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Original

Cholecalciferol versus calcitriol to manage secondary hyperparathyroidism in hemodialysis patients

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Abstract

Introduction: Secondary hyperparathyroidism, is a matter of concern in hemodialysis patients that cause renal osteodystrophy eventually.

Objectives: The objective of the study was to compare the efficacy of cholecalciferol with calcitriol for treating secondary hyperparathyroidism.

Materials and Methods: This study is a randomized, controlled study. Around 80 patients with hyperparathyroidism (PTH >300 ρg/mL) and 25(OH)D level <20 ng/mL were divided into two groups to receive cholecalciferol 50 000 IU/3 times in one week or calcitriol 0.25 μg/daily for 12 weeks. Additionally calcium carbonate 1000-1500 mg/d/tablets is prescribed for both groups. Reduction of parathyroid hormone (PTH), changes of plasma albumin-corrected calcium and phosphorus and levels of 25(OH)D were analyzed.

Results: Around 40 patients were randomized into each group. At baseline, plasma albumin-corrected calcium, phosphorus and intact PTH and 25(OH)D had no difference between groups. At week 12, intact PTH levels in cholecalciferol and calcitriol groups were 242.38 ± 16.38 ρg/mL and 237.84 ± 13.65 ρg/mL in respectively. Patients who achieved target intact PTH of <300 ρg/mL were 90% in the cholecalciferol and 95% in the calcitriol group ($P = 0.447$). Serum calcium and phosphorus were not significantly different in both groups. Serum calcium; 9.07 ± 0.36 mg/dL versus 9.00 ± 0.38 mg/dL ($P = 0.607$), phosphorus; 4.81 ± 0.55 mg/dL versus 4.15 ± 0.42 mg/dL ($P = 0.126$) in cholecalciferol and calcitriol groups respectively. Furthermore, serum 25(OH)D levels significantly rise in cholecalciferol group. Serum 25(OH)D levels were 62.98 ±21.03 ng/mL in cholecalciferol group and 18.95 ± 22.70 ng/mL in calcitriol group ($P < 0.05$).

Conclusion: cholecalciferol can be administered to control secondary hyperparathyroidism and vitamin D(25OH) deficiency in hemodialysis patients . The two drugs are equally efficacious and lead to similar changes in calcium and phosphorus levels.

Keywords: Hyperparathyroidism, Hemodialysis, Cholecalciferol, Calcitriol

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Introduction

Kidney failure is a major problem in diabetic and hypertensive patients affecting these individuals after many years of initial illness. One of the main problems in patients with impaired kidney function is bone disorders which are characterized by high bone turnover along with the increased level of parathormone (1,2). The main pathophysiology of secondary hyperparathyroidism and bone disease is due to the reduction of glomerular filtration rate (GFR), which reduces phosphate excretion and retention leading stimulation of parathyroid hormone (PTH) production and parathyroid gland growth (3). Reduced levels of ionized calcium can also induce PTH production due to the reduced production of active forms of vitamin D from damaged kidneys and also due to phosphate retention (4). Low levels of the active form of vitamin D can contribute to hyperparathyroidism by inducing hypocalcemia as well as through a direct effect on the transcription of the PTH gene (5). Resistance to the normal level of PTH is a major contributor to hypocalcemia, which in turn acts as a stimulant for the growth and enlargement of parathyroid glands (6). However, new findings suggest an increase in fibroblast growth factor 23 (FGF23), production by osteocytes (and possibly osteoblasts) in the bone before increasing PTH levels (7). FGF23 is a potent inhibitor of the 1-alpha-hydroxylase renal enzyme and reduces 1α,25-dihydroxyvitamin D3. FGF23 and vitamin D both may be important stimulants for the development of secondary hyperparathyroidism (8). The occurrence of hyperparathyroidism in renal disease patients leads to the induction of bone turnover and osteitis fibrosa cystica that characterized by a combination of manifestations including, pain and bone fragility, hemorrhagic bone cysts, and rare syndromes due to the compressive effects of these cysts and resistance to erythropoietin (9). It

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Implication for health policy/practice/research/medical education

Renal osteodystrophy is one of the complication in renal failure and hemodialysis patients that cause several morbid conditions. Cholecalciferol can be suitable to control secondary hyperparathyroidism and vitamin D(25OH) deficiency in hemodialysis patients. The two drugs are equally efficacious and lead to similar changes in calcium and phosphorus levels.

should be noted that the main cause of hypocalcaemia as one of the causes of hyperparathyroidism in renal failure patients is vitamin D deficiency (10). The hydroxylase stage related to the production of vitamin D is processed in the kidney that can be impaired in cases with renal failure. Then, the absorption of calcium and phosphorus from the intestine decreases that leads to secondary hyperparathyroidism (11). Calcitriol is currently used for the treatment of vitamin D deficiency and prevention of its related complications in hemodialysis patients that reduces the plasma concentration of parathormone in a 3-6 month course of treatment (12).

Objectives

In the present study, we aimed to compare the efficacy of cholecalciferol and calcitriol in the treatment of hyperparathyroidism in hemodialysis patients.

Patients and Methods

Patients

This clinical trial was conducted on 80 hemodialysis patients aged 30 to 85 years referring to Imam Reza hospital in Kermanshah city with secondary hyperparathyroidism and vitamin D deficiency (lower than 20 ng/mL). The non-random sampling method was used to select the patients. After obtaining written informed consent, venous blood samples were taken to assess the blood levels of 25-hydroxy vitamin D, calcium, phosphorus and intact PTH (iPTH). The patients with lower levels of vitamin D (below 20 ng/mL) and high iPTH levels (greater than 300 ρg/mL) were randomly assigned into two groups. Both groups received calcium carbonate tablets 1500-1000 mg/d. The first group received cholecalciferol (50 000 units, 3 times a week) and the second group received calcitriol (0.25 μg, once a day), both produced by Zahravi Company. After 3 months, blood samples were collected again from both groups and reanalyzed according to the laboratory indices.

Ethical issues

The research followed the tenets of the Declaration of Helsinki and its later amendments. Patients gave their written and informed consent to participate in this investigation by completing the consent form. This research has been supported by Kermanshah University of Medical Sciences regarding financial budget and has been approved by this university (The study was conducted as an internal medicine residency thesis of Ali Daraizade # 92348).

Statistical analysis

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of the data was analyzed using the Kolmogorov–Smirnov test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of the cells with expected count of less than 5 were observed. The quantitative variables were also compared with *t* test or Mann-Whitney U test. For the statistical analysis, the statistical software SPSS version 20 for Windows (SPSS Inc., Chicago, IL) was used. *P* values of 0.05 or less were considered statistically significant.

Results

In this study, two groups of 40 patients matched for baseline characteristics were planned to receive cholecalciferol or calcitriol. At the beginning of the study as well as three months later, serum levels of calcium, phosphorus, vitamin D and parathormone were measured and compared across the two groups. Cholecalciferol but not calcitriol could significantly increase serum vitamin D levels and thus improve vitamin D deficiency ($P<0.05$). Also, similar to calcitriol, cholecalciferol reduces the levels of iPTH and thus improved secondary hyperparathyroidism in hemodialysis patients ($P=0.047$). No significant association between serum levels of calcium and phosphorus and gender in the two groups was found. The mean serum level of PTH at baseline was 404.22 ρg/mL in cholecalciferol group and 369.53 ρg/mL in calcitriol group. After three months of treatment, secondary hyperparathyroidism improved significantly in both treated groups by achieving the final iPTH revels of 242.38 ρg/mL and 237.84 ρg/mL respectively. In the groups receiving cholecalciferol and calcitriol, the mean serum level of vitamin D was as 8.80 ng/mL and 9.98 ng/mL respectively that reached to 62.98 ng/mL and 18.95 ng/mL after 3-month treatment period (normal range defined between 30 and 100 ng/mL). The mean serum level of calcium was initially 8.21 mg/dL in that reached to 9.07 mg/dL in cholecalciferol group after treatment. A similar change was revealed in those who treated with calcitriol from 8.18 mg/dL primarily to 9.00 mg/dL after treatment with no significant difference between the two treatment groups. The condition for the mean serum level of phosphorous was similar that in the groups receiving cholecalciferol or calcitriol. The mean level of serum phosphorus was 5.17 mg/dL and 4.87 mg/dL respectively that reached to 4.81 mg/dL and 4.15mg/dL respectively after treatment with no difference across the two groups.

Discussion

Various studies could demonstrate the efficacy of cholecalciferol in the treatment of secondary

hyperparathyroidism especially among those suffering hemodialysis. A cohort study including 158 hemodialysis patients receiving cholecalciferol supplementation revealed higher 25(OH)D, and 1,25-dihydroxyvitamin D levels, but reduced serum calcium and iPTH (13). The main limitation of that study was its nonrandomized nature that could not demonstrate the causality between the use of cholecalciferol and improvement of hyperparathyroidism or the changes in the level of biomarkers. In another study including seven hemodialysis patients who received cholecalciferol supplementation, reducing levels of pro-inflammatory biomarkers including, IL-8, IL-6, and TNF were reported following the administration of this supplement (14), but the potential limitation of the study was remarkable due to small sample size. Along with the pointed studies, some clinical trial studies compared the beneficial effects of cholecalciferol to other regimens such as ergocalciferol, doxercalciferol, or even placebo leading controversial results on its efficacy (15-21). Besides, because of impairing production of calcitriol at very early stages of chronic dysfunction, it is no suggested that the administration of calcitriol analogues can improve its concentration as well as its metabolic functions in those patients. However, conducting trials on its efficacy led to paradox regarding its benefits. Various studies had shown, calcitriol therapy resulted in increase risk of hypercalcemia or hyperphosphatemia. Additionally, calcitriol therapy had not led to a consistent reduction in PTH concentration. (22). Contrarily, Shoben et al reported a survival benefit of therapy with calcitriol versus no therapy in patients with advanced chronic kidney disease so that those who were treated with calcitriol had a 26% lower mortality compared with those who were untreated (23). In this regard, our study could indicate similar treatment effects of both medications (cholecalciferol and calcitriol) on hyperparathyroidism manifested by improvement of the related biomarkers. In other words, administrating both medications led to diminishing the levels of PTH with no significant effects on serum calcium or phosphorus. The main probable similarity in the effects of two drugs could be that the administration of cholecalciferol or vitamin D supplements affects the level of native calcitriol in the body (24). In other words these is a direct interaction between the concentration of cholecalciferol use and level of calcitriol in the body. In total, administrating both medications studies in the present study can effectively improve hyperparathyroidism in hemodialysis patients.

Conclusion

Cholecalciferol in high doses can be administered to control secondary hyperparathyroidism and vitamin D(25OH) deficiency in hemodialysis patients . The two drugs are equally efficacious and lead to similar changes in calcium and phosphorus levels.

Limitations of the study

This investigation has several limitations. This research is a single center investigation conducted on a limited proportion of individuals. This investigation can be a pilot investigation to be completed by larger multi-centric studies.

Authors' contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. HRO and MR conducted the research. AD prepared the primary manuscript. HRO prepared the final paper. All authors read and signed the edited manuscript.

Conflicts of interest

The authors declare that they have no conflict of interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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