Efficacy of High vs. Conventional Ergocalciferol Dose for Increasing 25-Hydroxyvitamin D and Suppressing Parathyroid Hormone Levels in Stage III-IV CKD with Vitamin D Deficiency/Insufficiency: A Randomized Controlled Trial

Paramat Thimachai MD*, Ouppatham Supasyndh MD*, Amnart Chaiprasert MD*, Bancha Satirapoj MD*

*Division of Nephrology, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand

Background: Vitamin D deficiency/insufficiency is common in chronic kidney disease (CKD) patients and it contributes to secondary hyperparathyroidism, which occurs early in CKD. It is not clear whether the Kidney Disease Outcomes Quality Initiative (K/DOQI) recommended doses of ergocalciferol are adequate for correction of vitamin D insufficiency and hyperparathyroidism.

Objective: To evaluate the parathyroid hormone (PTH)-lowering effect, safety, and tolerability of high-dose ergocalciferol compared with conventional-dose ergocalciferol in CKD subjects.

Material and Method: We enrolled CKD stage III-IV patients who had 25-hydroxyvitamin D (25-OH-D) level <30 ng/mL. The patients were randomized into two groups, control group treated with ergocalciferol as recommended by K/DOQI guidelines, and treatment group treated with double dosage of ergocalciferol from the recommendation. We compared serum 25-OH-D, intact-PTH, phosphate, calcium, and bone biomarker levels, during the 8-week intervention.

Results: Sixty-eight patients were included (34 controls and 34 treatments). Baseline characteristics of both groups were similar except calcium level 9.12±0.56 mg/dL in control group and 9.44±0.38 mg/dL in treatment group (p = 0.009), but not clinically significant. At the end of the 8-week, the mean 25-OH-D level significantly increased from 20.99±6.68 to 33.41±8.92 ng/mL in the treatment group (p = 0.001) and increased from 20.84±7.21 to 23.42±7.89 ng/mL in the control group (p = 0.026). There was also a significantly greater increase of 25-OH-D levels in the treatment group. Additionally, PTH levels significantly decreased from 90.75±67.12 to 76.40±45.97 at 8 weeks (p = 0.024) in the treatment group, and there was no change in the control group (97.14±83.52 vs. 101.13±95.03 pg/mL, p = 0.546). Serum calcium, phosphate, and adverse effects did not significantly change in either group throughout the study.

Conclusion: In addition to improving vitamin D levels, oral high-dose ergocalciferol was safe and had a beneficial effect in decreasing PTH in patients with stage III-IV of CKD.

Keywords: Hyperparathyroidism, Chronic kidney disease, Ergocalciferol, Chronic kidney disease-Bone metabolism
disease (CKD-BMD) is the important factors in patients with kidney disease and it is related to increased morbidity and mortality rate in patients with CKD. This condition is characterized by alteration of calcium and phosphate metabolism especially phosphate retention and calcitriol deficiency resulting in hyperparathyroidism. Calcitriol or 1, 25-hydroxycholecalciferol (1, 25-OH-D) is produced in renal tubular cells by 1-alpha hydroxylation of 25-hydroxycholecalciferol. In the decline of the renal function, especially in chronic tubulointerstitial disease, calcitriol deficiency will develop. A reduction of serum 25-hydroxyvitamin D (25-OH-D), the substrate for the kidney’s generation of calcitriol (1, 25-OH-D), produces secondary hyperparathyroidism (2°HPT) in individuals with normal kidney function[1,2], and may aggravate 2°HPT in those with CKD and decreased kidney function[3,4]. Recently, 25-OH-D insufficiency and deficiency is more common and associated with the level of kidney function in the CKD population especially advanced stage of CKD[5]. Moreover, the deficiency of 25-OH-D was found to be associated with...
cardiovascular mortality in CKD\(^6,7\). In patients with CKD, nutritional vitamin D deficiency and insufficiency can both be prevented by supplementation with vitamin D\(_2\) (ergocalciferol). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) guideline in patients with CKD and those requiring dialysis is to receive a modest supplementation with ergocalciferol to raise serum 25-OH-D levels to 30 to 60 pg/mL. In addition, they might have an increase in the plasma levels of 1, 25-OH-D or lower the elevated serum levels of intact parathyroid hormone (PTH)\(^8\). However, it is not clear whether the KDOQI recommended doses of ergocalciferol are adequate for correction of vitamin D insufficiency and hyperparathyroidism. In addition, high dose ergocalciferol supplement successively increased serum 25-OH-D levels in the prospective observational study and there was no other side effect associated with the treatment in predialysis CKD\(^9\). Thus, there was limitation of evidence for dosage of ergocalciferol supplement in CKD population. The present study examined the effect of short-term high dose ergocalciferol therapy on serum 25-OH-D, PTH levels, serum calcium, and phosphate compared with conventional dose ergocalciferol as KDOQI recommendation.

Material and Method

This was an 8-week open labeled, randomized, controlled study conducted in Outpatient, Department of Medicine, Phramongkutklao Hospital. Data was collected between October 2013 and February 2014. The study was approved by the Institutional Review Boards of the Phramongkutklao Hospital and College of Medicine. Inclusion criteria into the study were age greater than 18 years, CKD stage III-IV (estimated GFR 15-60 ml/min/1.73 mm\(^2\) by CKD-EPI creatinine base formula), serum 25-OH-D less than 30 ng/dL. Exclusion criteria were primary or tertiary hyperparathyroidism, hypoparathyroidism, receiving vitamin D analogue within four weeks, serum calcium greater than 10.5 mg/dL, serum phosphate greater than 5.5 mg/dL, chronic liver disease, malabsorption syndrome, malignancy, chronic illness whose life expectancy was less than six months. All patients gave informed written consent. Eligible patients were randomized by a block of four randomization assigned to two groups. The sample size calculated from previous study was to determine the mean difference of conventional dose and high dose at least 10 pg/mL\(^9\). To test the hypothesis, approximately 28 persons per group and plus dropout rate 20%. Finally, 68 patients were included into the present study.

Clinical protocol

The patients in the conventional group was received ergocalciferol according to KDOQI recommendation\(^10\), that were classified by 25-OH-D level (50,000 IU/week x 8 weeks if 25-OH-D <5 ng/mL, 50,000 IU/week x 4 weeks then 50,000 IU/month if 25-OH-D 5-15 ng/mL and 50,000 IU/month x 2 months if 25-OH-D 16-30 ng/mL). For treatment with high dose ergocalciferol, the patients will received the double dose of ergocalciferol according to KDOQI recommended dose. All patients were advised to take the medicine weekly before bedtime and were monitor the medication prescription based on pill counts.

Clinical laboratory measurements

Laboratory testing including serum 25-OH-D, serum intact PTH, serum phosphate, serum calcium, serum albumin, complete blood count (CBC), blood urea nitrogen and serum creatinine were performed in the both groups at baseline and at 8-week. The method to measure serum 25-OH-D and intact PTH were the electrochemiluminescence binding assay. It is intended for use on Elecsys and Cobas e 601 immunoassay analyzers. The principle test of 25-OH-D and intact PTH used competitive principle and sandwich principle method.

Safety monitoring

Adverse events that were or were not considered to be related to treatment were monitored four weeks. The patients were questioned in a systematic way about their experiences concerning adverse events during the previous eight weeks.

Statistical analysis

Statistical analyses were performed using the SSPS 16.1 software program. Continuous variables between study and control groups were compared with unpaired t-tests. Continuous variables between baseline and at the end of study for each group of patients were compared using paired t-tests. Chi-square test was used to examine the categorical outcome. Statistical significance was taken as \(p<0.05\).

Results

Eighty-eight patients in outpatient department were screened for possible study enrollment. Sixty-eight patients were eligible according to the entry criteria.
Thirty-four patients were assigned to the high dose ergocalciferol group and remainder were assigned to conventional dose ergocalciferol group. All the patients adhered to the ergocalciferol prescription based on pill counts. The patients’ baseline characteristics are shown in the Table 1. Baseline characteristics of the both groups were similar except serum calcium level was significantly higher in the high dose ergocalciferol group (9.44±0.38 vs. 9.12±0.56 mg/dL, p = 0.009).

At the end of the 8-week, the mean serum 25-OH-D level significantly increased from 20.99±6.68 to 33.41±8.92 ng/mL in the high dose ergocalciferol group (p = 0.001) and increased from 20.84±7.21 to 23.42±7.89 ng/mL in the conventional dose ergocalciferol group (p = 0.026). There was also a significantly greater increase of 25-OH-D levels in the high dose ergocalciferol group (Fig. 1A).

Additionally, serum PTH levels significantly decreased from 90.75±67.12 to 76.40±45.97 at 8-weeks (p = 0.024) in the high dose ergocalciferol group, and there was no change in the conventional dose ergocalciferol group. (97.14±83.52 vs. 101.13±95.03 pg/mL, p = 0.546). There was a significantly greater decrease in serum intact PTH in the high dose ergocalciferol group as compared to the conventional dose ergocalciferol group (Fig. 1B).

Moreover, in comparison to baseline status, the high dose ergocalciferol group displayed significantly increased percentage of normalization of serum 25-OH-D levels than conventional dose ergocalciferol group (25-OH-D level >30 ng/mL: 60% vs. 19%, p<0.05) (Fig. 2). Serum calcium, and phosphate did not significantly change in either group throughout the study and this parameters were shown in Table 2.

During the 8-week study period, the patients with serum calcium between 10.2 and 10.5 mg/dL were 5.8% and serum phosphate between 4.5-5 mg/dL were 2.9% in the high dose ergocalciferol group, but no significant difference was detected in the both groups. No patients had any serious adverse events during the study.

Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Conventional dose (n = 34)</th>
<th>High dose (n = 34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18</td>
<td>18</td>
<td>0.895</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.9±15.5</td>
<td>66.7±15.4</td>
<td>0.852</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.07±0.92</td>
<td>2.16±1.03</td>
<td>0.711</td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min/1.73 m²)</td>
<td>35.3±15.6</td>
<td>33.1±13.3</td>
<td>0.522</td>
</tr>
<tr>
<td>Intact-PTH (pg/mL)</td>
<td>97.7±80.3</td>
<td>90.7±65.4</td>
<td>0.812</td>
</tr>
<tr>
<td>25-OH-D (ng/mL)</td>
<td>20.8±7.3</td>
<td>20.9±7.8</td>
<td>0.552</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>9.12±0.56</td>
<td>9.44±0.38</td>
<td>0.009</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL)</td>
<td>3.58±0.54</td>
<td>3.46±0.59</td>
<td>0.378</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>60.6%</td>
<td>70.6%</td>
<td>0.390</td>
</tr>
</tbody>
</table>

25-OH-D = 25-hydroxyvitamin D; intact-PTH = intact-parathyroid hormone
Data are mean ± SD and percentage

Fig. 1 Mean changes in serum 25-OH-D levels and plasma PTH after treatment.

Fig. 2 Serum 25-OH-D status after treatment with high dose ergocalciferol compared with conventional dose ergocalciferol.
Discussion

Ergocalciferol is a synthetic derivative of 25-OH-D and is recommended for the treatment of vitamin D deficiency, vitamin D resistant rickets, and hypophosphatemia in the general population and CKD patients. K/DOQI 2003 clinical practice guidelines for MBD-CKD recommended supplementation with ergocalciferol dose as general population in CKD patients whose 25-OH-D level less than 30 ng/mL(10). Our study demonstrated that high dose ergocalciferol had higher efficacy for increasing 25-OH-D and decreasing intact PTH level in patient with CKD than conventional dose ergocalciferol after eight weeks of treatment.

The KDOQI guidelines recommend treatment of vitamin D deficiency starting with CKD stage III, though no data are available showing an impact on serum PTH concentrations(10). Previous studies demonstrated that standard dose ergocalciferol/ cholecalciferol therapy did not appear to have benefits in serum PTH levels in stage III of CKD(11,12). In addition, previous retrospective study demonstrated that initiation of treatment with ergocalciferol had no significant effect on increasing 25-OH-D and decreasing intact PTH level in patients with CKD than conventional dose ergocalciferol after eight weeks of treatment.

In the present study, there were no side effects associated with the treatment. Serum calcium and phosphate had no significant changes in all study patients. This finding was similar to other studies in CKD patients that no adverse consequences were observed with high dose 25-OH-D supplements(13,15) and low incidence of hypercalcemia and hyperphosphatemia(16). However, the present study was limited by the short duration of follow up and no apparent treatment related benefits in prevent of cardiovascular events and impaired renal function in CKD patients. Additional research is needed to confirm these results and determine the optimal levels of serum 25-OH-D.

In conclusion, the present study results showed that ergocalciferol administration had a favorable effect on serum PTH levels and increase serum 25-OH-D levels in patients with CKD stage III and IV. Low incidence of adverse effects including hypercalcemia and hyperphosphatemia was detected.

What is already known on this topic?

Vitamin D insufficiency and deficiency are more common in the CKD population especially advanced stage of CKD. Moreover, the deficiency of 25-OH-D was found to be associated with all-cause and cardiovascular mortality in CKD. K/DOQI 2003 clinical practice guidelines recommended supplementation with ergocalciferol dose as general population in CKD patients whose 25-OH-D level less than 30 ng/mL. However, it is not clear whether the KDOQI recommended doses of ergocalciferol are adequate for correction of vitamin D insufficiency and hyperparathyroidism.

What this study adds?

Double standard dose ergocalciferol had higher efficacy for increasing 25-OH-D and decreasing intact PTH level in patient with CKD stage III and IV.
than standard dose ergocalciferol after 8 weeks of treatment. Low incidence of adverse effects including hypercalcemia and hyperphosphatemia was detected in the double standard dose ergocalciferol.

Acknowledgments
The authors wish to acknowledge the contributions of the following individuals to the present study, staffs at the Division of Nephrology and Biomedical Clinical Research Center, Phramongkutklao Hospital. This study was supported by the Department of Medicine, Phramongkutklao Hospital and College of Medicine.

Potential conflicts of interest
None.

References
การศึกษาแบบทดลองสุ่มเปรียบเทียบประสิทธิผลของ ergocalciferol ชนิดรับประทานขนาดสูงและขนาดมาตรฐาน ต่อการเพิ่มของระดับของ 25-hydroxyvitamin D และการลดลงของระดับพาราไทรอยด์ฮอร์โมนในเลือดในผู้ป่วยโรคไตเรื้อรังระยะ 3-4 ที่มีภาวะพร่องวิตามินดี

ประชี พิมพ์ชัย, อุปกรณ์ อุปสินธุ์, อานนท์ ชัยพรพิน, บัญชา สถิระพจน์

ภูมิหลัง: ภาวะพร่องวิตามินดีพบบ่อยในผู้ป่วยที่มีโรคไตเรื้อรังและพบรวมกับการเพิ่มขึ้นของระดับพาราไทรอยด์ฮอร์โมน โดยเฉพาะโรคไตเรื้อรังระยะท้าย ขณะที่การรับประทาน ergocalciferol รับประทานตามคำแนะนำของสมาคมโรคไตตาม Kidney Disease Outcomes Quality Initiative (K/DOQI) ในผู้ป่วยโรคไตระยะที่ 3-4 มีผลต่อการเปลี่ยนแปลงของระดับ 25-hydroxyvitamin D และระดับพาราไทรอยด์ฮอร์โมนไม่ชัดเจน

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบประสิทธิผลระหว่างการให้ ergocalciferol ชนิดรับประทานขนาดสูงเป็นสองเท่าและขนาดตามที่ K/DOQI แนะนำ ต่อการลดลงของระดับพาราไทรอยด์ฮอร์โมน และความปลอดภัยของการรักษาในผู้ป่วยโรคไตเรื้อรัง

วัสดุและวิธีการ: ผู้เข้าร่วมการศึกษาคือผู้ป่วยโรคไตเรื้อรังระยะ 3 และ 4 ที่มีระดับ 25-hydroxyvitamin D ในเลือดต่ำกว่า 30 เน็คกรัม/มิลลิลิตร ผู้ป่วยยังต้องมีค่ากรานีน ได้กลุ่มควบคุมให้ ergocalciferol ชนิดรับประทานขนาดตามที่ K/DOQI แนะนำ และในกลุ่มทดลองเพิ่มขนาด ergocalciferol เป็นสองเท่า จนที่ K/DOQI แนะนำ ตรวจวัดระดับ 25-hydroxyvitamin D หลังรักษา 8 สัปดาห์

ผลการศึกษา: ผู้ป่วยโรคไตเรื้อรังจำนวน 68 ราย มีกลุ่มควบคุมและกลุ่มทดลอง กลุ่มละ 34 ราย ข้อมูลที่ฐานข้อมูลของผู้ป่วยกลุ่มไม่มีความแตกต่างกัน ยกเว้นค่าเลือดของกลุ่มขาดเจ้าในเลือดของกลุ่มทดลองมีค่า 9.12±0.56 มิลลิกรัม/เดซิลิตร ต่ำกว่ากลุ่มควบคุมที่มีค่า 9.44±0.38 มิลลิกรัม/เดซิลิตร (p = 0.009) แต่ยังอยู่ในเกณฑ์ปกติซึ่งไม่มีนัยสำคัญทางสถิติ เมื่อสิ้นสุดการศึกษาที่ 8 สัปดาห์ ค่าเฉลี่ยของระดับ 25-hydroxyvitamin D ในเลือดของผู้ป่วยกลุ่มทดลองขึ้นอย่างมีนัยสำคัญทางสถิติ โดยในกลุ่มทดลองเพิ่มจาก 20.99±6.68 เป็น 33.41±8.92 เน็คกรัม/มิลลิลิตร (p = 0.001) และในกลุ่มควบคุมเพิ่มจาก 20.84±7.21 เป็น 23.42±7.89 เน็คกรัม/มิลลิลิตร (p = 0.026) แต่ระดับ 25-hydroxyvitamin D ในเลือดเพิ่มขึ้นอย่างมีนัยสำคัญในกลุ่มทดลอง เมื่อเทียบกับกลุ่มควบคุม นอกจากนี้ค่าเลือดของพาราไทรอยด์ฮอร์โมนในเลือดของกลุ่มทดลองลดลงครึ่งในกลุ่มทดลอง โดยเฉลี่ย 90.75±67.12 เป็น 76.40±45.9 เน็คกรัม/มิลลิลิตร อย่างมีนัยสำคัญทางสถิติ (p = 0.024) ส่วนในกลุ่มควบคุมกลับผ่าว ค่าเฉลี่ยของพาราไทรอยด์ฮอร์โมนในกลุ่มทดลองไม่มีการเปลี่ยนแปลงที่สำคัญ จาก 97.14±83.52 เป็น 101.13±95.03 เน็คกรัม/มิลลิลิตร (p = 0.546) จากการศึกษาที่นี้ พบว่าไม่มีการเปลี่ยนแปลงของระดับกรานีนในกลุ่มทดลองและสาเหตุที่ไม่มีการเปลี่ยนแปลงของพาราไทรอยด์ฮอร์โมนไม่มีผลต่อการควบคุมกรานีนของกลุ่มในผู้ป่วยโรคไตเรื้อรังระยะ 3-4