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Assessment of erythropoietin for treatment of anemia in chronic kidney failure- ESRD patients

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ABSTRACT

Background and objective: Currently there is an inadequate data regarding effective management of anemia in chronic kidney disease (CKD) patients who are on dialysis. In CKD patients' anemia mainly develops from decreased renal synthesis of erythropoietin (EPO) and iron deficiency. Our current study focused to effective management of anemia in CKD patients'.
Study design: Prospective observational case series study.
Methods: Eligible patients were assigned to three study groups according to initial hemoglobin level i.e. Group I having Hb level below 11 g/dL, Group II with Hb level of 11–13 g/dL, and Group III with Hb level more than 13 g/dL. Intravenous dosing of ESA's calculated according to the range of 150–300 IU or equivalent microgram quantity per kilogram body weight was administered to patients in divided doses per week; alone or in combination with iron supplements.
Results: Study population (n = 163; 100%), of which 124 subjects (76%) patients were treated with erythropoietin and iron supplements; rest of 39 (24%) patients were treated with only erythropoietin. The estimation of hemoglobin content revealed Group I (98 patients) Hb were increased significantly from 9.0 ± 1.2 g/dl at baseline to 10.9 ± 1.7 g/dl. No significant changes in Group II and Group III were observed.
Conclusions: Study suggests use of erythropoietin along with iron for treatment of renal failure associated anemia is more beneficial for CKD patients having low Hb. Also study conclude the use of lower than normal dose (150–300 IU) of ESA is appropriate when hemoglobin reaches 11 g/dl in hemodialysis patients.

1. Introduction

In patients with chronic kidney disease (CKD), anemia mainly develops from diminished synthesis of erythropoietin by kidneys. The anemia worsens, when patients' glomerular filtration rate (GFR) progressively decreases. Hematopoiesis is defined as the formation and maturation of RBCs as well as their components. Approximately more than 6 billion cells are produced per kilogram of body weight daily [1]. Each adult has nearly 1.7 l of bone marrow, which facilitates an optimal environment for the development and proliferation of hematopoietic cells. Stromal cells are thought to be important hematopoietic components, growth factors, collagen and cell adhesion proteins [2,3].

Anemia is highly prevalent in patients with CKD who have inadequate renal erythropoietin production [4,5]. For the last two decades' erythropoiesis-stimulating agents (ESA) have been used to treat anemia in CKD patients, but still optimal hemoglobin targets remain unclear. Current U.S. Food and Drug Administration (FDA) guidelines for management of anemia in CKD patients recommends to maintain Hb levels above 10 g/dl [6]. FDA as well as National Kidney Foundation Dialysis Outcomes Initiative (KDOQI) have issued warning for ESA treatment stating the upper limit for Hb value to be below 12 g/dl [6,7]. Whereas, updated version of the European Best Practice Guidelines recommends minimum target Hb value of 11 g/dl [8]. However, optimal Hb target level has not been explained clearly; also whether Hb should be normalized in patients who have ESRD, in context to improving their general as well as cardiovascular (CV) outcomes.

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2. Management

Erythropoietin is naturally produced by the kidneys but a synthetic form is also available for the treatment of anemia of CKD since 1989; however, it remains fairly expensive and its usage is not straightforward. Therefore, adjuvant therapy is required for optimal treatment. Against this background, the study has been commissioned to address appropriate management of anemia in CKD patients in an urban city of India.

Iron deficiency is also found in patients with CKD which may be unconditional; often due to poor nutritional iron intake, sometimes as a result of blood loss, even when there is an imbalance between demand and supply of iron to erythroid marrow. Iron deficiency leads to reduction in formation of red blood cell hemoglobin causing hypochromic microcytic anemia [9]. In addition, presence of uremic inhibitors like cytokines, parathyroid, shorten half-life of matured blood cells and either folate or vitamin B_{12} deficiencies result.

3. Methodology

3.1. Inclusion criteria

- Patients who came to the hospital with renal failure associated anemia for hemodialysis.
- Patients with history of dialysis using ESA therapy at least three months prior to study.
- Patients with iron deficiency anemia.

3.2. Exclusion criteria

- Patients in intensive care unit.
- Renal patients with hemoglobin value more than 13 g/dL.
- Kidney transplant patients.
- Pregnant women or nursing mothers.
- Patients with sepsis or active infections.
- Patients with advanced cardiovascular disease.
- Patients with non-renal causes of anemia (Folate and Vitamin B_{12} deficiencies).
- Patients who received blood transfusions within the last three months.

3.3. Study design

- Prospective observational case series study.

3.4. Study period

- The study was carried out over the period of 24 months.

3.5. Data collection

Data collection form was created after extensive literature review and made by considering variety of information i.e. patient demographic information, blood pressure (pre- and post-dialysis), body mass index (BMI), dose/frequency of ESA, co-administered drugs, erythropoietin adjuvant drugs, hematological tests (hemoglobin value, Hb, serum iron and ferritin levels. Data collection was performed after study subjects had provided written informed consent.

3.6. Procedure

Eligible patients were assigned into three study groups according to initial hemoglobin levels i.e. Group I having Hb level below 11 g/dL, Group II with Hb level of 11–13 g/dL and Group III with Hb level more than 13 g/dL. Among 163 patients, 98 patients (60%) had hemoglobin level below 11 g/dL, 49 patients (30%) had Hb level between 11–13 and 16 patients (10%) more than 13 g/dL prior to initiation of the study.

Intravenous dosing of ESA's calculated according to the rate of 150 300 IU or equivalent microgram quantity per kilogram body weight was administered to patients in divided doses per week based on their requirement. Epoetin alfa (EPREX 1000, 2000, 3000, 4000 6000, 8000, 10000 and 40,000 IU/mL, J&J (Ethnor) Pharmaceutical, India), was used in this study. Total of 147 patients (90%) having Hb level $\leq$ 13 g/dL received a dose of ESA to maintain target Hb level of at least 11 g/dL throughout the study. Group III patients (16) were managed with or without ESA along in combination with iron supplements.

Oral or intravenous iron supplements were prescribed to anemic CKD patients who required iron supplementation as deemed fit by their physician based on serum ferritin, serum iron and TIBC. Blood sampling for parameters measuring iron level were performed at least one-week post administration of >100 mg/dose of any i.v. iron preparation. This is required to establish whether an iron deficiency exists or too much iron supplementation is being administered. Inj. Encicarb 100 mg/2 ml of Ferric carboximaltose, Inj. Wofer S (Iron Sucrose) 100 mg/5 ml, Ferium XT 5 ml solution with 30 mg of elemental ferrous ascorbate, and Orofer XT tablets with 100 mg ferrous ascorbate and 1.1 mg of folic acid were administered to patients based on their requirement. Serum ferritin level <12 mcg/L indicates absence of iron stores. Fig. 1 provides an example of an algorithm for use of iron in CKD patients. Serum ferritin of 15 mcg/L in adults and 12 mcg/L in children with normal kidney function confirmed diagnosis of iron deficiency anemia, whereas ferritin levels 100 mcg/L rule out iron deficiency anemia [10]. Weiss and Gordeuk defines absolute iron deficiency by serum ferritin levels 15 mcg/L for men and 10 mcg/L for women. Inj. Encicarb 100 mg of Ferric carboximaltose/2 ml, Inj. Wofer S (Iron Sucrose) 100 mg/5 ml was administered depending upon patients' requirement.

3.7. Sample collection and analysis

Blood samples were collected from patients and hemoglobin content, serum iron and serum ferritin level was measured by spectrophotometer (SYSMEX XT-1800 series), Johnson and Johnson Vitros 1000 & Roche diagnostics analyzer. All the collected data from patient's case sheet was transferred to data collection form and it was used for statistical evaluation. Statistical analysis consists of only 163 patients who completed the 24-month study. Initial study (T_0) followed by 3-month interval hemoglobin levels (T_3, T_6, T_9, T_{12}, T_{15}, T_{18}, T_{21}, T_{24}) measurements. The study values have been calculated with descriptive methods like mean, standard deviation for the value with normal distribution and median. All values are expressed as Mean $\pm$ SEM, $^{a}p < 0.05$ compared to normal, $^{b}p < 0.05$ compared to standard. Using Repeated Measure Analysis of variance (or RM ANOVA) followed by post hoc Tukey's multiple comparison tests for data analysis. The statistical significance of p-value ≤ 0.05 was considered.

4. Results and discussion

Gender wise renal complications were more commonly observed in adult male than women. Major study population falls

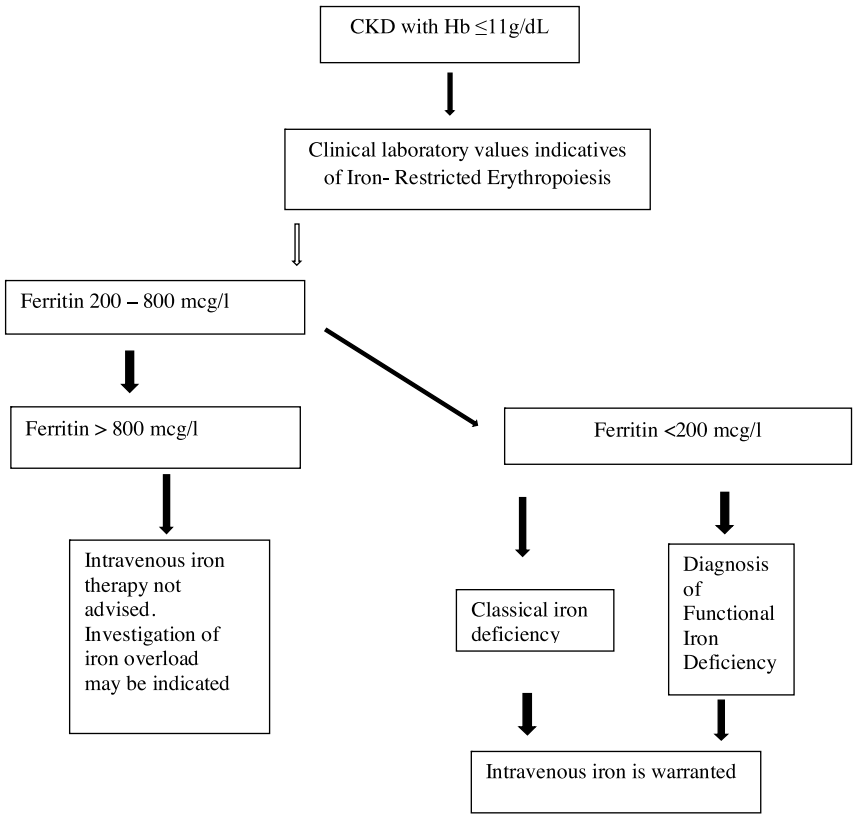

Fig. 1. Management of anemia in Iron-Restricted Erythropoiesis in patients with CKD on Erythropoiesis Stimulating Agents.

in the age group of 41–60 years, which consisted of 85 (52%) patients, followed by 39 (24%) patients in the age group of 61–80 years and 39 (24%) patients fall between 21–40 years. Patients were not found in the age of below 20 and above 80 years. Complications in the study population revealed that 68 (42%) patients were found to have end stage renal disease (ESRD), 15 patients with Chronic Glomerular nephritis (10%), 9 patients with Ig-A Nephropathy (6%), 3 patients with Ischemic renal disease (2%) and 3 patients with Chronic interstitial nephritis (2%). Other co-morbid status with CKD are listed in Table 1.

The renal anemia increases with raise in blood pressure hence 40% of CKD patients with renal anemia are associated with left ventricular hypertrophy [12]. In our study, the baseline detection of blood pressure revealed that 91 patients had Stage-1 hypertension, 29 patients had pre-hypertension, 42 patients with Stage-2 hypertension. This hypertensive status was significantly altered in the final review. In that, 75 patients had Stage-1 hypertension, 52 patients had pre-hypertension and 3 patients were found with normal blood pressure and Stage-2 hypertension was observed in 42 patients at baseline and 33 patients at final review. This shows

Table 1
Co-morbid status with chronic renal failure (n = 163).

Conditions	Number of patients[a]
Hypertension	80
Diabetes Mellitus	46
Hypothyroidism	8
Tuberculosis	8
Ischemic heart disease	6
Coronary artery disease	6
CVA	6
Asthma	2
Cerebral contusion	2
Parkinsonism	2
Spondylitis	2
Lymphadenitis	2
Panic disorder	2
Seizure	2
H-pylori infection	2
HCV positive	2
SVT	2
ADPKD	2
Osteoarthritis	2

[a] Number overlaps with more than one co-morbid conditions.

Table 2
Number of patient's baseline blood pressure and final blood pressure at starting of the study and end of the study respectively. *JNC 7.

Classification of Hypertension	Blood pressure (mmHg)*	Number of Patients (N = 163)	
		at base line review	at final review
Normal	<120/<80	1	3
Pre	120–39/80–89	91	52
Stage-1	140–159/90–99	29	75
Stage-2	160/100	42	33

N, Total Number of Patients.

Table 3
Progress in patients Hb levels during the study period.

Patients group N – 163	Period (quarterly) Hb (g/dl) Mean ± SD[a]								
	0	1	2	3	4	5	6	7	8
I (98)[b]	9.1 ± 1.2	9.7 ± 1.3	10.0 ± 1.6	9.8 ± 1.6	10.3 ± 1.3	10.8 ± 1.2	11.1 ± 1.0	11.3 ± 1.0	11.4 ± 1.1
II (49)[b]	11.6 ± 0.5	11.5 ± 0.2	11.7 ± 0.1	11.4 ± 1.0	11.4 ± 1.1	11.6 ± 1.2	11.9 ± 1.2	12.5 ± 0.9	12.2 ± 1.0
III (16)[b]	13.3 ± 0.1	12.5 ± 0.2	12.6 ± 0.2	11.7 ± 0.4	12.1 ± 0.7	12.2 ± 0.9	11.9 ± 1.0	11.5 ± 0.6	11.8 ± 0.8

N-163 eligible patients completing the 24 months' study.
[a] Mean ± SD.
[b] Statistically significant vs baseline ($p < 0.05$).

there is a significant correlation in the blood pressure from baseline to final review. Study has shown a direct correlation where the final blood pressure has reduced when compared to patients' baseline blood pressure after co-administration of Erythropoietin along with anti-hypertensives (Table 2).

Erythropoietin (EPO) is commonly used either in combination or alone in our study, 124 (76%) patients being treated with erythropoietin along with iron supplements and 39 (24%) patients were treated with erythropoietin only. Medication history shows our study population (n = 163; 100%) was prescribed with erythropoietin and Genevac (Hepatitis-B vaccine).

Efficacy of EPO was also observed in this study population showing EPO improved hemoglobin level in almost all of our patients (Table 3). The estimation of hemoglobin revealed that, Group I (98 patients) Hb increased significantly from 9.1 ± 1.2 g/dl at baseline to 11.4 ± 1.1 g/dl at the end of study period. Group 2 and Group 3 hemoglobin levels did not show any significant changes over the time period (Fig. 2).

Studies have shown anemia in CKD patients is substantial, causing significant morbidity and affecting their quality of life due to anemia [13–16]. Patients with chronic kidney disease who undergo hemodialysis, ESA's and iron supplements are proven to elevate low hemoglobin levels and improves anemic conditions [17–22].

5. Conclusion

This prospective observational case series study concludes; Erythropoietin in combination with iron are essential for treating anemic renal failure patients with mainly iron deficiency. The response to administration of erythropoietin in increasing hemoglobin value was significant in anemic patients. Hence, study suggests co-administration of erythropoietin with iron in study subjects had a direct effect in increasing hematocrit value in order to treat anemic renal failure patients. Study also showed ESAs when administered intravenously at dose of 50–150 IU/Kg body weight twice or thrice a week is effective in increasing hemoglobin levels in CKD patients. The response to ESA along with iron supplements in Group II and III suggests management with

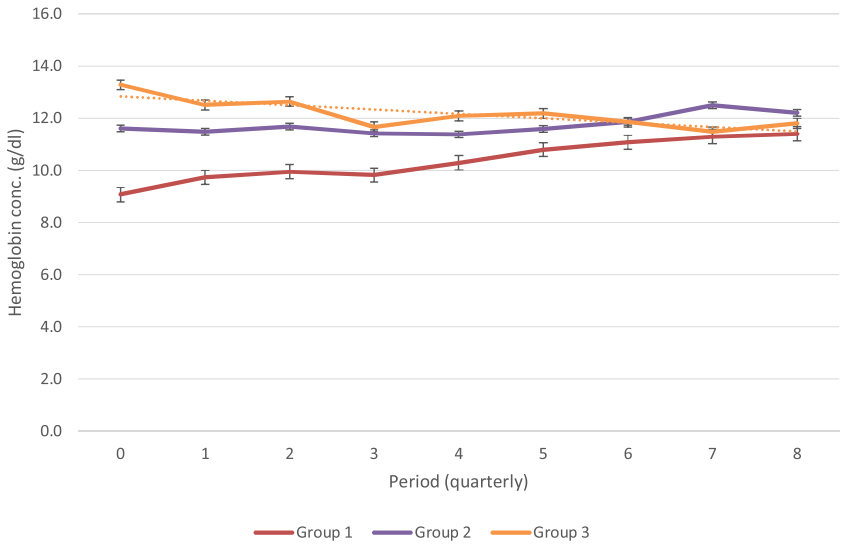

Fig. 2. Progress in patients Hb levels during the study period.

lower dose of ESA can be sufficient when hemoglobin levels are near 11 g/dl.

This observation study was limited by the fact that it was performed at a single location involving a small number of patients in each group. Detailed risk as well as benefits of erythropoietin therapy in anemic ESRD patients could not be evaluated. Risk of iron overload along with co-relation to increased serum ferritin level due to unforeseen complications such as patients' co-morbidity such as inflammation, infection, malnutrition or malignancy could not be studied. Hence the upper limit of serum ferritin at which iron treatment should be discontinued could not be established in this study.

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Conflict of interest

All authors have no conflicts of interest to declare.

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