoparathyroidism.
Material and methods. This retrospective cross-sectional study was conducted on patients with hypoparathyroidism treated with calcitriol (1–1.5 µg/day; *n* = 50) or cholecalciferol (5000 IU/day; *n* = 50) in the clinics of educational hospitals in Ahvaz between 2010–2020. Data was extracted from medical records, and patients who were treated for at least 6 months were included in the study. Response to treatment was defined as the absence of hypocalcaemia (corrected serum calcium < 8.5 mg/dl) and no hospitalisations or emergency department (ED) visits for hypercalcaemia. Therapeutic complications included hypercalcemia (corrected serum calcium > 10.2 mg/dl), kidney stones or nephrocalcinosis and renal failure.
Results. A total of 100 hypoparathyroidism patients with a mean age of 46.63 ± 10.85 years (range 25–70 years), including 82% females, participated in the study. The response to treatment was not significantly different between two groups of calcitriol and cholecalciferol (92% vs 100%; *p* = 0.117). There was no significant difference between the two groups in hospitalisation or ED visits for hypocalcaemia (*p* = 0.117), hypercalcaemia (*p* = 1.000), incidence of kidney stones and nephrocalcinosis (*p* = 1.000).
Conclusions. The use of both calcitriol and cholecalciferol supplements is effective in the treatment of hypoparathyroidism, and no significant difference was found in the response to treatment with the two drugs.
Key words: hypoparathyroidism, calcitriol, hydroxycholecalciferols.

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Background

Hypoparathyroidism is a relatively rare endocrine disorder characterised by hypocalcaemia due to low or inadequate serum levels of the parathyroid hormone (PTH). The most common cause of hypoparathyroidism is anterior neck surgery, which accounts for more than 75% of cases, while other causes of hypoparathyroidism include autoimmune diseases, metastases and radiation injuries [1–4].

Mild hypocalcaemia due to hypoparathyroidism has few side effects, but in severe cases, it causes seizures, heart failure or laryngospasm. Therefore, prevention and treatment of hypocalcaemia is of critical importance [5]. Treatments for hypoparathyroidism include maintaining serum calcium levels with the active metabolite 1,25-dihydroxyvitamin D (1,25 (OH) 2D) or calcitriol, recombinant human parathyroid hormone and high doses of vitamin D (ergocalciferol or D2) and calciphero D3 [6].

Since hypoparathyroidism is a chronic form of hypovitaminosis, use of the active form of vitamin D eliminates the major pathophysiological deficiency in parathyroid hypothyroidism caused by the lack of PTH, which is a failure of converting 25-hydroxyvitamin (25-OH-D) into its active metabolite 1,25 (OH) 2D [3, 7]. Therefore, calcitriol is a drug that is mostly used today for hypoparathyroidism [3, 5, 6]. However, due to its short half-life (about 5 to 8 hours), calcitriol should be taken daily at least two to three times a day to prevent hypocalcaemia [8]. Furthermore, due to its higher cost compared to other treatments and its limited accessibility, particularly in developing countries, including Iran, it is sometimes not accepted by patients. As a result, its irregular consumption causes hypocalcaemia symptoms and complications, which ultimately lead to disability and reduced quality of life and sometimes even life-threatening risks such as cardiac arrhythmias [9]. On the other hand, high doses of 25-hydroxycholecalciferol have been shown to sit on the vi-

tamin D receptor and act as an active form of vitamin D in these patients. Therefore, in the absence of active forms of vitamin D (including calcitriol), this drug can be used (in high doses) to reduce the frequency of possible hypocalcaemia [9–11]. Moreover, 25-hydroxycholecalciferol is associated with greater acceptance by patients due to its longer half-life, less frequent use (once a day), lower cost and greater availability. However, some concerns due to renal toxicity, including kidney stones, nephrocalcinosis and renal failure, have led to high doses of inactive forms of vitamin D being used less frequently in the treatment of hypoparathyroidism [8, 12]. Inactive forms can also lead to prolonged hypercalcaemia due to their storage in adipose tissue for a long time (about 2 to 3 weeks) [13–15]. Some studies have shown that although ergocalciferol and cholecalciferol are rarely used as a sole source of vitamin D in parathyroid hypothyroidism, these forms of vitamin D also prove to be beneficial [3, 8, 16]. Because the treatment of hypoparathyroidism remains a challenge and no treatment is completely satisfactory for all patients [17], and also due to the fact that a very limited number of studies have been conducted comparing the effects of the two different forms of vitamin D on the incidence of hypocalcaemia in patients with hypoparathyroidism, in order to help physicians and treatment staff to find appropriate treatment strategies to reduce the incidence of hypocalcaemia and medication side effects, and thus reducing patient visits to hospital, this study aimed to compare the response to treatment and the incidence of complications of treatment with calcitriol and 25-hydroxycholecalciferol in patients with hypoparathyroidism referred to the clinics of teaching hospitals in Ahvaz between 2010–2010.

Material and methods

The present descriptive-analytical study was performed retrospectively on patients with hypoparathyroidism treated with 1,25-dihydroxycholecalciferol and 25-hydroxycalciferol referred to the clinics of Ahvaz teaching hospitals in 2010–2011. The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Iran (Ethics Code. IR.AJUMS.HGOLESTAN.REC.1399.145), and throughout the study, all procedures followed were in accordance with the Declaration of Helsinki, and the principles of patient information confidentiality were observed.

The sample size was determined to be 100 individuals (50 patients in each group) according to the main purpose of the study, as well as similar articles [8, 16], and considering the extent of access to patients, and the mean and standard deviation of the amount of modified serum calcium in the two groups was based on a significance level of 0.05 and statistical power of 95%. Sample size was determined using RStudio statistical software, and the reliability of this size was also verified in PASS software. Hypoparathyroidism patients with at least six months of treatment with 1,25-dihydroxycalciferol (calcitriol) or 25-hydroxycalciferol alongside calcium supplementation who had a GFR > 60 ml/min/1.73 m^2 at baseline were included in the study. Patients whose medical records were incomplete or illegible, or who had received any medication other than calcitriol or calciferol, were excluded from the study.

Patient evaluation and grouping

Initially, baseline patient characteristics, including demographic and clinical information, were collected using patient records. The studied variables included age, gender, cause of hypoparathyroidism (surgical/non-surgical), presence of kidney stones or nephrocalcinosis based on ultrasound results or other imaging procedures, as well as laboratory and paraclinical parameters, including modified serum calcium, serum creatinine and 24-hour urinary calcium. Patients with hypoparathyroidism were divided into two groups receiving calcitriol at a dose of 1 to 1.5 micrograms per day or 25-hydroxycholecalciferol 50,000 IU per day, depending on the type of treatment, while both groups also received calcium supplements. The serum calcium of patients was modified based on serum albumin: Total serum calcium – [(4 – serum Albumin measured in mg/dl) × 0.8] = modified calcium (mg/dl). The mean of all modified serum calcium levels in every patient's file and their last serum creatinine was collected and calculated.

Study outcomes

The clinical results and treatment outcomes, including response to treatment and treatment complications, were collected from patients' medical records. Response to treatment was defined as no hypocalcaemia (total modified serum calcium less than 8.5 mg/dl) or its symptoms and no hospitalisation or admission to the emergency department due to hypocalcaemia. Therapeutic complications included hypercalcaemia (total modified serum calcium greater than 10.2 mg/dl), incidence of kidney stones or nephrocalcinosis and renal failure [8]. Renal failure is defined based on glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 and was also calculated using the CKD-EPI formula for patients. Additionally, adherence to treatment and regular use of medication (drug compliance) was also assessed. Patient compliance was expressed based on the history in the file (or contacting patients, if necessary) and was indirectly based on each patient's variables. In cases of any hypocalcaemia or seizures or a number of visits fewer than twice a year, the patient was considered non-compliant [18]. Finally, the treatment outcomes were compared between the two groups.

Statistical analysis

SPSS software (SPSS Inc., Chicago, IL, U.S.A.) version 24 was used for statistical analysis. In quantitative variables, mean and standard deviation were used to describe the data, and in qualitative variables, frequency and percentage were used to describe the data. The normality of the data was checked via the Kolmogorov-Smirnov test. The Independent *t*-Test was used to compare the means of variables between the two groups, and the Chi-square test was used to compare qualitative variables. The significance level in the tests was considered as 0.05.

Results

A total of 100 patients with hyperparathyroidism with a mean age of 46.63 ± 10.85 years (between 25 to 70 years), including 82% females and 18% males, participated in this study. A comparison of patient characteristics and information in the two treatment groups is presented in Table 1. As can be seen, there was no statistically significant difference between the response to treatment in the two groups of calcitriol (92%) and cholecalciferol (100%) (p = 0.117). Moreover, no significant difference was found between the two groups in the incidence of kidney stones and nephrocalcinosis (p = 1,000). However, the mean serum creatinine (p = 0.025), modified calcium (p = 0.001) and 24-hour urinary calcium (p = 0.005) in the calcitriol group were significantly lower than in the cholecalciferol group (p = 0.005). The frequency of hospitalisation or emergency department admission due to hypocalcaemia and hypercalcaemia did not show a significant difference between the two groups (p = 0.117 and p = 1.000, respectively). The frequency of treatment complications (hypercalcaemia, kidney stones or nephrocalcinosis and renal failure) was not significantly different between the two groups (p = 1.000).

Table 1. Comparison of information about hypoparathyroid patients and treatment outcomes in the two groups

Variable		Calcitriol (n = 50)	Cholecalciferol (n = 50)	p*
Age (years)		41.94 ± 10.05	51.32 ± 9.58	< 0.0001
Gender	male	7 (38.9)	11 (61.1)	0.298
	female	43 (52.4)	39 (47.6)	
Cause of hypoparathyroidism	surgical	48 (96)	46 (92)	0.400
	non-surgical	2 (4)	4 (8)	
Kidney stones or nephrocalcinosis		3 (6)	3 (6)	1.000
Modified Ca^{2+} (mg/dl)		8.64 ± 0.18	8.77 ± 0.17	0.001
24-hour urinary Ca^{2+} (mg/day)		178.32 ± 23.94	192.18 ± 24.00	0.005
Serum creatinine (mg/dl)		0.97 ± 0.19	1.05 ± 0.19	0.025
Hospitalisation or emergency dept. admission due to hypocalcaemia		4 (8)	0 (0)	0.117
Hospitalisation or emergency dept. admission due to hypercalcaemia		1 (2)	1 (2)	1.000
Treatment complications		6 (12)	6 (12)	1.000
Treatment response		46 (92)	50 (100)	0.117
Treatment non-compliance		4 (8)	1 (2)	0.362

Data is presented as Mean ± SD or frequency (percentage).
* $p < 0.05$ is significant.

Discussion

The results of the present study showed that both calcitriol supplements (active form of vitamin D) and cholecalciferol (D_3, inactive form of vitamin D) were similar in the treatment of patients with hypoparathyroidism, i.e. controlling blood calcium levels. There was no significant difference between the two groups in terms of response to treatment (incidence of hypocalcaemia and hospitalisation or emergency department admission due to hypocalcaemia), nephrocalcinosis and kidney stones and hospitalisation due to hypercalcaemia. The mean serum creatinine, modified serum calcium (based on albumin) and 24-hour urinary calcium in the calcitriol treated group, however, were significantly lower than in patients treated with cholecalciferol. Such findings, based on the high response rate in both groups, suggest that treatment with vitamin D supplementation should be considered in patients with hypoparathyroidism, particularly those with hypocalcaemia.

Other previous studies have reported that treatment with vitamin D supplements prevents hypocalcaemia in hypoparathyroid patients. In a study by Ravikumar et al. [19], the highest incidence of hypocalcaemia was found to be in patients who did not receive any vitamin D supplementation or received only calcium supplementation, and the lowest incidence of hypocalcaemia was observed in patients who received calcium, calcitriol and cholecalciferol supplements. Moreover, patients who took all three supplements needed less intravenous calcium supplementation than other patients [19]. Other studies have also shown that vitamin D supplements, along with oral calcium supplements, are more effective in preventing hypocalcaemia in patients with hypoparathyroidism than in patients on calcium alone or in patients who have not taken any supplements and can reduce the need for intravenous calcium supplementation [1, 19–22]. A study by Streeten et al. [9] also reported the effects of hypocalcaemia to be lower in patients with long-term hypoparathyroidism treated with ergocalciferol than in those treated with calcitriol. During the treatment period, in the group treated with ergocalciferol, no case of emergency department admission or hospitalisation due to hypocalcaemia occurred, whereas in the calcitriol group, 4 out of 14 patients referred to the emergency department. However, the two groups were not different in terms of kidney problems and kidney stones, hospitalisation or emergency due to hypercalcaemia, creatinine level and modified serum calcium [8]. These results are in line with the findings of the present study. Lack of significant differences between serum creatinine and serum calcium levels between the two groups could be due to the small sample size in the study by Streeten et al. [9], as well as differences in serum creatinine based on patients' gender. However, in the present study, the mean serum creatinine in both groups was in the normal range. The need for hospitalisation or emergency department admission due to hypocalcaemia is not unexpected in patients receiving an inactive form of vitamin D, i.e. calciferol in the present study, or in patients receiving ergocalciferol, as in the study by Streeten et al., in comparison with calcitriol due to its shorter half-life. Patients receiving calcitriol may become symptomatic if they do not take the drug for even one day [9]. However, inactivated vitamin D supplements, such as ergocalciferol and cholecalciferol, are rarely prescribed to patients due to concerns about possible toxicity due to long biological half-lives [12, 23]. As a result, calcitriol is still the most common treatment for hypoparathyroidism due to its rapid efficacy. In a clinical trial study by Choe et al. [16], the incidence of hypocalcaemia in patients after total thyroidectomy showed that hypocalcaemia occurred to a lesser extent in patients taking vitamin D supplements regardless of the type of vitamin D (calcitriol or 25-hydroxycalciferol), and no significant difference was observed in the effectiveness of calcitriol and cholecalciferol supplements in routine use. However, in this study, it was found that if hypocalcaemia occurs, administration of calcitriol-calcium is more effective than on-demand use of calciferol-calcium after hypocalcaemia as it exerts its effect faster. These results are consistent with the findings of the present study, although in our study, on-demand use was not examined, and only the routine use of drugs was compared.

Therefore, although the treatment of choice for hypoparathyroidism is an active form of vitamin D (calcitriol), as 25-hydroxycholecalciferol in high doses can activate the vitamin D receptor and act as an active form of vitamin D, this treatment can be used if calcitriol is not available. Furthermore, given that it has been observed that in patients with hypoparathyroidism, part of the 25-hydroxycholeciferol is converted into active forms of vitamin D despite impaired renal 1-alpha hydroxylase function, inactive forms of vitamin D, such as calciferol, can be used in the treatment regimen of these patients [11]. Moreover, although the main concern in treating patients with hypoparathyroidism with inactive forms of vitamin D (such as calciferol, ergocalciferol) is the development of long-term hypercalcaemia

[9], in the present study, as in similar studies [8, 16], no difference in the incidence of hypercalcaemia was observed between inactive forms of vitamin D and calcitriol. Therefore, in cases where calcitriol is not available, inactive forms of vitamin D can be used, taking into account the necessary precautions regarding vitamin D poisoning.

In the present study, the rate of compliance to treatment in the calciferol group was higher than the calcitriol group (98% vs. 92%), but this difference was not statistically significant. Other studies have reported low therapeutic acceptance of calcitriol as one of its disadvantages [8, 9]. Therefore, in patients who do not receive proper treatment or in people who do not take their medications regularly due to psychiatric illness and indulgence, calciferol can be used due to its long-term effect to decrease the possible frequency of hypocalcaemia in these patients.

Since various factors, such as the duration of hypothyroidism, the presence of malignancy, postoperative serum PTH levels, parathyroid autotransplantation and old age, can affect the incidence of hypocalcaemia [19, 24, 25], these can also impact the findings of studies. Finally, it should be noted that limited studies have been performed comparing the effectiveness of different forms of vitamin D supplementation in the treatment of hypoparathyroidism, which is why drawing a definite conclusion is not possible. Therefore, by conducting more prospective studies and controlling various factors affecting the incidence of hypocalcaemia, better results can be achieved.

Limitations of the study

This study faced some limitations, including the fact that due to the retrospective nature of the study and the incomplete information in the records, it was not possible to evaluate some parameters, including not being able to examine other confounding factors, such as other underlying diseases, duration of disease and postoperative PTH levels. Moreover, the two groups were not age-matched, which could have affected the results. Another limitation of the study was that we only had patient reports and records in the hospitals we studied, and some patients may have referred to other hospitals or emergency departments.

Conclusions

The results of this study showed that there was no significant difference in response to the treatment and side effects of calcitriol supplementation and cholecalciferol, and taking both vitamin D supplements and taking oral calcium supplements in the treatment of patients with hypoparathyroidism was almost equally effective in preventing hypocalcaemia and consequent hospitalisation. Since there were 4 cases of hypocalcaemia in calcitriol versus no hypocalcaemia in calciferol, cholecalciferol treatment can be considered as a more affordable alternative to calcitriol in the treatment of hypoparathyroid patients, especially patients with recurrent hypocalcaemia.

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