

CORRECTION OF ANAEMIA WITH ERYTHROPOIETIN IN CKD/ESRD PATIENTS

Madhukar Gaikwad¹, Shyamal Sinha², Rashmi Sinha³, Anitha Gore⁴, S. Bhattacharjee⁵, T. Anjaiah⁶, Abdul Hannan⁷, Kunal Patankar⁸

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ABSTRACT: Chronic kidney disease (CKD) is characterized by gradual and permanent loss of kidney function. One of the most common complications of CKD is Anaemia.^{1,3} Anaemia often appears earlier in course of CKD and worsens with disease progression.^{1,2} Erythropoietin is a hormone synthesized in the kidney is deficient in the majority of patients of CKD thereby predisposing them for developing anaemia. Erythropoiesis stimulating agents (ESAs) first became clinically available in 1989 and has contributed to the advances in the management of CKD related anemia. The present study highlights the correction of anaemia with erythropoietin (Eprex) in population having CKD on MHD and anaemia. Based on GFR CKD is divided into five stages from 1-5. Patients often become anaemic at stage 3 or 4 CKD but anaemia may develop as early as stage 2. And it is present in the majority of patients with stage 5 disease.^{2,4} The objective of this study is to evaluate efficacy of administration of 10000.U. Epotin alfa sc for once a week as initiation therapy in patients with anaemia of CKD/ESRD on MHD for 28 weeks of duration of treatment. It is a prospective study done at Central Hospital, South Central Railway, Secunderabad on patients with ESRD or stage 4 on maintenance hemodialysis and receiving subcutaneously EPO (Eprex). Serum ferritin and %transferrin saturation are estimated before the initiation of EPO(Eprex) & if the levels are below normal, IV IRON 100 mg is given once weekly and oral elemental Iron 200 to 400 mg to every to normalize the serum ferritin and % transferrin saturation levels. Hemoglobin level estimation has done before and after the initiation of the EPO (Eprex) and once in weekly and four weekly to see the response more than 1gm in four weeks to achieve the target hemoglobin level (11 to 12 grams) in 28 weeks. In the present study target hemoglobin level (11-12g/dl) was achieved in 42 out of 50 patients under consideration (84%) in 28 weeks of duration of treatment and not achieved for 8 amongst 50(16%) patients. Increase in the hemoglobin level of 1/dl is seen in 13(26%), >1 g/dl in 29(58%) and <1 g/dl in 8(16%) patients.

KEYWORDS: Anaemia, Erythropoietin, CKD.

INTRODUCTION: Chronic kidney disease (CKD) is characterized by gradual and permanent loss of kidney function that worsens as it progresses from stages 1-5. One of the most common complications of CKD is Anaemia.^{1,3} which is defined as hemoglobin (Hb) concentration below 13.0 g/dl for adult males and post-menopausal women, and a hemoglobin below 12.0 g/dl for premenopausal women, is a major component of CKD and is common in all stages but becomes more pronounced at the later stages of kidney failure. Anaemia is associated with increased morbidity in these patients. Erythropoietin is a hormone synthesized in the kidney responsible for red blood cell maturation in the bone marrow. It is deficient in the majority of patients with advanced kidney disease thereby predisposing them to anaemia. Until the late 1980s, blood transfusions and androgen

ORIGINAL ARTICLE

therapy to stimulate erythropoiesis were the only tools available to clinicians for the treatment of CKD-related anaemia⁵. Erythropoiesis stimulating agents (ESAs) first became clinically available in 1989 and have contributed to the advances in the management of CKD related anaemia since that time. Mean Hb levels have increased as a result of the use of ESAs and the prevalence of Hb levels <11 g/dl has decreased significantly.

The present study highlights the correction of anaemia with erythropoietin (Eprex) in patients having CKD on MHD and anemia. Anaemia in patients with CKD causes debilitating weakness and fatigue, altered cognitive function, and a negative impact on the quality of life and well-being. Amongst the other consequences of CKD, Anaemia contributes to the development and progression of cardiovascular disease(CVD) and corresponding increases in hospitalization, cost of care, and mortality.^{6,7}

Patients with CKD are grouped into five stages, based on evidence of kidney damage and decreasing glomerular filtration rates (GFR).⁸ Stage five patients have a GFR <15ml/min and require kidney replacement therapy, either dialysis or transplantation.⁶ Kidney damage is usually diagnosed based on the presence or absence of certain markers: persistent proteinuria; abnormalities in urine sediment, blood, and urine chemistries; and abnormal findings on imaging studies.^{6,7}

STAGE	DESCRIPTION	GFR (ml/min/1.73m ²)	PLAN OF TREATMENT
1	Kidney damage with normal or increased GFR	>=90	Diagnosis and treatment of comorbidites
2	Kidney damage with mild or decreased GFR	60-89	Estimate progression
3	Moderate decreased GFR	30-59	Evaluate and treat complications
4	Severe decrease in GFR	15-29	Preparation for kidney replacement therapy
5	Kidney failure	<15	Dialysis or transplant if uremia present

Table 1: STAGES OF CKD BY GFR

ETIOLOGY OF ANAEMIA IN CKD:

- Erythropoietin deficiency.
- Iron deficiency.
- Hyperparathyroidism.
- Chronic inflammation and infection.
- Angiotensin converting enzyme inhibitors.
- Pure red cell aplasia.
- Malignancy.
- B12 and folic deficiency hemoglobinopathies, eg; sickle cell Anaemia. Hemolytic Anaemia.
- Malnutrition.

ORIGINAL ARTICLE

CLINICAL PRACTICE GUIDELNES: EPO deficiency is by far the leading cause of Anaemia in patients with CKD. The Kidney is the primary site of erythropoietin production in adults.⁹ Studies utilizing transgenic mice suggest that a population of interstitial fibroblasts (Also known as the type 1 interstitial cell) is the major source of renal erythropoietin synthesis. Deficiency of EPO, as occurs with patients with CKD retards maturation of red blood cells. The progenitor cells mature into normoblasts and reticulocytes. Furthermore, deficiency of EPO decreases the survival of these immature red blood cells, a process known as neo cytolysis, there by resulting in Anaemia.¹⁰ Therefore EPO supplementation is indicated in patients with CKD, who have anaemia. In the absence of other causes, Anaemia due to EPO deficiency is often normocytic and normochromic, implying a reduction in number but not the quality of these cells.

Because of the strong association between CKD &EPO deficiency, it is often not necessary to measure serum erythropoietin levels prior to treating Anaemia in these patients.

In patients with early kidney disease should be carefully monitored and treatment with an ESA initiated as soon as anaemia is diagnosed, before Hb concentration falls to a level that is likely to induce serious and possibly irreversible effects. (CKD- related anaemia is defined as the Hb levels consistently below 11g/dl(hematocrit <33%) where all other causes of anaemia have been excluded).¹¹ The benefits of ESAs include increased Hb levels, reduced need for blood transfusion, and improved quality of life and exercise capacity. The US Food and Drug Administration (FDA) issued an advisory (Public Health Advisory: Information of health care professionals) recommending hemoglobin within the range of 10-12g/dl, with more frequent hemoglobin measurement (Twice weekly), so that early changes in ESA therapy may be instituted to avert significant over treatment and related complications such as increase in risk of cardiovascular events, progression to dialysis and cancer progression.

ERYTHROPOIESIS-STIMULATING AGENTS: Five ESAs are currently approved for treatment of anaemia in CKD.

PATIENTS:

- 1) First generation ESA:
 - Epoetin alfa (Eprex/ epogen / procrit/ erypo).
 - Epoetin beta (Neorecormon/ recormon/ epogin).
 - Epoetin beta (NeoRecorman).
- 2) Second generation ESA:
 - Darbepoetin alfa (Aranesp/ nespo)
- 3) Third generation ESA:
 - CERA (Methoxy poly ethylene glycol-epoetin beta), continuous erythropoietin receptor activator. (Roche)

MATERIALS AND METHODS: All patients irrespective of age and sex who are on maintenance hemodialysis.

DESIGN OF STUDY: Prospective study/ Observational study.

ORIGINAL ARTICLE

PLACE AND DURATION: Central Hospital, South Central Railway, Secunderabad. From: March 2007 to March 2009.

INCLUSION CRITERIA: ESRD or stage 4 patients on maintenance hemodialysis. And receiving subcutaneously EPO (Eprex).

EXCLUSION CRITERIA:

- Non-Renal causes of Anaemia.
- Gastrointestinal Bleed.
- Iron Overload State.
- Cancer.

STUDY PROTOCOL: All patients irrespective of age and sex with anaemia of ESRD/ CKD on maintenance hemodialysis on OPD basis in railway hospital which were receiving inj epo, iv iron and supplementation of oral elemental Iron of 200-400 mg. All patients were subjected to detailed history and physical examination with reference to history of HTN, DM, NSAID Abuse, Urinary tract infection and Obstructive Uropathy.

Routine investigations, CBP, Hemoglobin level, Periperal Smear for type of anaemia, blood urea, serum creatinine, serum electrolytes, serum uric acid, serum phosphorus, serum albumin once weekly before and after hemodialysis was done serum ferritin and %transferrin saturation before the initiation of EPO (Eprex) were estimated & when the levels were below normal, IV iron 100 mg once in weekly and oral elemental Iron 200 to 400 mg was given to every patient to normalize the serum ferritin and % transferrin saturation levels.

Hemoglobin level estimation was done before and after the initiation of the EPO (Eprex) and once weekly to see the response more than 1gm / in four weeks to achieve the target hemoglobin level (11 to 12 grams) in 28 weeks. A patient was considered a treatment failure, if he required the maximum EPO dosage of 20000 units once weekly for 6 consecutive weeks, and Hb response <1 grams in the 4 weeks.

OBSERVATIONS AND RESULTS:

Age Group	Achieved				Not Achieved			
	No. of patients			Percentage	No. of patients			Percentage
	Total	Male	Female		Total	Male	Female	
30-40	4	3	1	8	1	1		2
41-50	11	6	5	22	3	3		6
51-60	14	13	1	28	3	2	1	6
61-70	10	7	3	20	1	1		2
71-80	3	2	1	6				

Table 2 : Distribution of target hemoglobin achieved or not achieved according to the age group

In the present study, target hemoglobin levels according to age group is achieved more in the age group of 51-60 years is 14(28%), in 41-50 years is 11(22%), in 61-70 years is 10(20%) and low

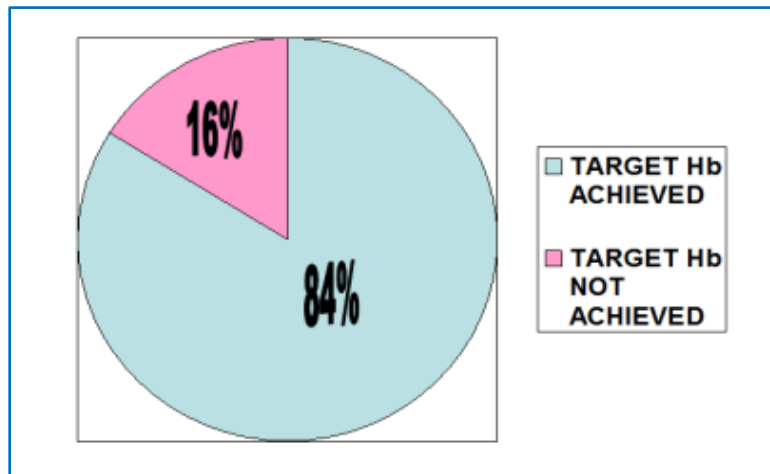
ORIGINAL ARTICLE

response seen in the age group of 30-40 years is 4(8%) and 71-80 years is 3(6%) and target hemoglobin not achieved in age group of 51-60 is 3(6%),41-50 years is 3(6%) and in the 30-40 and 61-70 years is 1(2%).

TARGET HEMOGLOBIN	PERCENTAGE
ACHIEVED	42(84%)
NOT ACHIEVED	8(16%)

Table 3: Target hemoglobin (11-12g/dl) achieved in 28 weeks

In the present study it was seen that, target hemoglobin level (11-12g/dl) was achieved for 42 patients (84%) after 28 weeks of treatment and not achieved in case of 8 (16%) patients.

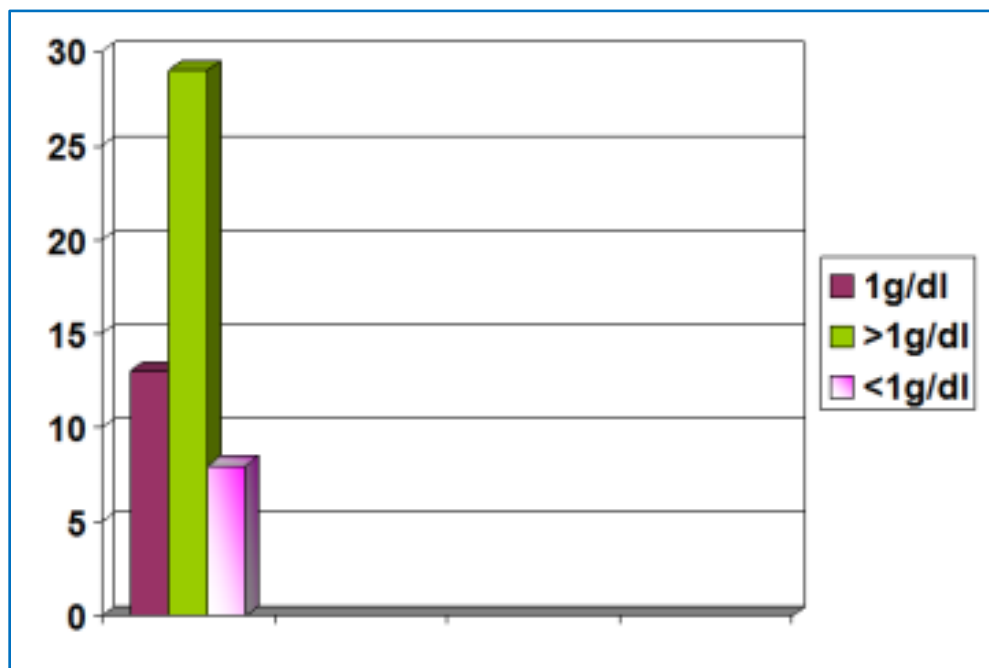


Graph 1

INCREASE IN HEMOGLOBIN LEVEL	NO. OF PATIENTS
1 g/dl	13(26%)
>1	29(58%)
<1	8(16%)

Table 4 : Increase in hemoglobin in 4 weeks

In the present study increase in the hemoglobin level of 1 g/dl is seen in 13 patients (26%), >1 g/dl in 29(58%) and <1 g/dl in 8(16%) patients.

Graph 2: DISTRIBUTION OF INCREASE IN HAEMOGLOBIN IN 4 WEEKS.**Graph 2**

DISCUSSION: In the present study, target hemoglobin levels (11 to 12 gms) were achieved in 84% in 42 out of 50 patients with the 10000 units of EPO (Eprex) subcutaneously once in week in 28 weeks of duration of treatment which is comparable with Robert Benz et al study in which target hemoglobin achieved in 88.1% in 59 out of 67 patients. With the epoetin alfa 20000 units subcutaneously once every two weeks in 28 weeks of duration of treatment. In non-dialysis CKD patients with increase in hemoglobin 1 gram in 4 weeks. In the present study it was comparable with another studies like, Weiss et al study in which target hemoglobin level achieved in 73% in 64 out of 88 patients with epoetin- β subcutaneously once in weekly in 24 weeks and in N P Singh et al study target hemoglobin achieved in 90.2% in 74 out of 101 patients with the shanpoetin (R-HUEPO) intravenously or subcutaneously 175-150 IU/Kg body weight three times a week or weekly for 12 weeks.

Present study		In Robert Benz et al ⁶⁶		In Weiss et al ⁷⁷		NP Singh et al ⁶⁷	
No. of patients	Percentage	No. of patients	Percentage	No. of patients	Percentage	No. of patients	percentage
42 out of 50	84	59 out of 67	88.1	64 out of 88	73	74 out of 101	90.2

Table 5

The target hemoglobin level could not be achieved in 16% patients (8 out of 50) patients which is comparable with Robert Benz et al study in which target Hb was not achieved in 12%

ORIGINAL ARTICLE

patients (8 out of 67). The target hemoglobin may not have achieved due to poor response, hypertension, sepsis, tuberculosis.

Present study		In Robert Benz et al ⁶⁶	
No. of patients	Percentage	No. of patients	Percentage
8 out of 50	16	8 out of 67	12

Table 6

In the present study hemoglobin levels after the initiation of 10,000 units of Epo administered subcutaneously once a week, after the four weeks of the treatment till 28 weeks, increase in hemoglobin level in four weeks is 1 grm 13 (26%), > 1grm in 29 patients (58%) and <1grm is in 8 (16%). In Robert Benz et al study hemoglobin level more than 1grm 62.7, 85.7, 91.0 and more than 2grm in 22.4, 55.2 and 77.6 in 5th, 9th and 28th weeks respectively.

In the Robert Benz et al study increase in hemoglobin level more than 2grms in 4 weeks was observed. In present study, more than 2grm in four weeks was not observed.

Present Study			In Robert Benz et al ⁶⁶			
Hemoglobin level	No. of patients	Percentage	Hemoglobin level	5 th	9 th	28 weeks
1 grm	13	26	> 1grm	62.7%	85.1%	91.0%
> 1grm	29	58	> 2grm	22.4%	55.2%	77.6%
<1grm	8	16				

Table 7

SUMMARY:

1. Latest literature of CKD, anemia, EPO with regards to etiology, risk factors, clinical factors, biochemical, diagnostic, treatment response and complications referred.
2. 50 patients of CKD/ESRD with their hemoglobin response with EPO 10000 units subcutaneously studied with particular references.
3. Target hemoglobin level (11-12 gram%) was achieved in 42 patients out of 50(84%), within 28 weeks of duration of treatment with help of the inj EPO 10000 units subcutaneously once in weekly given after the hemodialysis, after the normalization of serum ferritin and serum % saturation by giving the iv iron 100-200mg once in weekly and supplementation of oral elemental iron up to 200-400 mg, not given any blood transfusion to increase the hemoglobin level.
4. Inj EPO 10000 units subcutaneously once in a week in anemia due to CKD/ESRD is very effective and safe to achieve the target hemoglobin level within 28 weeks of duration.
5. Target hemoglobin level (11-12 gms%) could not be achieved in 8 (16%) patients out of 50 which may be due to poor response, HTN, or sepsis and tuberculosis.
6. Increase in hemoglobin level of 1 gram in four weeks is seen in 13 (26%) patients, > 1 gram was seen in 29 (56%) patients and less than 1 gram was seen in 8(16%) patients after the initiation of 10000 units of inj EPO sc once a week in anemia of ckd/esrd patients.

7. Mean hemoglobin level of 50 patients before the initiation of inj EPO is 5.39 gms%, which was increased to 11.93 gms after treatment.

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AUTHORS:

1. Madhukar Gaikwad
2. Shyamal Sinha
3. Rashmi Sinha
4. Anitha Gore
5. S. Bhattacharjee
6. T. Anjaiah
7. Abdul Hannan
8. Kunal Patankar

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of General Medicine, Grant Government Medical College & J. J. Group of Hospitals, Mumbai.
2. Assistant Professor, Department of Pharmacology, Grant Government Medical College & J. J. Group of Hospitals, Mumbai.
3. Assistant Professor, Department of Anatomy, Grant Government Medical College & J. J. Group of Hospitals, Mumbai.
4. MBBS, Ex-Student, Grant Government Medical College & J. J. Group of Hospitals, Mumbai.

5. General Physician, Head of Unit Department of General Medicine, Central Hospital, South Central Railway, Secunderbad.
6. HOD, Department of General Medicine, Central Hospital, South Central Railway, Secunderbad.
7. Assistant Professor, Department of Pharmacology, Grant Government Medical College & J. J. Group of Hospitals, Mumbai.
8. MBBS, Ex-Student, Grant Government Medical College & J. J. Group of Hospitals, Mumbai.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Madhukar Gaikwad,
Assistant Professor, Department of General,
Medicine, Grant Government Medical
College & J. J. Group of Hospitals, Mumbai.
E-mail: drmadhugg@yahoo.co.in

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