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Research Article

Comparison the Effect of Oral Pulse Therapy Calcitriol with Oral Daily Calcitriol in Hemodialysis Patients

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Abstract

Introduction: Disorders in bone metabolism are common in chronic kidney disease (CKD). Secondary hyperparathyroidism is a common complication of chronic kidney disease and is managed using vitamin D replacement therapy. This condition is caused by various factors such as calcitriol deficiency, advanced hyperphosphatemia, partial hypocalcemia, and parathyroid hormone resistance

Objectives: Calcitriol oral pulse therapy has been suggested as the treatment of choice for secondary hyperparathyroidism, but its efficacy and safety are still under discussion. Therefore, in the present study, we compared the effect of calcitriol pulse therapy with daily oral calcitriol in patients referred to the hemodialysis ward of Dr. Sheikh Hospital.

Patients and Methods: In this cross-sectional descriptive study, patients undergoing hemodialysis who were referred to the hemodialysis center of Dr. Sheikh Hospital in Mashhad between 2019 and 2020 were studied. Calcitriol tablets were administered orally 0.25 mg daily and pulse therapy twice a week at 0.75 mg for 2 months after dialysis. The serum levels of Ca, P, PTH at the beginning of the study and 2 months after that were assessed. Demographic information (age and gender), type of underlying renal disease, and hours and number of dialysis sessions were recorded in information forms for each patient, and the data were analyzed using SPSS software version 20.0.

Results: During the study, 21 patients with a mean age of 9.18 years in the case group and 10.9 years in the control group were included in the study, of which 27.3% in the case group and 40% in the control group were boys. The mean dialysis time and session duration were 2.63 days and 3.4 hours in the case group and 2.7 days and 3.4 hours in the control group, respectively. Regarding the type of disease, 63.6% in the case group and 60% in the control group had congenital anomalies of kidney and urinary tract (CAKUT). There was no statistically significant difference between the case and control groups in terms of serum levels of Ca, P, hemoglobin, Kt/V, and PTH.

Conclusion: Based on the findings of the present study, switching daily calcitriol therapy to twice-weekly calcitriol pulse therapy seems safe and convenient, especially for hemodialysis

Keywords: oral calcitriol; serum level of pth; hemodialysis

Introduction

The prevalence of electrolyte disorders in patients with renal insufficiency and under dialysis, including imbalance in calcium and phosphorus levels, which usually results in bone deformities, requires an accurate control of these electrolyte disorders. In pediatric patients, it is more vital because they are in growing age, and bone metabolism disorder and hyperparathyroidism critically affect their height growth, thus their social life and future performance. Moreover, considering the use of various drugs in this group of patients, different methods in administering drug,

such as oral pulse therapy as an alternative method of oral daily therapy, should be taken into account for systemic absorption and effectiveness of treatment. These alternative methods can reduce long-term treatment costs by minimizing the number of oral pills taken.

Calcium (Ca) and phosphorus (P) are involved in the regulation of homeostasis by various hormones that act on the kidney, intestine, and bone. The most important regulatory hormone is parathyroid hormone (PTH). The production and secretion of PTH by the parathyroid glands increase in response to decrease in extracellular Ca concentration. PTH accelerates the activity of 1α hydroxylase in proximal tubule to produce the biologically active form of vitamin D (1.25 dihydroxyvitamin D) from its precursor, 25 hydroxy vitamin D (1). Therefore, it increases the intestinal absorption of calcium and phosphorus (2), stimulates the releases of Ca and P (3), and increases the reabsorption of Ca from the distal tubule and stimulates the urinary secretion of phosphorus (4).

Chronic increase in PTH level is common in end-stage renal disease (ESRD) and is associated with parathyroid hyperplasia and excessive increased secretion of this hormone. The first intervention to solve this problem is to maintain a normal phosphorus level in diet, to have proper dialysis, and to use phosphate binders. By controlling serum phosphorus levels, administration of the active form of vitamin D is necessary to prevent the occurrence of secondary hyperparathyroidism in patients undergoing chronic hemodialysis. The active form of vitamin D can shift the calcium set point in parathyroid glands to left, which decreased PTH secretion in response to decreased serum calcium levels. The active form of vitamin D can be administered orally (3) and intravenously during dialysis.

The past studies showing the effect of daily oral and pulse therapy of active form of vitamin D have conflicting results (10-13). There is still no certainty about the optimal method of administering the active form of vitamin D.

Objectives

Therefore, in the present study, we compared the efficacy and side effects of oral pulse therapy versus daily oral calcitriol in patients referred to the hemodialysis ward of Dr. Sheikh Hospital.

Patients and Methods

Study design

This study included patients with chronic renal failure (CRF) on a regular hemodialysis as well as secondary hyperparathyroidism. In this study, after a full explanation of the plan for the parents of the patient, informed consent was obtained. Demographic information (age and gender), type of underlying renal disease, and hours and number of dialysis sessions were recorded in information forms for each patient. The 21 patients were divided into two groups. One group received the calcitriol oral tablet 0.25 mg daily, and the second group had the calcitriol oral pulse therapy two times a week 0.75 mg in two hemodialysis sessions for eight weeks by a single nurse. Biochemical and PTH tests and serum levels of Ca and P were assessed in the beginning of the study and two months after.

The data were analyzed by SPSS software version 20.0. The inclusion criteria were age < 18 years and CKD patients undergoing hemodialysis who needed to receive calcitriol for the treatment of secondary hyperparathyroidism. The exclusion criteria were primary metabolic disease, intestinal malabsorption, malignancy, underlying endocrine disease, and underlying liver disease.

Statistical analysis

The collected data were categorized and analyzed in SPSS software version 20.0. Qualitative data are presented as percentages and quantitative data with mean and standard deviation (STD). The frequency distribution of qualitative data categories was compared using chi-square test. The Smirnov-Kolmogorov test was used to check the normality of the data. To compare the data groups with normal distribution, the independent student t-test was used, and for the data with not-normal distribution, the Mann-Whitney nonparametric test was applied. The Wilcoxon test was used to compare quantitative variables before and after the study in each of the two groups (dependent samples). The significance level of the tests was considered 5%.

Results

A total of 21 patients were enrolled in this study in the form of daily oral consumption and oral pulse therapy. The mean age of the patients was 9.18 ± 2.64 years in the case group and 10.9 ± 2.13 years in the control group, and 72.2% of patients in the case group and 60% in the control group were female. The mean number of dialysis sessions was 2.63 ± 0.5 in the case group and 2.7 ± 0.48 in the control group. The mean number of dialysis hours was 3.4. ± 0.47 in the case group and 3.1 ± 0.31 in the control group.

Variable	Group	min	max	mean	STD	Test statistic	P-value
Age (years)	Case	6	12	9.18	2.64	t = -1.63	0.119
	Control	8	14	10.9	2.13		
Dialysis sessions	Case	2	3	2.63	0.5	Mann-Whitney U=32	0.809
	Control	2	3	2.7	0.48		
Dialysis hours	Case	3	4	3.4	0.47	Mann-Whitney U=5.51	0.052
	Control	3	4	3.1	0.31		
Diagnosis age (months)	Case	96	99	98.36	1.02	Mann-Whitney U=5.15	0.004
	Control	92	99	95.6	2.36		

Table 1. Comparison of case and control groups in terms of age, dialysis time, dialysis hours, and age of diagnosis.

As can be seen in **Table 1**, the case and the control group at the beginning of the study did not have any statistically significant difference in terms of age, number of dialysis sessions, and dialysis duration. However, the age at the time of diagnosis was statistically different between the two groups, and the control group were in average younger at diagnosis (P = 0.004).

	Number (%)			**Test statistic**
Group	**boy**	**girl**	**total**	Pearson Chi-Square = 0.389
Case	3 (3.27)	8 (7.72)	11 (100)	P-value = 0.659
Control	4 (40)	6 (60)	10 (100)	

Table 2. Sex frequency distribution in the case and control groups

We can see in **Table 2** that the frequency difference of gender in the case and control groups was not statistically significant. Likewise, the frequency of kidney diseases between the case and control groups was not statistically different (Table 3).

Disease type	**Number (%)**			**Test statistic**
Group	**CAKUT**	**GN**	**total**	Pearson Chi-Square = 0.029
Case	7 (63.6)	4 (36.4)	11 (100)	P-value =1
Control	6 (60)	4 (40)	10 (100)	

Table 3. Frequency distribution of kidney disease in the case and control groups

Variable	**Group**	**Min** (mg/dl)	**Max** (mg/dl)	**Mean** (mg/dl)	**STD**	**Test statistic**	**P-value**
Calcium	**case**	7.8	10.4	9.02	0.82	Mann-Whitney U=48.5	0.646
	control	7	11.7	9.05	1.24		
Phosphorous	**case**	3.6	12.4	6.51	2.25	t=0.93	0.927
	control	4.6	8.9	6.44	1.44		
Potassium	**case**	4.4	5.9	5.2	0.51	t=-1.526	0.143
	control	3.7	7.5	5.8	1.31		
Hb[1]	**case**	5.6	12.8	9.32	2.82	t=-1.094	0.288
	control	7.2	13.5	10.49	1.9		
Kt/V[2]	**case**	4.4	5.9	1.54	0.58	t=-0.231	0.820
	control	1.27	2	1.59	0.29		
PTH[3]	**case**	2	755	287.24	284.43	Mann-Whitney U=39	0.260
	control	36	1000	420.7	284.41		

[1]**Hb:** hemoglobin

[2]**Kt/V**:clearance the amount of urea your dialyzer can remove (liters/minute) t: time the duration of treatment (minutes) V: volume the amount of body fluid (liters)

[3]**PTH:** Parathyroid Hormone

As provided in Table 4, at the beginning of the study, the case and control groups in terms of serum levels of calcium, phosphorus, potassium, hemoglobin, PTH, and Kt/V were not statistically different.

Table 4. Comparison of the studied parameters in case and control groups before the intervention

Variable	Group	Min (mg/dl)	Max (mg/dl)	Mean (mg/dl)	STD	Test statistic	P-value
Calcium	**case**	8.4	10.8	9.40	0.85	Mann-Whitney U=44.5	0.459
	control	7.5	10.7	8.90	1.02		
	case	2.2	13.5	6.10	3.4	t=0.675	0.508
Phosphorus	**control**	3.8	6.8	5.37	0.87		
	case	4.2	8.2	5.90	1.35	t=1.748	0.097
Potassium	**control**	4.4	6.4	5.07	0.63		
Hb[1]	**case**	7.2	13.7	10.58	2	t=2.370	0.029
	control	6.8	10.4	8.85	1.19		
Kt/V[2]	**case**	1.13	2.46	1.57	0.42	Mann-Whitney U=41	0.324
	control	1.32	2.31	1.65	0.4		
PTH[3]	**case**	9	730	321.09	299.68	Mann-Whitney U=49	0.673
	control	34	1000	370.10	279.40		

[1]**Hb:** hemoglobin

[2]**Kt/V**:clearance the amount of urea your dialyzer can remove (liters/minute) t: time the duration of treatment (minutes) V: volume the amount of body fluid (liters)

[3]**PTH:** Parathyroid Hormone

Table 5. Comparison of the studied parameters in case and control group after the intervention (mg/dl)

As can be seen in the Table 5, at the end of the study, the case and control group did not have a statistically significant difference in serum level of calcium, phosphorus, potassium, Kt/V, and PTH. Only serum hemoglobin level in two groups had a significant difference and was higher in the case group after the intervention (P = 0.029).

Group	time	Min (mg/dl)	Max (mg/dl)	Mean (mg/dl)	STD	Test statistic	P-value
Case	Pre intervention	2	755	287.24	284.43	Wilcoxon Signed Ranks z= -0.133	0.894
	Post intervention	9	730	321.09	299.68		
Control	Pre intervention	2	755	287.24	284.43	Wilcoxon Signed Ranks z = -0.889	0.374
	Post intervention	34	1000	370.10	279.40		

Table 6. Comparison of serum PTH level before and after the study in the case and control group

As can be seen in **Table 6,** there was no statistically significant difference in serum PTH level before and after the study, in neither of the groups.

Discussion

This clinical trial study demonstrated that intermittent (pulse) calcitriol therapy did not have any significant advantage in comparison with oral daily administration in controlling intact PTH (iPTH) level in children with CRF prior to dialysis. Calcitriol is an important regulator of PTH secretion. It decreases PTH synthesis by genomic actions on PTH mRNA. In this study, examining two methods of oral administration, not significant difference was found in Ca and PTH levels. In contrast, in the study of Myriam (2014) et al., the effect of intermittent oral alfacalcidol versus intravenous injection on the control of PTH was investigated. They showed that oral administration of alfacalcidol three times a week is more effective than intravenous injection. Oral administration of alfacalcidol is associated with increased in serum Ca level and lower level of PTH and alkaline phosphatase (ALKP) (2).

One of the factors that can affect the response to active vitamin D treatment is the severity of secondary hyperparathyroidism compared to the prescribed vitamin D method (9-11). As well, the patient's collaboration in treatment with oral active vitamin D affects the effectiveness of treatment (12). The other benefit is that oral therapy is less costly than the injection method, in terms of therapeutic cost (13). For better control of secondary hyperparathyroidism, it is necessary to start the treatment with active vitamin D as soon as possible, which is more available and cheaper when taken orally, saving on additional costs and ancillary care, including nursing services.

In Ardissino's study, similar to our study, calcitriol was used in two methods of pulse therapy and daily consumption (3). No advantage was seen between the two methods. However, that study was conducted with a different dose of calcitriol in patients who were not undergoing hemodialysis in renal failure, which may have affected the unresponsiveness to calcitriol. One of the key observations in the study by Ardissino et al was the lack of correlation between the decrease in PTH

level at the end of the study and the initial serum PTH level, which was also observed in our study. Furthermore, the incidence of hypercalcemia and hyperphosphatemia in that study was low, which could be due to low administration dose of calcitriol (70 ng/kg per week). Another reason could be that the children who were not on hemodialysis were included in their study (3).

Due to the role of calcitriol in suppressing the parathyroid receptors and controlling hyperparathyroidism, the use of calcitriol pulse therapy can provide better control in secondary hyperparathyroidism by creating the peak effect faster and saturating parathyroid receptors [3,17,18)]. Injectable calcitriol may be considered superior, but Bacchini's study showed that injectable therapy was not superior to oral paracetamol suppressants and had more side effects, such as hypercalcemia and hyperphosphatemia (9). In addition, a crossover study by Moe et al. in children undergoing hemodialysis showed that intestinal absorption of calcium did not increase by injection in comparison to oral consumption [7].

In the study of Herrmann et al., which was performed on adults undergoing hemodialysis, there was no difference between the levels of PTH with the same dose of calcitriol given as pulse therapy and daily oral administration, in agreement with our results (17). This study was performed over two weeks. No benefits or side effects were seen in pulse therapy with calcitriol. The study also showed that the best suppressor in PTH level occurs within four to eight weeks from the start of the treatment (17); in our study, the duration of eight weeks was considered as the duration of treatment.

Some in vitro studies have shown that calcitriol has a biphasic effect on cell proliferation. At low doses in the range of 10^{10} nm ,it inhibits the cell proliferation in cells of various organs, but at high doses in the range of 10^{12} nm, it stimulates cell proliferation (18). In the study of Kuizon et al., it was shown that daily consumption of oral calcitriol was superior to calcitriol pulse therapy in stimulating growth plate and mineralization. Assuming these findings are conclusive, in vitro use of calcitriol pulse therapy for the treatment of secondary parathyroidism in bone growth should be replaced with calcitriol daily (15). In our study, the effect of calcitriol pulse therapy on growth retardation was not investigated. Due to the vulnerability of children to growth disorders and the effect of calcitriol pulse therapy on the induction of low turnover bone disease, perhaps the safety of this treatment can be examined more closely in future studies.

In Moe et al. study(7), similar to our study, the sample size was small, but the compliance of drug use was guaranteed, considering the administration in hemodialysis unit in a controlled manner. The results were thus more reliable. In our study, the results were reliable in the group undergoing pulse therapy due to the tight control of drug administration in the hemodialysis ward. However, in the group who received daily oral treatment, the results have been affected by the lack of proper compliance of children taking oral medications. Another point in Samantha et al. study like ours was the short duration of treatment, which was six weeks. In our study, it was eight weeks and perhaps by extending the treatment period, different results can be obtained.

The use of Alphacalcidole for three months had a similar clinical effect on serum PTH level after three months (8). As secondary hyperparathyroidism is a chronic disease, it is not clear whether rapid PTH suppression is necessary to prevent complications. Therefore, future studies are needed to evaluate the effect on clinical manifestations after a long period of treatment.

It seems that more interaction between the care team and patients, accurate knowledge on how to use the drugs in children, and better information from family members, especially mothers who are traditionally more involved in drug consumption of children, can mitigate the bone problems that these patients suffer from. One of the positive and strong points in the study was the assurance of drug administration in pulse therapy, controlled by the hemodialysis nurse.

Moreover, this study was conducted in a special center for children, and the results are expected to be more accurate than in other studies conducted in not specialized centers for children. Future studies in a larger statistical population and by separating the subjects into different age and sex groups could provide further statistical insights and achieve different results. In addition, in collaboration with other centers and use of other forms of active vitamin D, including the injectable forms, the study can be broadened to different geographical areas and by examining different forms of the drug. Providing a variety of incentive methods and preparing accurate charts to record the use of oral medications at home will help to accurately control the medications consumption and their impact on improving clinical symptoms.

Conclusion

Overall, the results of the present study showed that the administrations of oral calcitriol as pulse therapy or daily oral administration have no difference in the control of secondary hyperparathyroidism in patients undergoing hemodialysis. In term of parents and children cooperation in use of medications and acceptance of pulse therapy treatment, there was often acceptable cooperation. The most important limitation was the patients who received daily oral treatment at home, and we did not have accurate information about the quality and regularity of drug use.

In our study, most factors such as hemodialysis time, number of hemodialysis sessions, Kt/V and anemia in patients,were not significantly different between the two groups. It can be concluded that the duration and the number of hemodialysis sessions has no significant role in secondary hyperparathyroidism. Children with ESRD on hemodialysis are one of the most vulnerable groups of chronic patients with underlying problems. Considering the relationship between the serum level of different electrolytes and secondary hyperparathyroidism and height growth disorders in children, the efficient interaction and communication among the nephrologist, endocrinologist, and the pediatric orthopedist can be very helpful.

In recent decades, the importance of using oral and injectable forms of drugs used by patients undergoing hemodialysis has increased, and in various studies, different forms of drugs have been used for hemodialysis patients, including for anemia and hyperparathyroidism, to find the effective treatment in this group of patients. It is necessary that in future studies with a larger sample size, various forms of treatment are investigated to provide further findings.

Limitations of the study :

Limitation in number of patients

Author contributions :

Author contributions should be clarified based on the following items:

Conceptualization: A A, S S K

Methodology: YR

Validation: S S K

Formal Analysis: Y R

Investigation: A A, S S K, Y R, M N, F GH

Resources:

Data Curation:

Writing—Original Draft Preparation: S S K

Writing—Review and Editing: S S K

Visualization: S S K

Supervision: A A

Project Administration: A A

Funding Acquisition: A A The study was performed at a single institutional center. This study was approved by the Mashhad university of medical science. (IR.MUMS.MEDICAL.REC.1399.442) Moreover, This study was extracted from M.D thesis of Sepideh Sadat SeyedKaboli at this university (thesis#981802). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

The authors declare that they have no competing interests.

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References

1. Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein S.(2016) Pediatric Nephrology. 7th ed. New York: Springer Heidelberg,p.296 - 339
2. Lessard M, Ouimet D, Leblanc M, Nadeau-Fredette AC, Bell R, Lafrance J, et al. (2014); Comparison of oral and intravenous Alfacalcidol in chronic hemodialysis patients. BMC Nephrologhy 15(27):1-5
3. Ardissino G, Schmitt CP, Testa S, Claris-Appiani A, Mehls O. (2000); Calcitriol pulse therapy is not more effective than daily calcitriol therapy in controlling secondary hyperparathyroidism in children with chronic renal failure. European Study Group on Vitamin D in Children with Renal Failure. Pediatr Nephrol 14(7):664-668.
4. Borazan A, Ustun H, Cefle A, Sekimenz N, Yilmaz A. (2003);Comparitive efficacy of oral and and intravenous calcitriol treatment in haemodiyalisis patients: effect on serum biochemistery and cytokins. J Int Med Res 31:489-496
5. Terrass F, Yazidi A, Sif H, Zamd M, Benghanem MG, Ramdani B. (2006) A randomized trial of intermittent versus continuous oral alfacalcidol treatment of hyperparathyroidism in end stage renal disease. Clin Nephrol;65(6):415-418
6. Zhou H, Xu C. (2009);Comparison of intermittent intravenous and oral calciteriol in the treatment of secondary hyperparathyroidism in chronic hemodialysis patient ;a meta-analysis of randomized controlled trials. Clin Nephrol 71(3):276-285
7. Moe S, Wazny LD, Martin JE. (2008) Oral calciteriol versus oral alfacalcidol for the treatment of secondary hyperparathyroidism in patients receving hemodialysis: A randomized crossover trial. Can J clin Pharmacol ;51(1):e36-e43.
8. Gu Y, Ding F, Chen N, Mei C, Qian J, Wang X, et al. (2005)Comparisons between oral pulse alfacalcidol therapy and daily therapy in maintenance hemodialysis patients with secondary hyperparathyroidism: a randomized, controlled, and multicenter study. Ren Fail;27(2):205-212.
9. Bacchini G, Fabrizi F, Pontoriero G, Marcelli D, Di Filippo S, Locatelli F. (1997) “Pulse oral” versus intravenous calcitriol therapy in chronic hemodialysis patients: a prospective and randomized study. Nephron;77(3):267–272.
10. Quarles LD, Yohay DA, Carroll BA, Spritzer CE, Minda SA, Bartholomay D, et al. (1994); Prospective trial of pulse oral versus intravenous calcitriol treatment of hyperparathyroidism in ESRD. Kidney Int 45(6):1710–1721.
11. Indridason OS, Quarles LD. (1995) Oral versus intravenous calcitriol: is the route of administration really important? Curr Opin Nephrol Hypertens;4(4):307-312
12. Andress DL: (2001) Intravenous versus oral vitamin D therapy in dialysis patients: what is the question? Am J Kidney Dis;38(5 Suppl 5):S41–S44
13. Joy MS, Karagiannis PC, Peyerl FW. (2007);Outcomes of secondary hyperparathyroidism in chronic kidney disease and the direct costs of treatment. J Manag Care Pharm 13(5):397–411.
14. Ritz E. Is intermittent oral calcitriol safe and effective in renal secondary hyperparathyroidism? Lancet 1991;337(8744):800–801
15. Kuizon BD, Goodman WG, Juppner H, Boechat I, Nelson P, Gales B, et al. (1998);Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. Kidney Int 53(1):205-211.
16. Slatopolsky E, Weerts C, Thielan J, Horst R, Harter H, Martin KJ. (1984); Marked suppression of hyperparathyroidism by intravenous administration of 1,25-dihydroxy-cholecalciferol in uremic patients. J Clin Invest 74(6):2136–2143.
17. Herrmann P, Ritz E, Schmidt-Gayk H, Schäfer I, Geyer J, Nonnast-Daniel B, et al. (1994);Comparison of intermittent and continuous oral administration of calcitriol in dialysis patients: a randomized prospective trial. Nephron 67(1):48-53.
18. Pena YT, Soyibo AK, Mc Growder D, Clarke TR, Barton EN. (2010);The importance of bone biomarkers in the diagnosis of renal osteodystrophy. West Indian Med J 59(3):332–337

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