INTENSIFICATION OF ANEMIA BY SECONDARY HYPERPARATHYROIDISM IN HEMODIALYSIS PATIENTS

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SUMMARY: Secondary hyperparathyroidism is listed among the possible reasons for intensifying the anemia and causing it to be resistant to erythropoietin therapy in hemodialysis patients. Although its exact mechanism is not entirely clarified, shift of bone marrow cells to adipocytes, bone marrow fibrosis and lowered calcitriol can be the cause. However, the role of secondary hyperparathyroidism in severe anemia and resistance to erythropoietin treatment in comparison to other factors like inflammation and iron deficiency is minor. In this study we evaluated the role of secondary hyperparathyroidism in severity of anemia in hemodialysis patients.

This is an analytical study carried on 36 hemodialysis patients of Hajar Medical Educational and Therapeutic Center in Shahrekord. Hgb, Hct, calcium, phosphorus, alkaline phosphatase, intact PTH (iPTH), serum iron, total iron binding capacity, transferrin saturation in percent, ferritin, and also dialysis adequacy by Urea Reduction Rate (URR) in per cent were measured.

All data were analyzed with SPSS software and categorized into mean ± SD, correlations were carried out using Pearson Co-efficient Test.

Total number of patients were 36 of whom 55.5% were male of latter 66.1% were over 40 years of age. Mean ± SD of iPTH were 439.4 ± 433 pg/mL, Hgb were 9 ± 1.9 g/dL and Hct were 28.8 ± 6.3 percent respectively.

This study showed that there were reverse correlations between intact PTH with hematocrit and hemoglobin; and between alkaline phosphatase and Hgb, Hct ($p<0.05$ for all correlations).

Secondary hyperparathyroidism by itself can intensify anemia encountered in hemodialysis patients. This conclusion needs further attention to control hyperphosphatemia and parathormone hypersecretion for better management of anemia in hemodialysis patients.

Key Words: Anemia, secondary hyperparathyroidism, erythropoietin.

INTRODUCTION

Anemia is common in patients suffering from chronic renal failure (CRF), and is one of the leading causes of increased cardiovascular morbidity and mortality in these patients. This anemia is normocytic and normochromic in origin, hypoproliferative with a low reticulocyte count (1-3). The main defect responsible for anemia of CRF is absolute or relative erythropoietin deficiency (1, 4). Introduction of recombinant human erythropoietin (r-HuEpo) has revolutionized the care of patients suffering from renal anemia (1). Availability of this treatment has almost erad-

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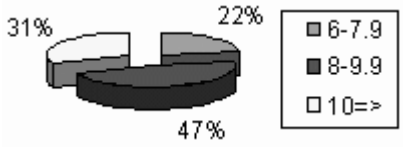
Figure 1: Frequency distribution of hemoglobin in patients.



icated the severe anemia of end stage renal disease (ESRD) (1, 5). However, despite increases in the use and average dose of r-HuEpo, a substantial portion of ESRD patients still fail to achieve the recommended target hematocrit above 33% during this therapy (1,6,7-9). In fact the anemia of ESRD is a complex disorder in which many factors other than Epo deficiency are known to play a role (1). These include deficiencies of iron and folic acid, inflammation, aluminium intoxication, hyperparathyroidism with myelofibrosis, external blood loss, as well as hemolysis and bone marrow suppression (1, 2), and is probably induced by retained toxic metabolites (1, 3). These factors can all contribute to anemia and blunt the response to r-HuEpo, and need to be further evaluation (1). In this study we checked the effect of secondary hyperparathyroidism (SHPTH) in aggravating the anemia of hemodialysis patients.

MATERIALS AND METHODS

This is an analytical study carried on 36 patients in hemodialysis unit of Hajar Medical, Educational and Therapeutic Center in Shahrekord. For hemodialyzed patients, serum calcium (Ca), phosphorus (P), alkaline phosphatase, Hgb, Hct, Urea Reduction Rate (URR) and serum iron, total iron binding capacity (TIBC), ferritin, transferrin saturation (TS%) and intact PTH were measured in this study.

None of patients took ACE-Inhibitors, Nsaids and none had external blood loss or ADPKD. At the end of dialysis session all of the patients received an equal dose of Eprex 2000 U Iv. All data were analyzed by SPSS software, for correlations we used Pearson Co-efficient Test.

RESULTS

Total number of patients were 36 of whom 55.6% were male of latter 66.1% were over 40 years of age. The mean duration of hemodialysis was 25.1 months and the range was 2-100 months. Fifty eight per cent of the patients were dialized 3 times per week, 39% two times and 3% once per week. Figures 1 and 2 show the frequency distribution of ferritin and hemoglobin. Mean value of MCV was 93.8±5.6 fL.

Transferrin saturation (TS%) in 94.4% of the patients

Figure 2: Frequency distribution of ferritin in patients.

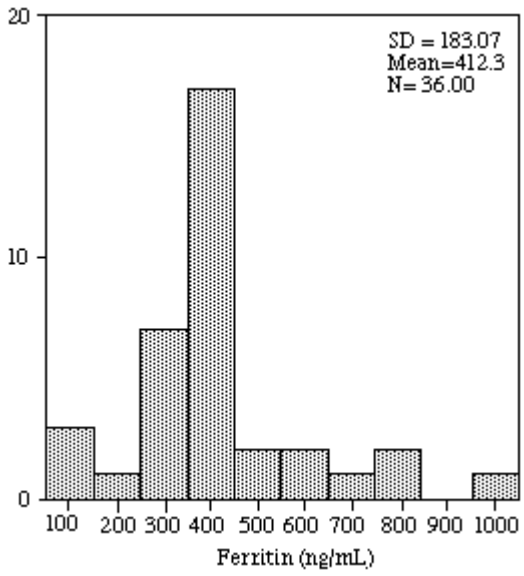


Table 1: Minimum, maximum and Mean ± SD of data.

Variable	Minimum	Maximum	Mean ± SD
Hgb	6	14.5	9 ± 1.9
Hct	20	52	28.8 ± 6.3
Ferritin	94	1000	183 ± 4.2
TS%	22	100	45.5 ± 18
URR	49	77	59.5 ± 6.1
P	3	12	6.6 ± 2.3
Caxp	30	95	54 ± 16
ALP	100	1280	385 ± 227
iPTH	25	2234	439.4 ± 433.6

was more than 25%. Moreover 77.8% of our patients had URR below 65%. As well as 58.3% of patients had phosphorus more than 5 mg/dL, 88.9% of patients iPTH was more than 75 pg/mL (Table 1).

In this study we found that a reverse correlation between iPTH and Hgb (R = -0.520, P = 0.001) (Fig. 3). Likewise, there was a reverse correlation between ALP and hemoglobin (R = v-0.382, P = 0.021) (Fig. 4).

There were reverse correlations between hemotocrit and iPTH (R=0.502) and ALP (R=0.322) (p<0.05).

DISCUSSION

This study showed that in hemodialized patients there were reverse correlations between both iPTH and Alp with Hct and Hgb levels which means development of secondary hyperparathyroidism. The factor producing this severe anemia in hemodialysis patients is this secondary hyperparathyroidism. Trovato reported that 45 hemodialysis patients showed a significant reverse correlations between higher degree of anemia and hyperparathyroidism and significant higher r-HuEpo requirements in patients with high serum concentrations of iPTH (10). Neves showed that elderly patients with hyperparathyroidism have lower Hct and Hgb levels than younger patients on a similar Epo dose (total patients were 86) (11). Other studies reported that parathyroidectomy (PTX) on a hemodialized patients, who had developed secondary HPTH revealed that their anemia improved (12, 13). On twenty nine patients under hemodialysis therapy with SHPTH, Yasunga *et al.* showed a significant increase of hemoglobin level and a consistent increase of the reticulocyte count after PTX (14). Fujita (15) observed that a 10% increase of RBC volume occurred in hemodialized patients after thyroidectomy. The studies of Grutzmacher and Podjarny showed a significant increase of Hct after PTX (16, 17). Secondary hyperparathyroidism (SHPTH) develops primarily, as a consequence of reduced active vit D production by the kidneys and phosphate retention, with development of hyperphosphatemia, hypocalcemia and increased parathyroid hormone levels. The same factors over the long term cause parathyroid gland hyperpla-

Figure 3: Reverse correlation of iPTH with Hgb (R=-0.520, P=0.001).

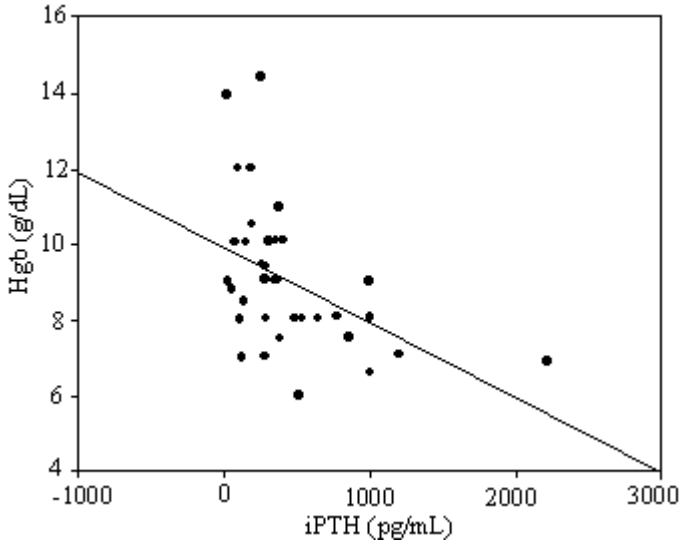
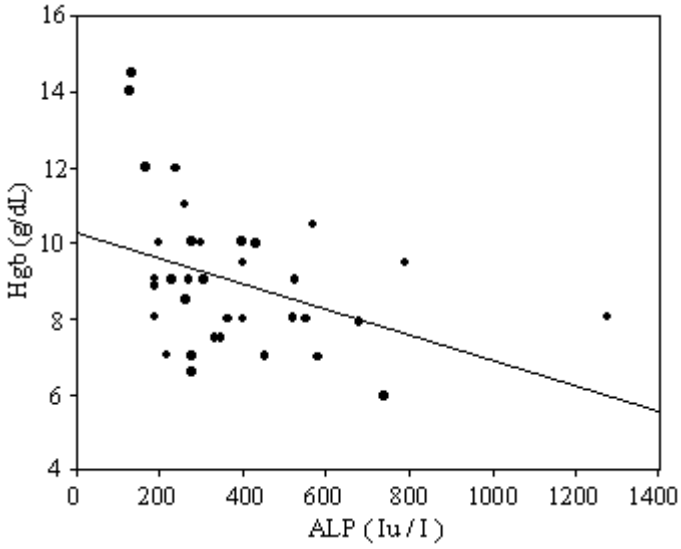


Figure 4: Reverse correlation of ALP with Hgb (R=-0.382, P=0.001).



sia and autonomous PTH production (2,18,19). In addition to factors mentioned above altered vit D metabolism and resistance to calcitriol, hypocalcemia, resistance to PTH (impaired calcemic response to PTH), altered degradation and abnormal regulation of PTH released secondary regulation of calcium-controlled parathyroid hormone secretion (set-point of calcium), are responsible for osteitis fibrosa due to SHPTH (5,10,20-23). One of the features of renal osteodystrophy is refractoriness to recombinant human erythropietin (r-HuEpo) treatment, can be observed in severe HPTH (2,24,25, 27-33,). In fact poor response to HuEpo in the presence of very elevated PTH levels (>500-100 pg/ml) should prompt radiographic evaluation of the skeleton for SHPTH (osteitis fibrosa) (24-29). A variety of pathophysiologic mechanisms have been postulated in the contribution of hyperparathyroidism to both anemia and r-HuEpo resistance. In the pre- r-HuEpo era, these centered on a direct toxic effect of PTH on red cell precursor proliferation in the marrow and antagonism of the effect of endogenous or exogenous erythropoietin, also reduced erythropoiesis due to calcitriol deficiency and direct effect of PTH on erythropoietin release, red blood cell (RBC) production, survival and loss (24,26,28,33). Studies of these mechanisms have produced disparate results possibly because secondary hyperparathyroidism may have only a relatively minor role in anemia that may be masked by confounding effects of other factors with greater impact (25,27,29,32-34). More recent studies have focused on the physical effects of high turnover bone disease on the size of erythron (25, 28). In the r-HuEpo treated patients, a clear relationship has been demonstrated between the degree of trabecular fibrosis and r-HuEpo dose (25, 28). Moreover, the high iPTH level could also shift bone cells toward adipocite (10). It is suggested that PTH, when in excessive amounts, interferes with normal erythropoiesis by down regulating the erythropoetin receptors on erythroid progenitor cells in the bone marrow (13). Therefore, physiologic concentrations of Epo can no longer sustain normal red cell count, so normocytic normochromic anemia ensues. In primary hyperparathyroidism (1-HPTH) this effect is observed, with very high concentrations of PTH in secondary HPTH, during chronic renal failure. This effect becomes more pronounced because erythropoetin synthesis is impaired (13). As mentioned above, in patients with much elevated PTH and alkaline phosphatase levels in whom other etiologies for poor response have been excluded aggressive treatment of secondary hyperparathyroidism and/or progressive increase in r-HuEpo dose can improve response (25, 34). Treatment of hyperparathyroidism with vit D could have a role in enhancing erythrocyte maturation or augmenting the erythropoietic

effect of r-HuEpo (25, 30). Effective therapy of SHPTH (PTX) may result in decreasing PTH levels and finally, r-HuEpo requirements as well (24).

The other factor responding favorably to r-HuEpo therapy consists of aluminium intoxication (22). Measurement of aluminum blood level in hemodialysis patients in our country is limited to few research laboratories and is not done routinely. As aluminium induced resistance to erythropoietin therapy should be considered in patients with microcytic anemia (24,29,31). Low MCV can show the probability of aluminum intoxication, our MCV results can rule out serious Al-intoxication in our patients.

Reaching to acceptable Hgb and Hct levels and treatment of secondary HPTH are two major concerns in hemodialysis centers. Poor compliance to phosphorus restricted diets, lack of cooperation in using phosphate binders, inadequate hemodialysis, low educational level of some patients and unavailability of newer phosphate binders like Rena-Jel and drugs decreasing PTH hypersecretion are problems in SHPTH treatment programs. Thus efficient control of Hyperphosphatemia, successful control of parathyroid hypersecretion with newer drugs can prevent many debilitating side effects of SHPTH leads to prevention of anemia.

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