International Research Journal of Medical and Pharmaceutical Sciences
Volume.8, Number 3;July-September, 2023;
ISSN: 2836-9351 | Impact Factor: 7.01
https://zapjournals.com/Journals/index.php/irjmps
Published By: Zendo Academic Publishing

HYPERPARATHYROIDISM-INDUCED ERYTHROPOIETIN RESISTANCE: IMPLICATIONS FOR CKD MANAGEMENT

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Article Info

Keywords: Anemia, Chronic kidney disease, End-stage renal disease, Erythropoietin stimulating

Abstract

Anemia is a prevalent complication in patients with chronic kidney disease (CKD) and is particularly common in those with end-stage renal disease (ESRD). This anemia results from a decrease in endogenous erythropoietin production, which is closely linked to the progressive decline in kidney function. To manage anemia in CKD patients, the use of erythropoietin stimulating agents (ESAs), such as epoetin alfa (EPO), is recommended. Current practice involves titrating the ESA dose to achieve and maintain hemoglobin levels within the range recommended by KDIGO guidelines, typically not exceeding 11.5 g/dL.

1. Background

Anemia is a common complication of chronic kidney disease (CKD) that is present in more than 70% of those with end-stage renal disease (ESRD).12 The decline in endogenous erythropoietin production mirrors the decline in kidney function and is one of the main contributors to anemia in patients with CKD. Replacement of endogenous erythropoietin with an erythropoietin stimulating agent (ESA), such as epoetin alfa (EPO),is recommended for the management of anemia associated with CKD.2Titration of an EPOdose to a patient's hemoglobin is routine practice since current KDIGO guidelines recommend maintaining hemoglobin no higher than 11.5 g/dL when using an ESA therapy.3-6

1.1 ESA Hyporesponse

A subgroup of CKD patients may exhibit a muted response to conventiona lESA dosing. Patients requiring higher ESA doses to attain an increase in hemoglobin may be referred to as ESA hyporesponsive or as having ESA resistance.7A number of clinical studies have found the causes of ESA resistance are multi-factorial and include iron deficiency, inflammation, aluminum overload, malignancy, vitamin B12/folate deficiency.

ACEi/ARB use, malnutrition, and bone marrow disorders.1,7-11Secondary hyperparathyroidism, a condition resulting from the deregulation of calcium and phosphorus homeostasis in the kidney, has also been implicated

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due to an indirect effect that may result inbone marrow fibrosis.12-16The pathogenesis of this relationship is complex, beginning with excess intact parathyroid hormone (iPTH) impairing erythropoiesis by increasing osteoclast and bone turnover. Due to subsequent replacement of bone marrow cellular components by fibrous tissue, there is a diminished response to EPO in this subset of patients.14-15

The association between hyperparathyroidism and ESAresponsehas been evaluated in a small number of studies. In patients undergoing parathyroidectomy, Mandolfo et al. observed a 20% increase in hemoglobin anda 34% decrease in EPO dosage in patients following parathyroidectomy.17 In a similarly conducted study, Lee et al. comparable results were found in 32 hemodialysis patients in which EPO doses needed to maintain a hematocrit target range of 30-33% decreased gradually by 29% and hematocrit levels showed a significant increase three months after parathyroidectomy ($p<0.05$).18Four separate multivariate analyses conducted in the Unites States, Canada, and Sweden evaluated hemodialysis patients not undergoing parathyroidectomy and found associations between higher iPTH, lower hemoglobin concentrations (<11 g/dL), and higher EPO dosing (U/kg/wk).8

1.2 Healthcare Implications

Recent attention to the use of erythropoiesis stimulating agents has raised awareness of their costs to the healthcare system. Initially Medicare reimbursed dialysis providers using a fee-for-service cost-based reimbursement method. In this model, providers received separate payments for the provision of dialysis, each billable medication, each laboratory test ordered, and for each ancillary dialysis-related service.19This model allowed providers to maximize on services rendered per session.

Over the past two decades Medicare spending on dialysis services drastically increased due mainly to the introduction of ESAs. Based on the 2012 United States Renal Data System (USRD) annual data report, Medicare ESA costs rose to nearly $2 billion making this the single largest drug expenditure in the Medicare program.21Fueled by the high healthcare costs of ESAs, Medicare replaced the fee-for-service model with bundled dialysis payments in January 2011. Under the bundled payment plan, providers would receive approximately $230 per dialysis treatment per patient.21 The actual cost of dialysis as well as all related laboratory tests and medications would be included in this payment. This reimbursement regime does not allow providers to maximize on Medicare reimbursements by increasing the use of ESAs. Subsequently, providers may be financially impacted by patients requiring larger doses of ESAs such as those who are erythropoietin resistant.

1.3 Landmark Trials

Coupled with the added costs of increased ESA dosing in dialysis patients, hypo responsiveness has also been found to be a strong predictor of mortality and cardiovascular events. A post hoc analysis of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study found that patients in whom anemia did not improve with administration of large doses of ESAs had poorer outcomes compared to those patients who did attain an adequate hemoglobin response after ESA administration.22-23Additionally a report from Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease (TREAT) investigators found that in 1,872 patients studied, those with a poor response (<2% change in hemoglobin after 1 month) had higher rates of composite cardiovascular events (adjusted HR 1.31, 95% CI 1.09-1.59) compared to those with a better response.4 Given the disproportionate burden of morbidity and mortality these patients bear in addition to the accompanying ESA expense, resistance to ESAs merits more scrutiny than it has previously received. Prompt identification and correction of hypo responsive predictors would improve management and subsequent outcomes in CKD patients. At a single-center outpatient dialysis clinic, a retrospective study was conducted to further assess this relationship between hemoglobin, iPTH and the EPOdosing over a continuous11-monthperiod.

2. Study Population and Methods

This study was a retrospective chart review conducted at anan outpatient hem dialysis clinic affiliated with a university hospital. The study was approved by the university's institutional review board and the administrators of the dialysis center.

The objective of the study was to assess the relationship between iPTH and EPO response as reflected by hemoglobin values. Adult patients 18 years and older who were actively receiving hem dialysis and EPO therapy were included in the study. Patients with a documented diagnosis known to cause EPO hypo responsiveness were excluded from the study (Table 1).

Table 1. Patient selection criteria

Inclusion	Exclusion
Age 18 years or older Actively receiving hemodialysis Receiving EPO	Active malignancy Hematologic disorders Aluminum toxicity HIV infection Pure red cell aplasia

Patients were divided into one of two groups depending on their parathyroid concentration at the beginning of the study period. In accordance with the Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations for iPTH, those with a baseline iPTH>300pg/ml were deemed to have hyperparathyroidism while normo-parathyroid patients had a baseline iPTH ≤300pg/ml. Patient data collected included: age, race, gender, dialysis vintage, serum ferritin, intact parathyroid hormone, hemoglobin, serum calcium, serum phosphorus and albumin. Laboratory values were compiled using monthly averages. Patients included in the study received intravenous EPO three times a week with dialysis. The EPO dose reflects the monthly average administered per dialysis session.

The primary endpoint of the study compared vershemoglobin (g/dl) versus iPTH (pg/ml) in each group over the study period. Statistical analysis was performed with Chi-square tests, Fisher's exact test, or Wilcoxon rank-sum test depending on the data type. The differences between iPTH concentrations over versus hemoglobin were assessed through Pearson correlation (Microsoft Excel 2016).

3. Results

Seventy-four74patients met the inclusion criteria for the study. Review of iPTH for each patientat study initiation found 38 patients had an iPTH ≤ 300 pg/ml and 36patients with an iPTH >300pg/ml. Baseline demographics were similar in both groups except for age, past medical history of diabetes, and activeinsulin use. While the average age of patients in the hyper parathyroid group was younger (55.5 years vs. 68 years), this group was found to have a longer dialysis vintage. Significantly higher values of serum creatinine and phosphorus are consistent with this group's longer dialysis vintage. Although not statistically significant, the hyperparathyoid group was found to have a higher median EPO dose (p=0.1286) potentially resulting in increased costs to the dialysis center based upon the bundled reimbursement model enacted during the study period. In both groups, hemoglobin was maintained between 10-11 g/dl and no statistically significant differences were observed between ferritin and transferring saturation in either group.

Table 2. Patient Demographics

	All patients (N=74)	**iPTH ≤ 300** (n = 38)	**iPTH>300** (n = 36)	P-value
Age (yr) [Median (IQR)]	62.5 (50-73)	68.0 (56-77)	55.5 (40.5-68.0)	0.0059
Gender				
Female	42 (76%)	23 (61%)	19 (53%)	0.5013
Male	32 (43%)	15 (39%)	17 (47%)	
Race				
African American	40 (54%)	19 (50%)	21 (58%)	0.1705
Hispanic	5 (7%)	1 (3%)	4 (11%)	
Caucasian	29 (39%)	18 (47%)	11 (31%)	
Dialysis Vintage (years) [Median (IQR)]	3.4 (1.2-6.1)	2.5 (0.7-5.7)	3.7 (1.7-8.1)	0.0969
Dry weight (kg) [Median (IQR)]	78.7 (64.5-103.0)	76.5 (64.0-100.0)	83.4 (65.4-110.8)	0.4107
Medical history (%)				
Hypertension	63 (85%)	34 (89%)	29 (81%)	0.2811
Congestive Heart Failure	16 (22%)	8 (21%)	8 (22%)	0.9028
Diabetes	44 (59%)	27 (71%)	17 (53%)	0.0369
Atherosclerotic Heart Disease	15 (20%)	5 (13%)	10(28%)	0.1179
Renal Transplant	3 (4%)	1 (3%)	2 (6%)	0.6096
Medications (%)				
ACEi/ARB	28 (38%)	15 (39%)	13 (36%)	0.7656
Steroids	6 (8%)	2 (5%)	4 (11%)	0.4238
Beta blocker	54 (73%)	25 (66%)	29 (81%)	0.1528
Calcium channel blocker	28 (38%)	14 (37%)	14 (39%)	0.8560
Insulin	39 (53%)	27 (71%)	12 (33%)	0.0012

Phosphate Binders	53 (72%)	25 (66%)	28 (78%)	0.2529
Cinacalcet	15 (20%)	5 (13.16%)	10 (28%)	0.1179
EPO; **median dose (IQR)**	4000 units (2000-8200)	4350units (2350-4350)	3200units (1200-10000)	

**Comparisons based on iPTH concentrations

Table 3. Baseline Laboratory Measurements

	All Patients (N=74)	**iPTH ≤ 300 pg/ml (n = 38)**	**iPTH>300 pg/ml (n = 36)**	P-value
Albumin (g/dl)	4.0 (3.7-4.2)	3.9 (3.6-4.1)	4.1 (3.8-4.3)	0.0647
Calcium (mg/dl)	9.1 (8.7-9.7)	9.2 (8.8-9.6)	9.1 (8.7-9.8)	0.6243
PO4 (mg/dl)	5.5 (4.7-6.2)	5.0 (4.0-5.6)	6.1 (5.1-7.7)	0.0002
iPTH (pg/ml)	298.2 (214.9-530.9)	259.6 (129.2-185.5)	607.6 (433.1-915.9)	<0.0001
Scr (mg/dl)	7.6 (5.3-9.7)	5.9 (4.8-8.6)	9.4 (6.9-10.3)	0.0021
Hemoglobin(g/dl)	10.8 (9.8-11.3)	10.9 (9.9-11.5)	10.6 (9.7-11.2)	0.2501
Hematocrit (%)	33.9 (31.6-36.8)	34.7 (32.4-37.3)	33.1 (30.0-35.3)	0.1321
Ferritin(ng/mL)	469.0 (361.0-747.0)	466.0(313.0-726.0)	469.0 (372.0-762.0)	0.5106
TSAT (%)	25.0 (18.0-33.0)	25.0 (18.0-32.0)	25.5 (19.0-33.5)	0.3711
Mg (mg/dl)	1.9 (1.7-2.1)	1.8 (1.7-2.1)	1.9 (1.7-2.2)	0.7209

*Expressed as Median (IQR)

**Comparisons based on iPTH concentrations

Primary outcome results were mixed between each arm. In the normo-parathyroidgroup, no statistically significant association between hemoglobin and iPTH was observed (r = 0.004) (Figure 1a). However, a stronger negative correlation was observed in the hyperpa rathyroidgroup(r = -0.21) (Figure 1b). In this group, it was observed that patients with higher iPTH tended to have lower average hemoglobin. This trend was most apparent in patients whose iPTH was >1500 pg/mL.

The average iPTH in the normo-parathyroid and hyper parathyroid groups was significantly disparate at 259.6pg/mLand 607.7pg/mL respectively. EPO doses administered at each dialysis session was not found to be higher in the hyper parathyroid arm.

Figure 1a. Scatter Diagram: Normo-parathyroid Arm

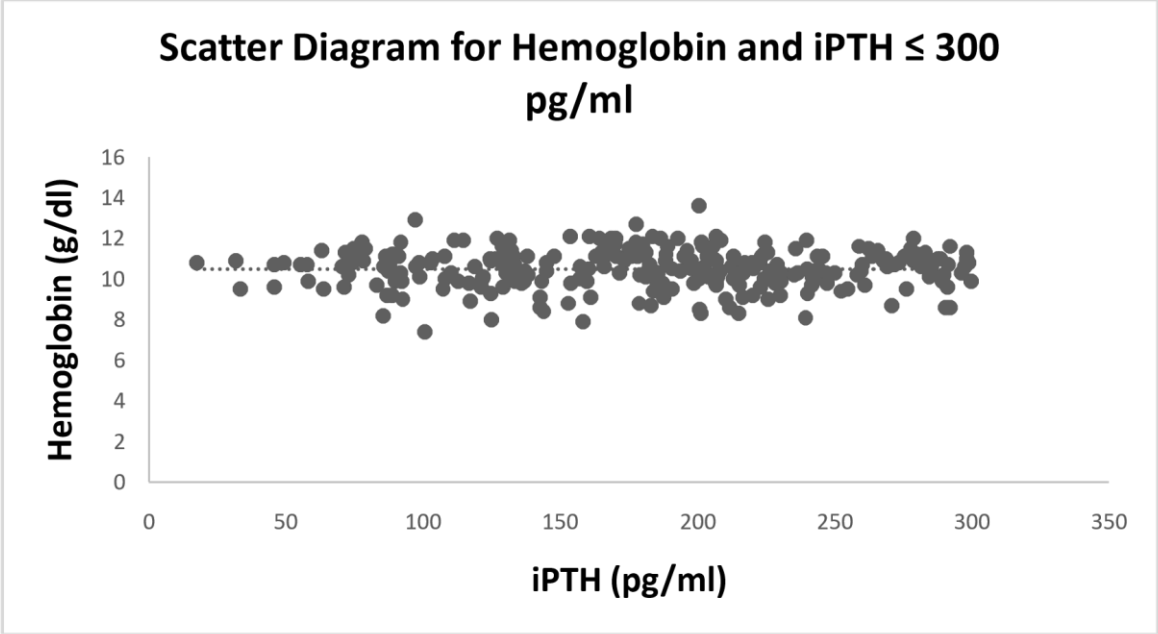
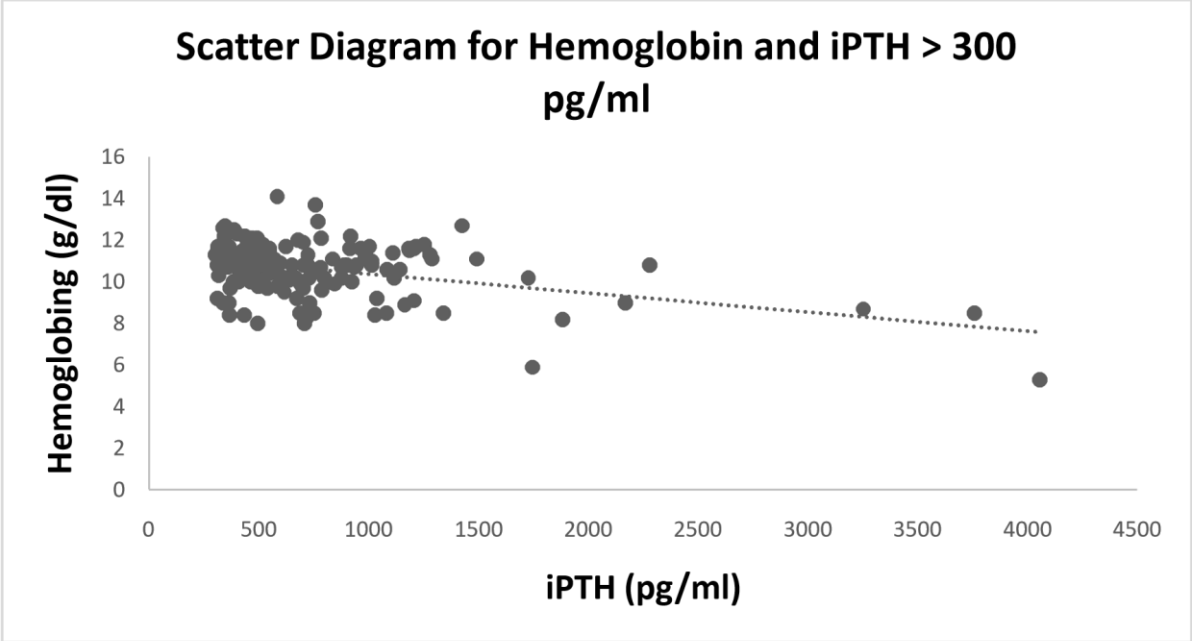


Figure 1b. Scatter Diagram: Hyperparathyroid Arm



4. Discussion

In this study, we sought to observe a potential correlation that has not been extensively studied in the selected patient population. A number of previous studies have demonstrated a reduction in EPO dose requirements after normalization of iPTH, inferring hyperparathyroidism to be a predictor of ESA resistance. Our results support the notion that severe hyperparathyroidism, if not appropriately addressed and treated, can contribute to continued anemia and increased EPO dose requirements in hem dialysis patients.

There has been extensive interest in the role of ESA use and cardiovascular events in patients. Some evidence points to potential pleiotropic effects of ESAs contributing to ESA toxicity observed with higher doses.

Lowering of hemoglobin targets for CKD patients and using the lowest ESA dose to achieve this goal has been accepted to help reduce the risk of adverse outcomes.12,13 In our study, we did not assess mortality or morbidity in this retrospective study and are therefore unable to determine the clinical impact hyperparathyroidism and EPO dose has in this patient population. In fact, a recently published systematic review and meta-analysis found that surrogate markers such as iPTH, phosphorus, and calcium weakly and imprecisely correlate with cardiovascular and all-cause mortality in the setting of chronic kidney disease.22Still, a mortality benefit cannot be excluded from these results and future trials evaluating the clinical impact of surrogate markers in this patient setting would be beneficial.

We do realize the limitations of this study being a single center, retrospective study. Infections and administration of packed red blood cells were not tracked which may potentially impact fluctuations in hemoglobin. Extending the study length would help to better assess iPTH and EPO relationship over time, especially seeing that response to ESAs is multi-factorial.

5. Conclusions

This study observed patients presenting with significant hyperparathyroidism (iPTH > 1500 pg/dl) to have an association with lower hemoglobin. Further research is warranted to elucidate the long-term relationship between iPTH and EPO resistance, the impact on mortality and morbidity of patients, as well as financial consequences to providers. As many dialysis clinics are protocol driven, it would benefit institutions to incorporate methods that can effectively capture potential hypo responsive patients (reviewing last ESA dose and hemoglobin change) and using iPTH as an indicator for hypo responsiveness. In doing so, clinicians can anticipate improved management of the patient's anemia and potential reduction in EPO dose and drug cost.

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