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Effect of hyperparathyroidism on anemia management in patients with hemodialysis dependent end stage renal disease

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ABSTRACT

Anemia is the most serious and significant complication in patients with chronic kidney disease, especially hemodialysis dependent end stage renal disease. Hyperparathyroidism may hamper the management of anemia by multiple mechanisms. So the aim of this study is to define the effect of elevated parathyroid hormone level on anemia management in hemodialysis patients at (The Iraqi center of hemodialysis, Baghdad teaching hospital, Iraq). A retrospective cohort study was conducted in (The Iraqi center of hemodialysis, Baghdad teaching hospital, Iraq). The duration of the study was through six months from the 1st of February to 31st of July of 2022 on 85 hemodialysis patients (after excluded). The data was collected (mentioned in patients and method) and analyzed by the researchers. Results: There was a significantly higher level of hemoglobin (Hb.) with mean 10.55 gm/dl in patients with parathyroid hormone (PTH) level less than 300 pg/ml (G1) comparing 8.6 gm/dl in patients with (PTH) level more than 300 pg/ml(G2) with p value >0.001 .

Other parameter there was a significant difference in serum Ferritin (S. Ferritin) which was higher in G1 than G2 (p value 0.045), although it was within the target range of H.D. patients in both study groups.

Serum phosphate (S. PO4), alkaline phosphates and weekly Eprex dose required to achieve targeting Hb. were significantly higher in G2 (p value 0.007, 0.012 and <0.001 respectively.

Keywords: *Effect, Patients, Stage, management*

INTRODUCTION

Anemia is one of the most common complications of chronic kidney disease (CKD) (1). There are many causes of renal anemia such as decreased production of erythropoietin (EPO), shortened life span of red blood cells (RBCs), uremic and cytokine release in response to infections and inflammatory conditions inhibit erythropoiesis, iron deficiency, active blood loss, hemolysis, folic acid or vitamin B12 deficiency and hyperparathyroidism (HPT) is a significant cause of renal anemia in hemodialysis patients. Parathyroid hormone (PTH) has been considered as a uremic toxin that potentially inhibits EPO synthesis, shortens the survival of RBCs, and can cause bone marrow remodeling and fibrosis and thereby decreases hematopoiesis (2).

Studies have provided evidence suggesting that secondary HPT plays important roles in renal anemia, which is mediated via multiple pathways (2).

The classical theory was that excess secretion of PTH leads to bone marrow fibrosis and higher percentage of osteoclast cells and consequent interference with erythropoiesis and lead to poor response to EPO (3). This theory indicates that the severity of secondary HPT and the extent of bone marrow fibrosis increase the dose of EPO needed to achieve hemoglobin target.

Elevated parathyroid hormone may lead to Inhibition of EPO synthesis (4), and can shortened RBCs survival (5).

Furthermore, emerging data have indicated that fibroblast growth factor 23 (FGF23),which is a bone-derived circulating hormone that plays an important role in vitamin D and phosphate metabolism, is also involved in ineffective erythropoiesis in CKD(6).

Parathyroidectomy is the most violent treatment for SHPT, and can lead to improve erythropoietin stimulating agents hypo-responsiveness, Parathyroidectomy for severe secondary HPT lead to a significant decrease in EPO doses need to achieve targeted hemoglobin (7).

Cinacalcet hydrochloride is calcimimetic agent approved for the treatment of secondary HPT (8). This agent modulates the parathyroid calcium-sensing receptor (CaSR) and increases its sensitivity to extracellular calcium, thereby decreasing PTH synthesis and secretion (9).

Since the introduction of cinacalcet hydrochloride , several small-scale studies reported an increase in hemoglobin levels or a reduction in the doses of erythropoiesis-stimulating agents (ESA) following the use of cinacalcet hydrochloride for SHPT(10,11).These studies reported an increase in hemoglobin levels or a reduction in the doses of erythropoietin-stimulating agents (ESA) following the use of cinacalcet hydrochloride for hyperparathyroidism .

There are several possible mechanisms explain that cinacalcet hydrochloride could improve renal anemia. The most rational mechanism is that decreased PTH levels by cinacalcet attenuate the inhibitory effects of PTH on erythropoiesis. In addition, because cinacalcet lead to inhibit FGF23 secretion (12, 13).

Treatment with vitamin D receptors activators, such as alphacalcidol and calcitriol has long been the primary strategy for the management of hyperparathyroidism , Several studies examined the effect of vitamin D receptors activators on renal anemia and demonstrated a reduction in EPO doses and improved hemoglobin levels among patients treated with vitamin D receptors activators(14) .

The most possible mechanism for the effect of vitamin D receptors activators on renal anemia is via the decreased PTH levels, also accumulating evidence suggests potential health benefits of vitamin D beyond suppressing PTH secretion . It remains unknown whether administered vitamin D receptors activators directly affect erythropoiesis independently of the effect on PTH levels (15).

PATIENTS AND METHODS

This retrospective cohort study was conducted from February 2022 to July 2022 in (The Iraqi center of hemodialysis, Baghdad teaching hospital, Iraq).

The study approved by the scientific Council of nephrology, Scientific Council of clinical pharmacy and the Iraqi board for medical specializations.

The patients were informed about the purpose of the study and an informed written consent was provided from each participant.

This study included patients on scheduled hemodialysis for at least 3 months, who used ESAs for the treatment of anemia. Patients who met the following criteria were excluded from the study:

(1) Age <18 years.

(2) Patients with active infection, malignancy, bone marrow disorders, iron deficiency anemia (defined as serum ferritin <200 ng/mL and transferrin saturation <20%) (16), or active bleeding within 3 months.

(3) Patients with hemoglobinopathy (includes hemoglobin C disease, hemoglobin S-C disease, sickle cell anemia, and thalassemia).

(4) Malnourished patients by clinical assessment, change in dry body weight and serum albumin less than 2.5 g/dl.

(5) Body mass index (BMI) less than 18.5 kg/m2.

(6) Under dialysis patients (fluids overload by clinical assessment and uncontrolled hypertension which defined as systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥80 mm Hg on average of two or more measurement on two or more hospital visits (17))and

(7) Patients with pure red blood aplasia (PRCA).

Consultations from hematologist were done for all patients to exclude any patient with hematological disorder including (PRCA).

The aim of this study is to demonstrate the effect of secondary hyperparathyroidism on the ESAs doses needed to maintain hemoglobin above 10 mg/dl.

Patients were divided into two groups, the first group (G1) of participants has been chosen with serum parathyroid hormone (S.PTH) within the target level (150-300 pg/ml) (16), the second group (G2) with serum PTH more than 300 pg/ml. Data was reported for all patients include the following:

Age.

Medical history.

Erythropoietin stimulating agent dose / week (Eprex).

Body mass index (BMI).

Complete blood count (CBC).

C-reactive protein (CRP).

Erythrocyte sedimentation rate (ESR).

Iron study which include serum ferritin (S. ferritin), transferrin saturation (TSAT).

Blood film.

Anti- EPO antibodies by (Enzyme-linked immunosorbent assays).

Serum calcium (S.Ca).

Serum phosphate (S.Po4).

Alkaline phosphates (ALP).

Serum albumin (S.Alb).

Serum parathyroid hormone (S.PTH).

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Patients older than 50 years send for chest X-ray, fecal occult blood test and prostate specific antigen for male and mammography for female to exclude malignancy.

The data of hemodialysis patients were analyzed by application of Microsoft excel program and Statistical Package for Social Sciences (SPSS) version 24. Outcomes of analysis were arranged in scales variables (means & standard deviation) and categorical variables. Multiple contingency tables conducted and appropriate statistical tests performed, a Chi- square test was used for categorical variables. Independent sample t-test was used to compare between two means. In all statistical analysis, level of significance (p-value) set at ≤ 0.05 and the result presented as tables.

RESULTS:

The total number of Hemodialysis patients (H.D. pts.) was 85 (36 female ,49 male)with no significant different between group 1 with intact parathyroid gland (G1) and group 2 with hyperparathyroidism (G2) consisting of 24 male in G1 and 25 in G2 while the female distribution was 16 female in G1 and 20 in G2 (table 1).

The mean age was 53.55 years in G1 and 49.8 years in G2 with no significant difference between the study groups (table 2).

There was 25, 32 H.D. patients with hypertension (HTN) in G1 and G2 respectively and the same number of diabetic H.D. patients (16) in both groups (table 1).

Statically there was no significant difference in body mass index (BMI) , erythrocytes sedimentation rate (ESR) , transferrin saturation (TSAT) , serum calcium (S.Ca.) , C-reactive protein (CRP.) and Serum albumin (S. Alb.) between the two study groups(table 2) .

The parathyroid hormone level was about three folds higher in G2 (mean 567.5 ng / dl) comparing G1 (mean 195.25 ng/ dl) with highly significant difference (table 2).

Anti- EPO antibodies was not detected (negative) in all patients of both study groups.

There was significantly higher level of hemoglobin (Hb.) with mean 10.55 gm/dl in G1 comparing 8.6 gm/dl in G2 (table 2).

Other parameter there was a significant difference in serum Ferritin (S. Ferritin) which was higher in G1 than G2 (401.88, 365) respectively, although it was within the target range of H.D. pts. (200-500) (table 2).

Serum phosphate (S. PO4), alkaline phosphates and weekly Eprex dose required to achieve targeting Hb. were significantly higher in G2 (means 5.63 , 173.38 and 13622.22 i.u.) compared to G1 (means 4.77 , 115.9 and 9675 i.u.) respectively(table 2) .

		Group 1 G1	Group2 G2	P-value
Gender	Male	24	25	0.679
	Female	16	20	
HTN		25	32	0.399
DM		16	16	0.673

Chi-square test

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Parameters	Group 1(G1) Mean ± SD	Group 2(G2) Mean ± SD	P-value
Age(years)	53.55±13.31	49.8±12.77	0.189
PTH(pg/dl)	195.25±57.93	567.5±236.56	<0.001
BMI(Kg/m^2)	25.06±4.6	25.23±4.7	0.869
Hb(gm/dl)	10.55±1.12	8.6±1.73	<0.001
CRP(mg/L)	5.45±1.8	5.6±1.83	0.453
ESR(mm/hr)	48.77±19.09	44.48±23.1	0.357
Sr. Ferritin(ng/ml)	401.88±101.7	365±106.2	0.045
TSAT (%)	30.27±6.95	29.08±7.06	0.439
S.Ca(mg/dl)	8.22±0.94	9.78±11.95	0.415
S. PO4(mg/dl)	4.77±1.31	5.63±1.5	0.007
ALP(IU/L)	115.9±58.73	173.38±129.5	0.012
S. Albumin(gm/dl)	3.75±0.49	3.89±0.45	0.172
Eprex dose (i.u./week)	9675±3682.16	13622.22±2994.6	<0.001

Independent t-test

DISCUSSION

Patients with hemodialysis dependent CKD and anemia have poorer outcome and quality of life, so anemia in CKD patients is the most common complication that may lead to decrease quality of life among hemodialysis dependent patients (18). Both groups of the current study were with no significant difference in demographic data corresponding gender and age. Also there was no significant difference in the distribution of hypertension and diabetes mellitus between both study groups. This study find that a group (G2) of higher serum PTH level (567.5±236.56 in G2 vs 195.25 in G1) associated with more severe anemia (8.6±1.73 in G2 vs 10.55±1.12 in G1) , this result is consistent with Azeem SM et al. (19) ,which conclude that patients with hemodialysis dependent CKD and hyperparathyroidism frequently develops anemia . Bone marrow fibrosis that may be caused by secondary HPT decreased production of erythropoietin and resistance of produced and therapeutics erythropoietin are some factors responsible for the severity of anemia in G2.

Although serum ferritin was at the target range of both study groups(200-500 ng/ml (16)) , but it was significantly higher in G1 with serum PTH less than 300 pg/ml , and this result is consistent with Li J et al (20) , which found that significant difference in serum ferritin between patients groups with serum PTH more than 300 pg/ml vs less than 300 pg/ml and it was higher in patients group with serum PTH less than 300 pg/ml .In current study all patients with serum ferritin with in the target (200-500 ng/ml(16)) was on maintenance iron therapy (400 mg iron sucrose/ moth) , Patients with serum ferritin less than 200 ng/ml have been loaded iron therapy (1000 mg iron sucrose/ moth) but were excluded from this study .

Also Torun, D. et al (21) in Adana, Turkey found that the management of secondary HPT improve Hemoglobin, serum ferritin level and transferrin saturation. These observations and the results of the current study suggest that increase serum parathyroid hormone level leads to bone marrow fibrosis and consequent interference with erythropoiesis and may interfere with iron distribution , metabolism , transformation and

storage so that patients with serum PTH within the target range have better serum ferritin level .

The response to recombinant erythropoietin stimulating agents was better and the dose needed to reach the target hemoglobin level was lower (highly significant) in G1 vs G2 (9675±3682.16 i.u/week vs 13622.22±2994.6 i.u/week).

This result consistent with Massimetti C et al (22), which found that adequate control of secondary HPT was associated with concomitant improvement of anemia and decrease in ESAs needed. Resistant to recombinant ESAs therapy in G2 could be explained to the elevation of serum PTH in corresponding to G1.

The present study showed that hyperphosphatemia occur more frequently in G1 with secondary HPT compare to G2. This finding was similar to results reported by Streja E et al (23), which find more sever hyperphosphatemia may be a consequence of secondary hyperparathyroidism independent of dietary phosphorus load. Management of hyperphosphatemia should include correction of hyperparathyroidism with maintaining adequate intake of high protein foods with low phosphorus content .Another recently OPTIMA trial (24) found that serum phosphorus control was improved when secondary HPT was effectively treated.

This study also showed significant increase in serum ALP level in G2 compared with G1with serum PTH less than 300 pg/ml. This result was similar to finding reported by Li J et al (20), which find that serum phosphorous and ALP levels were a highly predictor of the serum PTH level. In addition, the serum PTH level showed a significant, incremental and linear association with increased risk of hyperphosphatemia and elevated serum ALP level. The explanation of this increment in ALP in G2 related to the high turnover bone disease associated with elevated serum PTH, Serum PTH binds to PTH receptor-1 found in osteoblasts, and lead to increase the osteoblasts expression of receptor activator of nuclear factor-kB ligand (RANKL) (25).

In addition the binding of RANKL to osteoclast receptors augmented by serum PTH stimulates these osteoclast precursors to fuse, forming new osteoclasts, which highly increase bone resorption (26).

CONCLUSIONS

Hemodialysis patients in (The Iraqi center of hemodialysis with parathyroid hormone level less than 300 pg/ml have:

Higher level of hemoglobin than that of hemodialysis patients with parathyroid hormone level more than 300 pg/ml.

Reached the targeted hemoglobin level with less ESA doses than that of hemodialysis patients with parathyroid hormone level more than 300 pg/ml.

S. ferritin level more than that of hemodialysis patients with parathyroid hormone level more than 300 pg/ml.

S. phosphate level less than that of hemodialysis patients with parathyroid hormone level more than 300 pg/ml.

S. Alkaline phosphatase level less than that of hemodialysis patients with parathyroid hormone level more than 300 pg/ml.

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