Research Article

Efficacy of Weekly Split versus Single Doses of Ergocalciferol on Serum 25-Hydroxyvitamin D among Patients on Continuous Ambulatory Peritoneal Dialysis: A Randomized Controlled Trial

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Background. Vitamin D deficiency is a common problem among patients on continuous ambulatory peritoneal dialysis (CAPD). Vitamin D supplementation leads to reduced serum parathyroid hormone levels and improved cardiovascular markers. Different doses and time intervals of oral vitamin D supplementation may differ in each patient on dialysis. The study aimed to evaluate the efficacy of weekly split and single dose of ergocalciferol at 60,000 IU on serum 25-hydroxyvitamin D (25(OH)D) among patients on CAPD. Methods. A randomized study was conducted among patients on CAPD with vitamin D deficiency or insufficiency (25(OH)D < 30 ng/mL). Patients were randomly assigned to two groups: the split dose group was given ergocalciferol 20,000 IU three times weekly and the single dose group was given ergocalciferol 60,000 IU once weekly for 8 weeks. Main outcomes measured serum 25(OH)D concentrations, serum calcium, serum phosphate, and intact parathyroid levels at 8 weeks after being enrolled. Results. Of 128 screened patients, 50 met the criteria for eligibility and were randomized. At 8 weeks after treatment, mean serum 25(OH)D concentrations significantly increased from baseline 22.7 ± 5.9 to 29.5 ± 9.5 ng/mL (P < 0.004) in the split dose group and 22.9 ± 5.3 to 31.2 ± 12.3 ng/mL (P = 0.003) in the single dose group. No significant change was found in increase of serum 25(OH)D between the two groups (P = 0.561). At the end of study, a similar proportion of patients in both groups reached the desirable serum concentration of 25(OH)D ≥ 30 ng/mL (60% in the single group vs. 40% in the split group, P = 0.258). No significant cases of hypercalcemia, hyperphosphatemia, or serious adverse events occurred during the study. Conclusion. Weekly single and split doses of ergocalciferol 60,000 IU achieved similar effects on serum 25(OH)D levels among patients on CAPD with vitamin D insufficiency or deficiency, suggesting that weekly single dose would be prescribed for adequate vitamin D repletion. This trial is registered with TCTR20200821005.

1. Background

Among patients with advanced chronic kidney disease (CKD) and end-stage renal disease on dialysis, the incidence and prevalence of vitamin D deficiency and insufficiency has been reported to be higher than that of the general population [1–3]. The clinical impact of low serum 25-hydroxyvitamin D (25(OH)D) level among patients with CKD has been associated with secondary hyperparathyroidism, decreased bone mineral density, increased muscle weakness and risk of falls, increased risk for mortality, and progression to dialysis [4, 5]. Vitamin D supplementation among patients with CKD and on dialysis leads to decreased serum parathyroid hormone (PTH) level, reduced proteinuria, improved endothelial cardiovascular markers, and decreased inflammatory markers [6, 7]. Current systematic review and meta-analysis in CKD patients indicated that vitamin D treatment was associated with reductions in all-cause mortality in the observational studies, but significant association was not found in the randomized controlled studies [8]. Ongoing debate embraces which dose and type of vitamin D supplement should be used for supplementation, ergocalciferol or cholecalciferol, depending on availability [9].
National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines currently recommend vitamin D supplementation in advanced CKD patients with 25(OH)D levels <30 ng/mL [10]. Standard dose of ergocalciferol as recommended by K/DOQI guidelines was inadequate for correcting vitamin D deficiency and insufficiency in CKD patients [11], whereas high dose ergocalciferol was safe and significantly increased serum 25(OH)D level in advanced CKD patients [12]. Our study started initial high dose of ergocalciferol at 60,000 IU/week independent on baseline serum 25(OH)D level in all CAPD patients with vitamin D deficiency and insufficiency. Ergocalciferol is widely available in Thailand for oral use in 20,000 IU capsules. No strong evidence is available about drug administration, but ergocalciferol (20000 IU) was prescribed orally three times weekly or once a week with total dose of 60,000 IU/week in general practice [13]. However, to date, limited clinical trials and published literature have compared the efficacy of single or split high dose of ergocalciferol among patients on continuous ambulatory peritoneal dialysis (CAPD). This study aimed to examine the efficacy of single and split dose ergocalciferol weekly to treat vitamin D deficiency and insufficiency among patients on CAPD.

2. Methods

2.1. Study Design. This single-center, prospective, double-blind, randomized controlled study was conducted in Phramongkutklao Hospital from January 2018 to February 2019. The study was approved by the Ethics Committee of the Institute Review Board of the Royal Thai Army Medical Department, and all subjects provided written informed consent. The study complies with the Declaration of Helsinki. The study was registered at Thai Clinical Trials Registry (TCTR) (TCTR20200821005). Enrolled participants were randomly assigned to two groups at a ratio of 1:1; the split dose group was given ergocalciferol 20,000 IU three times weekly and the single dose group was given ergocalciferol 60,000 IU weekly for eight weeks, as illustrated in Figure 1.

2.2. Study Population. The inclusion criteria comprised patients on CAPD for at least three months before enrolling, aged ≥18 years, and having received a diagnosis of vitamin D deficiency defined by serum 25(OH)D less than 20 ng/mL or vitamin D insufficiency defined by 20 to 29 ng/mL. Subjects with a history of liver diseases, hypocalcemia, hypercalcemia, hyperparathyroidism, pregnancy, lactating women, and urinary tract stone were excluded from the study. Discontinuation criteria included unwillingness to continue study and intolerable side effects or allergy. All participants were examined physically, and their clinical history was noted. Age, weight, body mass index (BMI), and age were recorded.

2.3. Randomization and Outcomes. Enrolled participants were selected using block randomization and allocated to single or split dose groups by computer program. Primary outcome comprised the change of serum 25(OH)D concentrations at eight weeks after supplementation. The serum 25(OH)D level at the end of study was measured at 1 week after last dose of ergocalciferol by electrochemiluminescence binding assay, intended for use on Elecsys and Cobase 601 immuno-assay analyzers. Serum calcium, serum phosphate, and intact PTH levels were monitored before and after treatment. Safety outcomes included treatment-related adverse event, hypercalcemia, and hyperphosphatemia. All subjects were observed for adverse effects of excess vitamin D supplementation and hypercalcemic symptoms such as polydipsia, polyuria, dry mucosa membrane, vomiting, fatigue, anorexia, weakness, weight loss, and decreased appetite. The researcher verified consistent vitamin D supplementation by asking for the remaining tablets and followed up the side effects of vitamin D supplementation by using the adverse effects assessment form (Naranjo’s algorithm).

2.4. Statistical Analyses. Numerical data were expressed as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for skewed data, and categorical data were expressed as a count with number (N) and percentage (%). Comparisons used the paired t-test for continuous variables within group and Student’s t-test for continuous variables between groups. Categorical variables were compared using the chi-square test. Statistical inferences were made on the basis of a two-sided significance level of \( P < 0.05 \). All analyses were performed using SPSS, Version 13.0 for Windows (SPSS, Inc., Chicago, IL, USA).

3. Results

One hundred and twenty-eight patients on CAPD were screened from January 2018 until February 2019. A total of 50 patients met the criteria for eligibility and were randomly assigned to receive single or split doses of ergocalciferol 20,000 IU capsules three times weekly (one capsule of ergocalciferol with two capsules of placebo on Monday and one capsule of ergocalciferol on Wednesday and Friday) \((N = 25)\). The single dose group was given ergocalciferol 60,000 IU weekly (three capsules of ergocalciferol on Monday and one capsule of placebo on Wednesday and Friday) \((N = 25)\) for eight weeks, as shown in Figure 2. All patients (100%) completed the eight-week therapy and were included in the analysis. Patients in both groups had a medication possession ratio of 100%, indicating good adherence.

Baseline clinical characteristics and laboratory results of patients were similar in both groups, as shown in Table 1. Mean age was 62.4 ± 15.3 years, and the proportion of men was 54%. Mean BMI was 23.3 ± 4.7 kg/m². The main underlying disease was hypertension (100%). The mean duration to undergo peritoneal dialysis was 1.3 ± 1.8 years. Baseline serum 25(OH)D level, calcium, phosphate, and intact PTH levels were 22.8 ± 5.5 ng/mL, 9.1 ± 0.6 mg/dL, 4.5 ± 1.3 mg/dL, and 263.4 ± 217.1 pg/mL, respectively. Baseline serum 25(OH)D level in single and split dose
ergocalciferol was 22.9 ± 5.3 and 22.7 ± 5.9 ng/mL (P = 0.977), respectively.

4. Outcomes

At eight weeks of treatment, mean serum 25(OH)D concentrations significantly increased from baseline 22.7 ± 5.9 to 29.5 ± 9.5 ng/mL (P = 0.004) in the split dose group and 22.9 ± 5.3 to 31.2 ± 12.3 ng/mL (p = 0.003) in the single dose group. The mean absolute increase ± SD of serum 25(OH)D at 8 weeks did not differ between the single and split dose groups (8.4 ± 11.9 vs. 6.8 ± 10.5 ng/mL, respectively, P = 0.561) (Table 2). At the end of the study, a similar proportion of patients in both groups reached the desirable serum concentration of 25(OH)D ≥ 30 ng/mL (60% in the single group vs. 40% in the split group, P = 0.258) (Figure 3).
No statistically significant change was detected in serum phosphorus, calcium, and intact PTH levels between baseline and at eight weeks. Moreover, no participants experienced hypercalcemia or hyperphosphatemia and no serious adverse events occurred during the study.

5. Discussion

This randomized double-blind controlled trial investigated the efficacy of split and single doses of ergocalciferol 60,000 IU weekly to treat vitamin D deficiency and insufficiency among patients on CAPD. At eight weeks after treatment, both groups significant increased serum 25(OH)D compared with baseline, but there were no different outcomes between groups.

Vitamin D deficiency and insufficiency are frequent disorders in a CKD population [3], and serum 25(OH)D level is lower among patients on CAPD and hemodialysis compared with patients with CKD [14]. Low dietary vitamin D intake and minimal sun exposure commonly causes hypovitaminosis D among patients on long-term dialysis including CAPD. Oral ergocalciferol can be taken once daily but also at longer intervals because it has an average half-life of 24 hours and a duration of up to 6 months. The sustained effect of high-dose vitamin D may be attributed to its long half-life and converted slow release 25(OH)D form. Several studies have been undertaken to evaluate and determine the intake of vitamin D supplement needed to attain and maintain the optimal serum 25(OH)D level in the general population [15–18]. Few studies have evaluated the optimal dose and time intervals of oral vitamin D supplementation to improve 25(OH)D status in CKD populations [12, 19, 20]. Our study indicated that both regimens of oral vitamin D supplementation appeared to be effective, resulting in increased serum 25(OH)D levels. These results were similar to one study reporting that supplementation with vitamin D3 achieved equally well with daily, weekly, or monthly dosing frequencies in an elderly population [21], and one study also found that daily and monthly vitamin D3 supplementation exhibited equivalent adherence and improvements in vitamin D status in a CKD population [19].

Our study showed that ergocalciferol 60,000 IU weekly increased serum 25(OH)D levels without change of serum calcium, phosphate, and PTH at eight weeks. Similarly, several randomized controlled trials found that oral ergocalciferol or cholecalciferol increased serum 25(OH)D levels among advanced CKD patients and those on hemodialysis without significant alterations in plasma calcium, phosphate, or PTH [22–26]. However, a systemic review and meta-analysis indicated that vitamin D supplement was efficient for restoring 25(OH)D levels with a decrease in serum PTH level and low incidence of hypercalcemia and hyperphosphatemia among patients on CKD and dialysis [27]. The discrepancies may be due to differences in baseline serum 25(OH)D levels, vitamin D dosage, type of vitamin D supplement, duration of the study, patient population, and comorbid illness.

Our study encountered several limitations. The present study was limited by the short duration of follow-up without apparent treatment-related safety and benefits in preventing metabolic and bone outcomes among patients on CAPD at an academic medical center in Bangkok, Thailand. Our population may not be representative of the general CAPD population and may limit generalizability to other regions. Several studies have reported that cholecalciferol was more effective at raising serum 25(OH)D levels among healthy patients and those on CKD compared with ergocalciferol [28, 29]. We selected ergocalciferol because of being an easily available nutritional vitamin D supplement in Thailand, so our outcomes may not be generalizable to cholecalciferol.

6. Conclusion

Because of the long life of complex 25(OH)D and vitamin D binding protein, single and split doses of ergocalciferol 60,000 IU weekly efficiently restored 25(OH)D levels at eight weeks and 60% of the single dose group reached desirable

Table 2: Outcomes between split and single dose of ergocalciferol 60,000 IU weekly supplement at 8 weeks.

| Parameters                      | Split dose of ergocalciferol (N = 25) | Single dose of ergocalciferol (N = 25) | P value |
|---------------------------------|--------------------------------------|---------------------------------------|---------|
|                                 | Baseline | At 8 weeks | Mean change | Baseline | At 8 weeks | Mean change |         |
| Serum 25(OH)D (ng/mL)           |          |            |             |          |            |             |         |
| Serum calcium (mg/dL)           |          |            |             |          |            |             |         |
| Serum phosphate (mg/dL)         |          |            |             |          |            |             |         |
| Intact parathyroid hormone (pg/mL) |          |            |             |          |            |             |         |

Data in the table are shown with average ± standard deviation. 25(OH)D, 25-hydroxyvitamin D. *P* value < 0.05 vs. baseline. *P* value of mean change between the two groups.

![Figure 3: Serum 25-OH-D status after treatment with single and split dose ergocalciferol 60,000 IU weekly.](image)
concentrations of 25(OH)D, suggesting that single dose weekly might be required for adequate vitamin D repletion among patients on CAPD.

**Abbreviations**

BMI: Body mass index  
CKD: Chronic kidney disease  
CAPD: Continuous ambulatory peritoneal dialysis  
IQR: Interquartile range  
PTH: Parathyroid hormone  
SD: Standard deviation  
25(OH)D: 25-Hydroxyvitamin D.

**Data Availability**

The excel data used to support the findings of this study are available from the corresponding author upon request.

**Ethical Approval**

This study followed the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Institute Review Board of the Royal Thai Army Medical Department (R060h/61).

**Consent**

All patients gave written informed consent.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Authors’ Contributions**

NN conceptualized the study, conducted data extraction, analyzed the data, and wrote the first draft of the manuscript. JK and BS contributed to the conceptualization of the study and critically edited and proofread the manuscript, while PT and OS proofread the manuscript. All authors have read and approved the manuscript.

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**References**

[1] M. P. Cardoso and L. A. L. Pereira, "Native vitamin D in predialysis chronic kidney disease," *Nefrologia*, vol. 39, no. 1, pp. 18–28, 2019.
[2] G. Jean, J. C. Souberbielle, and C. Chazot, "Vitamin D in chronic kidney disease and dialysis patients," *Nutrients*, vol. 9, no. 4, p. 328, 2017.
[3] B. Satirapoj, P. Limwannata, A. Chaiprasert, O. Supasyndh, and P. Choovichian, "Vitamin D insufficiency and deficiency with stages of chronic kidney disease in an Asian population," *BMC Nephrology*, vol. 14, p. 206, 2013.
[4] H. F. DeLuca, "Overview of general physiologic features and functions of vitamin D," *The American Journal of Clinical Nutrition*, vol. 80, no. 6, pp. 1689S–1696S, 2004.
[5] G. M. London, A. P. Guérin, F. H. Verbeke, B. Pannier, P. Boutouyrie, S. J. Marchais et al., "Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency," *Journal of the American Society of Nephrology*, vol. 18, no. 2, pp. 613–620, 2007.
[6] A. Malabanan, I. Veronikis, and M. Holick, "Redefining vitamin D insufficiency," *The Lancet*, vol. 351, no. 9105, pp. 805–806, 1998.
[7] Q. Zhang, M. Zhang, H. Wang et al., "Vitamin D supplementation improves endothelial dysfunction in patients with non-dialysis chronic kidney disease," *International Urology and Nephrology*, vol. 50, no. 5, pp. 923–927, 2018.
[8] R. J. Lu, S. M. Zhu, F. L. Tang et al., "Effects of vitamin D or its analogues on the mortality of patients with chronic kidney disease: an updated systematic review and meta-analysis," *European Journal of Clinical Nutrition*, vol. 71, no. 6, pp. 683–693, 2017.
[9] H. Mazahery and P. von Hurst, "Factors affecting 25-hydroxyvitamin D concentration in response to vitamin D supplementation," *Nutrients*, vol. 7, no. 7, pp. 5111–5142, 2015.
[10] National Kidney Foundation, "K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease," *American Journal of Kidney Diseases*, vol. 42, pp. S1–S201, 2003.
[11] W. Y. Qunibi, A. Abdellatif, S. Sankar et al., ”Treatment of vitamin D deficiency in CKD patients with ergocalciferol: are current K/DOQI treatment guidelines adequate?" *Clinical Nephrology*, vol. 73, no. 4, pp. 276–285, 2010.
[12] P. Thimachai, O. Supasyndh, A. Chaiprasert, and B. Satirapoj, "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," *Journal of the Medical Association of Thailand*, vol. 98, no. 7, pp. 643–648, 2015.
[13] N. Bunyaratavej, "Study of the safe dosage of ergocalciferol," *Journal of the Medical Association of Thailand*, vol. 98, no. 8, pp. S13–S15, 2015.
[14] E. Çankaya, Y. Bilen, M. Keleş et al., "Comparison of serum vitamin D levels among patients with chronic kidney disease, patients in dialysis, and renal transplant patients," *Transplantation Proceedings*, vol. 47, no. 5, pp. 1405–1407, 2015.
[15] A. Giusti, A. Barone, G. Pioli et al., "Heterogeneity in serum 25-hydroxy-vitamin D response to cholecalciferol in elderly women with secondary hyperparathyroidism and vitamin D deficiency," *Journal of the American Geriatrics Society*, vol. 58, no. 8, pp. 1489–1495, 2010.
[16] V. Chel, H. A. H. Wijnhoven, J. H. Smit, M. Ooms, and P. Lips, "Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents," *Osteoporosis International*, vol. 19, no. 5, pp. 663–671, 2008.
[17] M. O. Premaor, R. Scafo, M. J. S. da Silva, P. E. Froehlich, and T. W. Furlanetto, "The effect of a single dose versus a daily dose of cholecalciferol on the serum 25-hydroxycholecalciferol and parathyroid hormone levels in the elderly with secondary hyperparathyroidism living in a low-income housing unit," *Journal of Bone and Mineral Metabolism*, vol. 26, no. 6, pp. 603–608, 2008.
[18] M. D. Kearns, J. A. Alvarez, and V. Tangpricha, “Large, single-dose, oral vitamin D supplementation in adult populations: a systematic review,” *Endocrine Practice*, vol. 20, no. 4, pp. 341–351, 2014.

[19] D. R. Mager, S. T. Jackson, M. R. Hoffmann, K. Jindal, and P. A. Senior, “Vitamin D3 supplementation, bone health and quality of life in adults with diabetes and chronic kidney disease: results of an open label randomized clinical trial,” *Clinical Nutrition*, vol. 36, no. 3, pp. 686–696, 2017.

[20] X. Barros, N. Y. Rodríguez, D. Fuster et al., “Comparison of two different vitamin D supplementation regimens with oral calcifediol in kidney transplant patients,” *Journal of Nephrology*, vol. 29, no. 5, pp. 703–709, 2016.

[21] S. Ish-Shalom, E. Segal, T. Salganik, B. Raz, I. L. Bromberg, and R. Vieth, “Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients,” *The Journal of Clinical Endocrinology & Metabolism*, vol. 93, no. 9, pp. 3430–3435, 2008.

[22] I. Bhan, D. Dobens, H. Tamez et al., “Nutritional vitamin D supplementation in dialysis: a randomized trial,” *Clinical Journal of the American Society of Nephrology*, vol. 10, no. 4, pp. 611–619, 2015.

[23] C. P. Kovesdy, J. L. Lu, S. M. Malakauskas, D. L. Andress, K. Kalantar-Zadeh, and S. Ahmadzadeh, “Paricalcitol versus ergocalciferol for secondary hyperparathyroidism in CKD stages 3 and 4: a randomized controlled trial,” *American Journal of Kidney Diseases*, vol. 59, no. 1, pp. 58–66, 2012.

[24] A. Massart, F. D. Debelle, J. Racapé et al., “Biochemical parameters after cholecalciferol repletion in hemodialysis: results from the VitaDial randomized trial,” *American Journal of Kidney Diseases*, vol. 64, no. 5, pp. 696–705, 2014.

[25] M. Mieczkowski, P. Żebrowski, E. Wojtaszek et al., “Long-term cholecalciferol administration in hemodialysis patients: a single-center randomized pilot study,” *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, vol. 20, pp. 2228–2234, 2014.

[26] P. J. Matias, C. Jorge, C. Ferreira et al., “Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters,” *Clinical Journal of the American Society of Nephrology*, vol. 5, no. 5, pp. 905–911, 2010.

[27] P. Kandula, M. Dobre, J. D. Schold, M. J. Schreiber Jr., R. Mehrrota, and S. D. Navaneethan, “Vitamin D supplementation in chronic kidney disease: a systematic review and meta-analysis of observational studies and randomized controlled trials,” *Clinical Journal of the American Society of Nephrology*, vol. 6, no. 1, pp. 50–62, 2011.

[28] J. B. Wetmore, C. Kimber, J. D. Mahnken, and J. R. Stubbs, “Cholecalciferol vs. ergocalciferol for 25-hydroxyvitamin D (25(OH)D) repletion in chronic kidney disease: a randomised clinical trial,” *British Journal of Nutrition*, vol. 116, no. 12, pp. 2074–2081, 2016.

[29] U. Lehmann, F. Hirche, G. I. Stangl, K. Hinz, S. Westphal, and J. Dierkes, “Bioavailability of vitamin D2 and D3 in healthy volunteers, a randomized placebo-controlled trial,” *The Journal of Clinical Endocrinology & Metabolism*, vol. 98, no. 11, pp. 4339–4345, 2013.