International Journal of Basic & Clinical Pharmacology
Hoseininia S et al. Int J Basic Clin Pharmacol. 2022 Sep;11(5):364-367
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20222131

Original Research Article

Relationship between oral cinacalcet therapy with CRP and anemia in hemodialysis patients with secondary hyperparathyroidism

Saeed Hoseininia[1], Sousan Mohammadi Kebar[1]*, Somaieh Matin[1], Saeed Sadeghieh-Ahari[2], Helia Salemi[3]

[1]Department of Internal Medicine, [2]Department of Community Medicine, [3]School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran

Received: 12 July 2022
Accepted: 01 August 2022

***Correspondence:**
Dr. Sousan Mohammadi Kebar,
Email: s.mohammadi.k@arums.ac.ir

ABSTRACT

Background: Cinacalcet is one of the newest calcium mimetic drugs in the treatment of patients with parathyroid cancer, secondary hyperparathyroidism in adults with chronic kidney disease. Due to the possible association between the effect of Cinacalcet on C-reactive protein and the pathophysiology of anemia in end-stage renal disease patients. The aim of this study was to evaluate the effect of oral Cinacalcet on rate of CRP and anemia in ESRD patients with secondary hyperparathyroidism.
Methods: This descriptive cross-sectional study was done on all 40 hemodialysis patients over 18 years of age underwent hemodialysis for at least 6 months. The levels of C-reactive protein, phosphorus, calcium, parathyroid hormone, ferritin, Total iron binding capacity, iron, hemoglobin before the start of treatment and based on the routine dialysis ward were repeated once every three months and recorded in the, in the checklist. Also, age, sex, weight, underlying disease, duration of dialysis and duration of use and dose of Cinacalcet were entered. The results of these experiments were reviewed and analyzed before and after treatment with Cinacalcet.
Results: In these patients, after treatment with Cinacalcet, the amount of hemoglobin increased and the amount of inflammation decreased and these changes were significant in hemoglobin rate but not significant in CRP rate. The relationship between patients' weight and inflammation was significant.
Conclusions: Treatment with Cinacalcet in hemodialysis patients, at least in this study, could be increased hemoglobin and decreased CRP rate and can be a hypothesis for large analytical studies.

Keywords: Cinacalcet, Inflammation, Anemia, Hemodialysis, Hyperparathyroidism

INTRODUCTION

End-stage renal disease (ESRD) is a life-threatening disease in which toxins, fluids and electrolytes that are normally excreted by the kidneys accumulate, affecting various organs and causing uremic syndrome. Decreased appetite, nausea, vomiting and involuntary weight loss are among the first symptoms of uremia.[1,2] One of the causes of mortality and loss of quality of life in ESRD patients and their association with cardiovascular disease and disorders such as increasing production of phosphorus and calcium, which was occurred by the development of secondary hyperparathyroidism and increasing in the exposure factors to metastatic calcifications and calcium and the hormone PTH (parathyroid).[3] Cinacalcet, sold under the Sensipar brand, was firstly approved in 2004 by the US food and drug administration. Cinacalcet increases the sensitivity of calcium receptors on parathyroid cells to lower parathyroid hormone (PTH) levels, thereby lowering serum calcium levels. It is used to treat high blood

calcium levels in patients with parathyroid cancer, secondary hyperparathyroidism and chronic kidney disease.[4,5] A number of studies have also shown the beneficial therapeutic effects of Cinacalcet on the control of anemia.[6,7] Anemia is another common complication of ESRD and can occur before the onset of uremic symptoms. Anemia in patients with ESRD is mainly due to decreased production of renal erythropoietin, increasing osmotic fragility of red blood cells, decreased red blood cell survival and inflammation.[8] Cardiac dysfunction and debilitating symptoms such as fatigue, weakness, depression, shortness of breath, anorexia and sleep disorders, which are associated with hospitalization and increased length of hospital stay and mortality are some of the symptoms of anemia in these patients. Another complication of the uremic environment in ESRD patients is chronic and reversible inflammations caused by an increase in inflammatory cytokines and infection. Acute phase reactants such as CRP (C-reactive protein) is one of the markers of inflammation that increase by more than 5 mg in three months.[9] Due to the annual growth of approximately 5-6% of ESRD patients in the world compared to the growth of 1.1% of the population, this disease is one of the major health problems in the world. The aim of this study was to evaluate the effect of oral Cinacalcet on rate of CRP and anemia in ESRD patients with secondary hyperparathyroidism.

METHODS

Study design

This was a cross-sectional descriptive study that was performed on all 40 hemodialysis patients with a diagnosis of secondary hyperparathyroidism who referred to the nephrology ward of Bu-Ali hospital in Ardabil city from May 2020 to December 2020. Inclusion criteria included patients over 18 years of age with at least 6 months of history of hemodialysis, despite treatment with rectal with serum phosphorus greater than 5.5 mg/dl, serum calcium greater than 8 mg/dl and serum PTH above 600 pg/ml. Patients with known bone marrow disease, active malignancy, active inflammatory disease over the past two months, acute gastrointestinal bleeding or active bleeding, iron deficiency anemia with ferritin less than 200 and transferrin saturation with less than 20 were treated with Venofer (iron sucrose) and if the dose of Aprex received during the study was changed based on the opinion of the treating physician, they were excluded from the study. Sampling was census and the amount of calcium and phosphorus of patients every month and the amount of hemoglobin, PTH, ferritin, TIBC, iron, CRP were repeated before the start of treatment and once every three months and were recorded in patients' files. The data required by patients were collected through a questionnaire including demographic information such as age and sex and clinical information including underlying diseases, duration of dialysis, test results before and after treatment, duration of use and dose of Cinacalcet. The research followed the tents of the Declaration of Helsinki. Accordingly, written informed consent taken from all participants before any intervention.

Statistical analysis

The collected data were analyzed by SPSS software version 22 using descriptive statistical methods and also independent t-test and the p value less than 0.05 was considered significant.

RESULTS

Out of 40 patients, 60% were female and the rest were male. The average age of patients was 60.1±12.5 in range 30-82 years old. 72.5% of patients had a history of hypertension and 27.5% had a history of kidney stones (Figure 1).

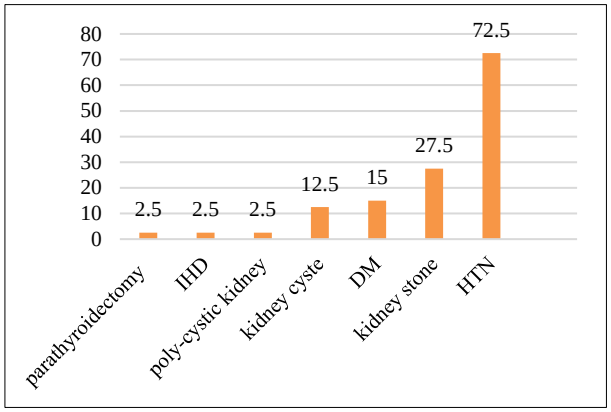

Figure 1: The frequency of underlying diseases among people.

Table 1: Compare the result of tests amounts before and after receiving Cinacalcet.

Tests	After	Before	P value
Hb (g/dl)	11.3±1.6	12.3±1.2	0.000
Iron	74±29	83±37.6	0.24
Ferritin	514.1±472	706.8±676	0.25
TIBC	302.9±71	304±35.7	0.18
PTH	1064.8±576.3	733±560	0.01
Ca	9.7±1.1	9.6±0.9	0.7
Pb	5.7±1.1	5.4±1.3	0.1
CRP	8.9±5.7	8.1±7	0.07

The results of tests amounts showed that the drug significantly increased hemoglobin levels (p=0.001) and significantly decreased PTH levels (p=0.01) but it had no significant effect on iron, ferritin, calcium, phosphorus, TIBC and CRP and the change between them before and after drug prescription wasn't significant (Table 1). This finding also showed that the use of Cinacalcet was effective in increasing hemoglobin in people over 60 years, especially in women but in patients under 60 years

and men, this increase was not significant (Table 2). Drug use in patients with hypertension and history of kidney stones increased rate of hemoglobin but no such increase was observed in other patients. Also, the change results of CRP based of underlying diseases except history of kidney stones before and after treatment was similar (Table 3). The results showed that CRP before and after drug administration was significantly (p=0.03) reduced only in male patients (Table 2).

Table 2: Compare the mean of hemoglobin-based variables age, gender and duration of dialysis before and after treatment.

Tests		Hemoglobin			CRP		
		Before	After	P value	Before	After	P value
Age (years)	30-40	11.4±1.3	12.8±1.14	0.41	7.6±1.4	7.55±1.2	0.72
	40-50	11.1±0.7	11.7±1.2	0.13	7.4±3.5	7.2±2.4	0.35
	50-60	12.8±0.4	12±1.3	0.08	15.8±9.6	14.9±8.4	0.12
	60-70	11.1±1.5	12.2±1.4	0.027	6.1±6.3	6.3±4.1	0.23
	70>	12.1±1.1	9.7±1.3	0.012	9.4±5.2	9.1±5.7	0.75
Gender	Female	10.8±1.5	12.1±0.9	0.001	9.6±7.3	9.2±7.1	0.76
	Male	12±1.4	12.6±1.4	0.062	8.4±5.9	8.1±6.1	0.03
Dialysis time duration		11.2±1.5	12.3±1.2	0.97	8.9±5.7	8.2±4.7	0.046

Table 3: Compare the mean of hemoglobin based of underlying diseases before and after treatment by Cinacalcet.

Tests		Hb			CRP		
		Before	After	P value	Before	After	P value
HTN	+	11.12	12.36	0.01	8.92	8.2	0.52
	-	11.43	12.06	0.31	9.71	9.1	0.06
DM	+	10.42	11.67	0.1	9.05	9	0.12
	-	11.39	12.39	0.01	9.16	9.1	0.21
History of stone in kidney	+	9.98	12	0.04	9.03	8.98	0.04
	-	11.72	12.4	0.01	9.18	9.1	0.37
Kidney cyst	+	11.04	12.3	0.12	4.3	4.2	0.89
	-	11.27	12.3	0.01	9.83	9.74	0.06
Polycystic kidney	+	10.1	12	-	14.2	13.8	0.32
	-	11.27	12.3	0.01	9.01	8.88	0.09
IHD	+	11.6	13.3	-	8	7.68	0.32
	-	11.23	12.3	0.01	9.17	8.7	0.08
Parathyroidectomy	+	11.6	12.8	-	10.7	10.2	0.32
	-	11.23	12.3	0.01	9.1	8.87	0.09

DISCUSSION

Because anemia in patients with renal insufficiency is a risk factor for mortality.[10] A drug that affects the anemia of these patients can reduce mortality. In this study, hemoglobin level increased after treatment with Cinacalcet, which was statistically significant. This result was in line with a 2016 study by Tanaka et al in Japan showed that Cinacalcet could improve anemia in patients with ESRD with SHPT.[11] The reason for the improvement in anemia seems to be the reduction of inflammation due to the use of Cinacalcet, the increase in the lifespan of RBCs by the reduction of PTH which is a uremic toxin and the reduction of myelofibrosis due to hyperparathyroidism. In addition, by reducing oxidative stress caused by taking Cinacalcet, it can also be effective in improving anemia. Also, another study conducted by Aktsiali et al to investigate the effect of Cinacalcet treatment on anemia parameters showed a positive effect of Cinacalcet on anemia which was consistent with the present study.[12] The level of hemoglobin in this study especially in women, in people over sixty years after treatment with Cinacalcet was significantly different from before consumption, which can be due to increased inflammation with age in the field of increased comorbidity and reduced lifespan of RBCs. In the present study, although we expected a significant reduction in CRP, but by using Cinacalcet the CRP reduction was not significant but the rate of inflammation was reduced, which was in line with the study of Fusaro et al.[13] However, the lack of significant reduction in CRP in this study could be due to the small number of samples. The decrease in PTH after taking Cinacalcet was significant, which could be due to the effect of Cinacalcet on CaSR, which leads to increased CaSR sensitivity in the parathyroid gland. A 2016 study by Alajnaf et al examined the effects of CaSR agonists and antagonists on intestinal inflammation in mice and it has been shown that inhibition of CaSR may have an effective effect on reducing inflammation in intestinal diseases and may

effect plasma IL-6 and TNF-alpha levels, which may be consistent with the present study.[14] Identifying the role of extracellular calcium sensitive receptors has led to advances in the development of calcium mimetic drugs that increase the sensitivity of parathyroid cells to the inhibitory effect of calcium. Cinacalcet causes a dose dependent decrease in PTH and plasma calcium concentrations in some patients.[15] However, in this study the use of Cinacalcet did not lead to a significant reduction in calcium of patients.

CONCLUSION

Results showed that treatment with Cinacalcet in hemodialysis patients lead to increase hemoglobin and decreased rate of CRP and PTH but had no effect on other tests, which may be due to the small number of samples. Therefore, big analytical studies should be performed to examine the effect of this drug in the treatment of such patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1-266.
2. Mitch WE. Chronic kidney disease. In: Goldman L, Ausiello DA, eds. 23rd ed. United States of America: Cecil Medicine; 2011:11-26.
3. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. Arch Dis Child. 2001;84:205-15.
4. Drug information for the health care professional, 27th ed. United States of America: Mermedex; 2007;1:816-9.
5. Ganesh NM, Ratanlal A, Venkat NK. HPLC method for estimation of cinacalcet in bulk and tablet dosage form. Am J Pharm Tech Res. 2015;5(1):26-32.
6. MacGregor MS, Boag DE, Innes A. Chronic kidney disease: evolving strategies for detection and management of impaired renal function. QJM. 2006; 99(6):365-440.
7. Mpio I, Boumendjel N, Karaaslan H, Arkouche W, Lenz A, Cardozo C, et al. Secondary hyperparathyroidism and anemia. Effects of a calcimimetic on the control of anemia in chronic hemodialysed patients, Pilot Study. Nephrol Ther. 2011;7:229-65.
8. KDIGO clinical practice guidelines for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:288.
9. Bray C, Bell LN, Liang H, Haykal R, Kaiksow F, Mazza JJ. Erythrocyte Sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. BMC Med J. 2016;18(6):96-106.
10. Mohammadi KS, Maleki N, Sharghi A. The incidence rate, risk factors and clinical outcome of acute kidney injury in critical patients. Iranian J Public Health. 2016;47(11):1717.
11. Tanaka M, Yoshida K, Fukuma S, Ito K, Matsushita, K. Effects of secondary hyperparathyroidism treatment on improvement in anemia: results from the MBD-5D study. PloS one. 2016;11(10):e48-65.
12. Aktsiali M, Papachrysanthou T, Griveas I, Andriopoulos C, Sitaras P. Treatment with Cinacalcet in hemodialysis patients with severe secondary hyperparathyroidism, influences bone mineral metabolism and anemia parameters. Current Drug Ther. 2014;15(3):249-312.
13. Fusaro M, D'Angelo A, Naso A, Chiara FG, Miozzo D, Gallieni MC. Treatment with Calcimimetic (Cinacalcet) alters epoetin dosage requirements in dialysis patients: preliminary report. Renal Failure. 2011;33(7):732-67.
14. Elajnaf T, Iamartino L, Mesteri I, Müller C, Bassetto M, Manhardt T, et al. Nutritional and pharmacological targeting of the calcium-sensing receptor influences chemically induced colitis in mice. Nutrients. 2019;11(12):3072.
15. Priscilla P, Alan H, Darins L, Lanmason VN. Current approaches in the treatment of CKD mineral and bone disease. Kidney Int. 2007;16(4):1103-30.

Cite this article as: Hoseininia S, Kebar SM, Matin S, Ahari SS, Salemi H. Relationship between oral cinacalcet therapy with CRP and anemia in hemodialysis patients with secondary hyperparathyroidism. Int J Basic Clin Pharmacol 2022;11:364-7.