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Effect of Erythropoietin as Combination Therapy and Monotherapy on Serum Hemoglobin Levels In Patients on Maintenance Hemodialysis

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ABSTRACT

Hemoglobin level variability is common in hemodialysis patients with chronic kidney disease. The main objective of the study was to assess the influence of combination therapy (erythropoietin + iron preparations) and monotherapy (erythropoietin) on hemoglobin levels in patients with CKD on maintenance hemodialysis. The study was conducted in 150 patients (102 (68%) males and 48 (32%) females; mean age 51 ±13.8 years) undergoing once/twice/thrice weekly maintenance hemodialysis and were prescribed with combination therapy of erythropoietin + iron preparations and monotherapy of erythropoietin. Hemoglobin levels were estimated once every month prior to hemodialysis session for a period of 5 months. Patients were regularly monitored for side effects. There were significant increases in the serum hemoglobin levels (8.5 ± 2.1 at 1st month to 9.1 ± 1.6 at 5th month) on treatment with combination therapy ($p < 0.05$). Combination therapy is effective than monotherapy in maintaining the hemoglobin levels (variability) in chronic kidney disease patients on maintenance hemodialysis.

Keywords: Anemia, Erythropoietin, Iron, Hemoglobin, Hemodialysis, Chronic kidney disease

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INTRODUCTION

Anemia is common in chronic kidney disease (CKD) patients because of lost kidney function and resultant inability to produce endogenous erythropoietin, which is predominantly derived from the kidneys.[1]

While anemia in CKD can result from multiple mechanisms (iron, folate, or vitamin B12 deficiency; gastrointestinal bleeding; severe hyperparathyroidism; systemic inflammation; and shorter life span of erythrocytes), decreased erythropoietin synthesis is the most important and specific etiology causing CKD-associated anemia. Erythropoietin is a glycoprotein secreted by the kidney interstitial fibroblasts and is essential for the growth and differentiation of red blood cells in the bone marrow. In CKD, tubular atrophy generates tubule interstitial fibrosis, which compromises renal erythropoietin synthetic capacity and results in anemia. [2]

Consequently CKD patients undergoing maintenance HD receive routine administration of exogenous erythropoietin stimulating agents (ESAs) to raise their hemoglobin levels. As iron is also essential to the process of hemoglobin (Hb) production, HD patients also receive routine administration of concomitant iron to help raise hemoglobin levels.[1]

In 2000, a panel of the Kidney Disease Outcomes Quality Initiative (K/DOQI) of National Kidney Foundation recommended that the target level of hemoglobin should be 11.0 to 12.0g/dl in patients with CKD, whether or not they were receiving dialysis.[3] A recent update of guidelines regarding anemia in such patients expanded the target range to 11.0 to 13.0g/dl. [4]

Achieved hemoglobin level is associated with both the Erythropoietin alfa doses administered and patient responsiveness to erythropoietin (EPO). Greater survival among patients with higher hemoglobin values may be partly due to greater erythropoietin responsiveness[5] in addition to a direct result of anemia correction. Likewise, lower survival among those with lower achieved hemoglobin values may be partly the result of lower relative erythropoietin responsiveness. [6]

Consistent administration of intravenous (IV) iron therapy is important because a patient's erythropoietic response is poor in the presence of inadequate iron stores, even with ongoing administration of EPO therapy.[7] Continued EPO administration without addressing the patient's iron needs is the primary reason for the development of EPO resistance. Regular use of intravenous (IV) iron overcomes EPO resistance, resulting in more efficient erythropoiesis. [8-13]

The most common side effects of EPO treatment, aside from hypertension and its related problems, are headache (which occurs in 15 percent of cases) and an influenza-like syndrome

affecting 5 %.[14, 15] The influenza-like syndrome is of unknown etiology, and managed with anti-inflammatory drugs. [16]

MATERIALS AND METHOD

A prospective study was conducted in the dialysis unit of a 1700-bedded tertiary care teaching hospital, over 10months period. The study was approved by institutional ethics committee and written informed consent was obtained from each patient before enrollment. The study population consisted of 150 CKD patients of all age groups, undergoing once/twice/thrice weekly hemodialysis for over 2 weeks. Patients who had vascular access complications and who received IV antibiotics were excluded from the study.

Study patients were prescribed with EPO (Monotherapy) and EPO + Iron preparations (Combination therapy). Hemoglobin levels of all patients were analyzed for 5 months period. EPO was given by either IV or subcutaneous (SC) route of administration, likewise iron preparations were prescribed by either IV or oral route of administration.

Counselling was given to all patients to improve the outcome of the treatment of anemia in CKD, on diet rich in iron, which included – intake of high iron rich vegetables and fruits, which leads increasing the iron absorption in the body.

Hemoglobin levels were estimated once every month for the period of 5 months prior to HD session. Patients' urine analysis, physical and general examinations were performed. Patients were regularly monitored for side effects like headache and hypertension during the study period. Comparison of hemoglobin levels at the end of 5 months of combination and monotherapy was done by using one way analysis of variance (ANOVA) and comparison was done using Bonferroni Multiple Comparison test. A p-value of <0.05 was considered significant.

RESULTS AND DISCUSSION

A total of 150 patients (6 patients on once weekly, 111 patients on twice weekly and 33 patients on thrice weekly dialysis) were included in the study. The study population consisted of 102 (68%) males and 48 (32%) females, of all age groups, with a mean age of 51±13.8 years. Majority of the patients were in the age group of 51-60 years (47 patients). The most commonly observed co-morbidity was hypertension in 146 patients (97%). There were 82 (55%) patients prescribed with combination therapy of EPO + Iron preparations and 68 (45%) patients prescribed with monotherapy of EPO (Table 1).

Table 1: Baseline characteristics of Study Population

Characteristics	No of patients (N= 150)	Percentage
Age		
Males	102	68
Females	48	32
Duration of dialysis (yrs)		
<1	45	30
1 to <3	61	40.7
3 to <5	29	19.3
≥5	15	10
Co morbidities		
HTN	146	97
DM	108	72
CAD	17	11.3
Combination therapy	82	55
Monotherapy	68	45

Among 150 patients, 111 patients had serum hemoglobin levels in the range of <10g/dl, 20 patients had 10-11g/dl and 19 patients had >11g/dl of Hb levels. There were 122 patients prescribed with EPO by intravenous route and 28 patients with subcutaneous route of administration both in combination with Iron and as monotherapy. EPO was given at the dose of 4000IU for 112 patients (once weekly for 6 patients, twice weekly for 89 and thrice weekly for 17 patients) and of this 112, 60 patients were on combination therapy and 52 were on monotherapy with EPO; 3000IU for 15 patients (once weekly for 3 patients, twice weekly for 7 and thrice weekly for 8 patients) and of this 15, 7 patients were on combination therapy and 8 were on monotherapy with EPO; 2000 IU for 23 patients (once weekly for 5 patients, twice weekly for 16 and thrice weekly for 2 patients) and of this 23, 15 patients were on combination therapy and 8 were on monotherapy with EPO (Table 2).

Table 2: Prescribing Pattern of EPO in Combination with Iron and as Monotherapy

Dose of EPO in IU	ROA		HB levels (g/dL)			Frequency of EPO			Type of treatment	
	IV	SC	<10	10-11	>11	Once/ week	Twice/week	Thrice/ week	EPO+ Iron(n=82)	EPO (n=64)
2000 (n=23)	14	9	20	3	0	5	16	2	15	8
3000 (n=15)	12	3	3	1	11	1	11	3	7	8
4000 (n=112)	96	16	88	16	8	6	89	17	60	52

Table 3 depicts the mean Hb values in patients on combination therapy and patients on monotherapy for the consecutive five months. There was a significant difference in mean hemoglobin values of patients from first month to the end of the fifth month in both therapies. The increase in the mean Hb levels was significantly higher in patients on combination therapy

with the EPO +Iron preparations (P <0.05*) when compared to that of the patients who were prescribed with EPO alone (P > 0.05).

Table: 3 Comparison of Efficacy of Combination Therapy and Monotherapy

Months	Hb values (g/dL) EPO + Iron therapy (Mean ±SD)(n=82)	P value	Hb values (g/dL) EPO therapy (Mean ± SD)(n=68)	P value
1st month	8.5±2.1	P<0.05*	9.1±1.9	P>0.05
2nd month	8.4±1.7		9.2±1.9	
3rd month	8.6±1.4		9.2±1.8	
4th month	9.0±1.5		9.3±1.6	
5th month	9.1±1.6		9.6±1.7	

*P value of <0.05 was considered statistically significant

DISCUSSION

The need for treating anemia of chronic renal failure with a renewable source of erythropoietin was first recognized in the 1960s, but cloning and expression of the human gene started only from 1983 only. Clinical testing of recombinant human erythropoietin (r-HuEPO) began in 1985, leading to the first license for EPO as a therapeutic agent in 1988. An increase in the hemoglobin concentrations to 10-12g/dl in >90% of hemodialysis patients with an intravenous dose of about 200 IU/kg/week was shown in the first clinical trials.[16]

Iron supply is the most important factor in optimizing the response to r-HuEPO. The marrow should be stimulated slowly, to allow mobilization of iron stores. Functional or absolute iron deficiency should be pre-empted by regular iron supplementation. Identifying the resistant states induced by inflammation and bleeding, and excluding severe hyperparathyroidism, aluminium overload and other hematological diseases is of prime importance in EPO therapy.

In the present study, EPO was prescribed to all patients irrespective of patients' hemoglobin levels. The study demonstrated that, relatively few patients (6.67%) were maintained in the range of 11.1-12g/dl, smaller percent (4%) was in the hemoglobin level of 4.1-5g/dl. This indicated that some hemoglobin level variability was beyond the control of nephrologists and dialysis facilities. Also the study demonstrated an increase in hemoglobin variability with increasing hemodialysis duration.

In the present study, among 150 patients, 10 patients had blood transfusions, of which 5 patients were with the hemoglobin level of 4.1-5g/dl; 3 patients with 5.1-6g/dl and 2 patients with 6.1-7g/dl levels of serum Hb. Out of 150 patients, 2 patients had renal transplantation, of which 1 patient had a hemoglobin level of 8.9g/dl and other patient had a hemoglobin level of 7.3g/dl.

The present study has yielded positive results with combination therapy by increasing hemoglobin levels substantially. A statistically significant increase of mean hemoglobin levels was found at the end of 3rd, 4th and 5th months of combination therapy.

CONCLUSION

The present study shows that combination therapy (EPO+Iron) was effective in maintaining the hemoglobin levels than monotherapy (EPO) in CKD patients on maintenance hemodialysis.

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