Original Research Article

Efficacy And Safety Profile of Erythropoietin in Chronic Kidney Disease Patients of Vizianagaram, Andhra Pradesh

Sindhura Nagisetty[1], Naga Sreenivasulu Jillella[2], Tulasi Madhuri Thotakura[3], Madhav P[4*]

[1]Assistant Professor, Department of Pharmacology, GITAM Institute of Medical Sciences and Research, Visakhapatnam, Andhra Pradesh, India

[2]Assistant Professor, Department of General Medicine, GITAM Institute of Medical Sciences and Research, Visakhapatnam, Andhra Pradesh, India

[3]Associate Professor, Department of Pharmacology, GITAM Institute of Medical Sciences and Research, Visakhapatnam, Andhra Pradesh, India

[4]Associate Professor, Department of Pharmacology, Apollo Institute of Medical Sciences and Research, Chittoor, Andhra Pradesh, India

Received: 28-11-2021 / Revised: 29-12-2021 / Accepted: 15-01-2022

Abstract

Background: Anaemia is a common complication of chronic kidney disease. The close relationship between haematopoiesis and the kidney was first recognized by Richard Bright in 1835 when he described the association between anaemia and chronic renal failure. Much of the morbidity in renal failure patients can be attributed to the consequences of their chronic anaemia. **Aim & Objectives:** The aim of this study is to evaluate the efficacy and safety of human recombinant Erythropoietin in the treatment of anaemic patients due to chronic renal failure. **Methods:** This study was conducted at Department of Nephrology and dialysis unit, MIMS, Vizianagaram. Study Period was from October 2013 to September 2015 who are on haemodialysis for duration of six months to two years. For this a total number of 46 participants were screened. All 46 patients were given erythropoietin [EPOFIT] manufactured by INTAS pharmaceuticals by subcutaneous route **Results:** Patients will undergo laboratory investigations for haemoglobin, haematocrit (Hct), reticulocytes, RBC counts, serum ferritin and TSAT at the baseline and end of the study. Haemoglobin, haematocrit and red cell count, reticulocytes, serum ferritin and TSAT will be done once in 4 weeks till the end of the study. **Conclusion:** Of the total 46 patients enrolled in the study, 31 patients required only regular conventional dose of 50 units /kg /dose and only 9 patients required incremental dose of erythropoietin 75 units/kg to achieve target haemoglobin level. In our study Haemoglobin increased progressively in 77% patients at 4 weeks and 23% patients at the end of 12 weeks.

Key words: Erythropoietin, Anaemia, Chronic Kidney Disease, Haemoglobin.

Introduction

Anaemia is a common complication of chronic kidney disease. The close relationship between haematopoiesis and the kidney was first recognized by Richard Bright in 1835 when he described the association between anaemia and chronic renal failure. Much of the morbidity in renal failure patients can be attributed to the consequences of their chronic anaemia. Anaemia is defined by the World Health Organisation (WHO) as haemoglobin <13 g/dl in men and <12g/dl in women and National Kidney Foundation (NKF) recommends an evaluation when Hb is<13g/dl in men and <12 g/dl in women. The prevalence of anaemia varies with a degree of renal impairment. Anaemia tends to worsen as kidney disease progresses. Nearly everyone with end stage kidney failure has anaemia, due to deficient production of erythropoietin. Several factors may contribute to the pathogenesis of uremic anaemia but inadequate secretion of erythropoietin is the main cause. Anaemia in CKD is also associated with functional and mobility impairment, increased risk of strokes and decreased health-related quality of life (QOL)[1].

Human Erythropoietin is an acidic glycoprotein hormone with a molecular weight of 34kDa.

*Correspondence

Dr Madhav P

Associate Professor, Department of Pharmacology, Apollo Institute of Medical Sciences and Research, Chittoor, Andhra Pradesh, India.

The first clinical trial with recombinant human erythropoietin was published in 1986-87.Since this time a large number of studies in patients with chronic renal failure have been published. They have established erythropoietin as an effective treatment for anaemia in more than 95% of patients. Erythropoietin also improves general wellbeing, symptoms of fatigue, exercise tolerance and cognitive function. Adverse effects that are attributed to erythropoietin in patients receiving haemodialysis include hypertension, flu like symptoms, seizures and clotted vascular access. Erythropoietin amounts are usually expressed in International units (IU), with one IU exerting the same erythropoiesis stimulating activity in rodents as 5 µmol cobaltous chloride[2,3]. However, the sugar side chains are not required for interaction of the hormone with its target cell receptors[4]. Further evidence suggests that apart from its effect as an erythropoietic hormone, erythropoietin acts as a paracrine, tissue-protective protein in the brain and possibly also in other organs[5]. A longer acting erythropoietin analogue, DARBEPOIETIN is also a normal erythropoiesis stimulating protein was launched in 2001[6]. Some people with an underlying disorder fall within the reference range for Hb concentration[7].

We studied the effect of Erythropoietin on the improvement of haemoglobin, haematocrit, red blood cell counts, reticulocyte levels, quality of life and adverse effects among anaemic chronic renal failure patients who were on maintenance haemodialysis.

Aim & Objectives

The aim of this study is to evaluate the efficacy and safety of human recombinant Erythropoietin in the treatment of anaemic patients due to chronic renal failure.

1. To evaluate the efficacy of erythropoietin by investigating the parameters like haemoglobin, haematocrit, reticulocyte, red blood cell count %, quality of life assessment in anaemic patients who are having chronic kidney disease.
2. To evaluate the safety of the erythropoietin by monitoring the adverse effects after giving the erythropoietin injection.

Materials and methods

1. Study design: Prospective, open label observational study.
2. Sample size: 46 (drop outs-6) anaemia with chronic kidney disease patients.
3. Study setting: MIMS college and hospital, Nellimarla, Vizianagaram.
4. Study period: 6 months.
5. Drug given: Inj. Erythropoietin (50 U/100U/150U)/kg body weight twice /week.

Inclusion criteria

Patients are included in the study, only if they meet the following criteria

1. Hb >5 gm/dl or < 10 gm/dl
2. Male or female between the age group 18-80 yrs.
3. Dialysis patients with chronic kidney disease.
4. Transfusion saturation > 20% and serum ferritin > 200ng/ml.
5. Have given informed consent to participate in the study.

Exclusion Criteria

Patients are excluded in the study only if they meet all the following criteria:

1. Patients who require immediate correction of anaemia.
2. Leucocytes > upper limit of the normal count.
3. Active inflammatory diseases like rheumatoid arthritis, inter current infection.
4. Patient with evidence of septic shock.
5. Have known allergy to mammalian cell product (or) albumin
6. History of stroke and history of Seizures
7. Patient with peripheral vessel diseases
8. Active thrombotic disease, any type of active bleeding
9. Patients with cancer
10. Pregnancy and breastfeeding females (pregnancy test should be done for all the females in reproductive age group and are advised to practice contraceptive methods during the study),
11. All chronic kidney disease patients whose haemoglobin levels are >12 gm/dl at the initial time of the study.
12. Patients who have been on any investigative drug, which is on clinical trial.
13. Patients who did not give consent to participate in the study.

Methodology

This study is conducted at Department of Nephrology and dialysis unit, MIMS, Vizianagaram. Study Period was from October 2013 to September 2015 who are on haemodialysis for duration of six months to two years. For this a total number of 46 participants were screened. All the subjects underwent medical examination including medical history, clinical examination, demographic data, study of renal function, history of illness, history of smoking and alcohol, drug usage, and drug allergy. The participants declared their willingness on the details of the study ant the treatment has been explained to the subjects enrolled into the study who gave written informed consent.

Enrolment of patients

No. of patients screened for enrolment: 46
No. of patients selected in this study: 46
No. of drop outs: 6
No. of patients completed the study: 40

46 patients (male- 26 patients, female- 20 patients) with chronic renal failure (stage-V) and who are on haemodialysis, age ranging from 18-80 years with clinical and laboratory evidence of anaemia were treated with erythropoietin.

Patients will undergo laboratory investigations for haemoglobin, haematocrit (Hct), reticulocytes, RBC counts, serum ferritin and TSAT at the baseline and end of the study. Haemoglobin, haematocrit and red cell count, reticulocytes, serum ferritin and TSAT will be done once in 4 weeks till the end of the study. All the selected patients were on dialysis twice a week with documented anaemia, haemoglobin <10 gm%. The enrolled patient must not receive any erythropoietin injections /blood transfusions in past one month at the time of enrolment. All 46 patients were given erythropoietin [EPOFIT] manufactured by INTAS pharmaceuticals by subcutaneous route.

Dosage and period of administration

The dosage was calculated as per the body weight and a starting dose of approximately 50 IU/kg/dose was administered. If haemoglobin increased by ≥ 2.5 g/dl in 4 weeks, the recombinant human erythropoietin dose was reduced by 25 units/kg. If haemoglobin value did not increase significantly during the first four weeks (≤ 1 g/dl), the dose was increased by 25 units/kg until the increment of haemoglobin was as per the target value. The maximum dose of 200 units / kg was not exceeded.

Prior to and during recombinant human erythropoietin therapy, the patients iron stores, including transferrin saturation and serum ferritin were evaluated regularly (transferrin saturation <20%, ferritin <100mng/ml) was found, supplemental iron was administered to increase or maintain transferrin saturation to adequate levels.

Statistical analysis

The statistical analysis was carried out with SPSS, version-19 software. All the data is presented as mean and standard deviation. All the parameters are analysed by Reaped ANOVA test. For statistical significance the probability value of less than 0.05 is considered.

Observation & results

In our study, a total of 46 patients of chronic kidney disease with end stage renal disease who were on maintenance haemodialysis twice weekly dialysis were enrolled during the period of October 2013 to September 2015 in MIMS COLLEGE Vizianagaram. Of them only 40 patients completed the study and rest of the 6 patients dropped out during the study.

Table:1 -Main characteristics

	Base Line	4 Weeks	8 Weeks	24 Weeks
Haemoglobin	6.7 ± 0.75 (46)	7.79 ±0.74 (40)	8.54 ± 0.79 (40)	11.55±0.74 (40)
Haematocrit (%)	20.29 ±2.8	21.50± 2.99	23.84± 3.38	31.11± 5.02
RBC millions/mm^3	2.49 ± 0.45	2.51± 0.59	2.60± 0.48	3.20± 0.71
Reticulocyte count	0.69 ± 0.77	0.87± 0.98	0.87± 0.98	1.10 ±0.67

TABLE 5: Male, female ratio according to age groups

Age (Years)	Male	Female	Total No
18-40	10	6	16
41-60	14	13	27

61-80	2	1	3

In All total 46 patients, were categorised in to 3 groups. Of them 27 patients are between 41 to 60 years,16 patients between 18-40 years, 3 are between 61-80 years.

Table 6: Changes of Hemoglobin

Follow up	No. of Cases	Hb(g/dl)	P- value
0 day	46	6.7 ± 0.756	
4 weeks	40	7.795 ± 0.748	<0.05
8 weeks	40	8.543 ± 0.799	<0.01
12 weeks	40	9.338± 0.669	<0.01
24 weeks	40	11.55± 0.749	<0.01

Of the study group, a total of 70% (28) patients had haemoglobin between 6 to 7 gm/dl with average mean of 6.7 ± 0.756 gm/dl at the time of enrolment. After 8 weeks therapy with 50 u/kg/dose of erythropoietin alfa, 77.5% (31) of patients documented a rise of haemoglobin >1.5 gm /dl from the baseline and the rest 22.5% (9) patients required increased dose of erythropoietin (75u/kg) to reach the target haemoglobin in the following study period.

Table 7: Changes of reticulocyte count

Follow up (Weeks)	No. of Cases	Reticulocyte Count %	P- value
0 day	46	1.010 ± 0.712	
4 weeks	40	1.120± 0.542	<0.05
8 weeks	40	1.34 ± 0.624	<0.041
12 weeks	40	1.831 ± 0.412	<0.035
24 weeks	40	2.08 ±0.678	<0.016

Table 8: Changes of hematocrit

Follow up (Weeks)	No. of Cases	HCT %	P- value
0 day	46	22.20 ± 2.759	
4 weeks	40	24.50± 2.993	<0.05*
8 weeks	40	26.84± 2.381	<0.01*
12 weeks	40	30.29± 1.702	<0.01*
24 weeks	40	33.00± 2.742	<0.01*

Table 9: Changes in RBC count

Follow up (Weeks)	No. of Cases	RBC Million/cu mm	P- value
0 day	46	2.468 ± 0.420	
4 weeks	40	2.521± 0.592	<0.04*
8 weeks	40	2.960± 0.484	<0.05*
12 weeks	40	3.144± 0.683	<0.01*
24 weeks	40	4.345± 0.623	<0.01*

Table 10: Quality of life

Kidney Disease Questionnaire	Score		P- value
	Before	After	
1.Physical	2.5±1.06	5.1±1.85	**0.0001***
2.Fatigue	3.0±1.80	5.6±1.26	**0.0001***
3.Relationship	2.9±1.64	5.7±1.89	**0.0001***
4.Depression	2.5±1.83	5.6±1.96	**0.018***
5.Frustration	2.07±1.64	6.3±2.64	**0.0001***

All the patients in the study had poor quality of life score in physical activity, fatigability, depression, relationship and low mood levels before the start of study mean of 2.5±1.06 but after therapy with erythropoietin alfa at 24 weeks all the 40 patients showed significant improvement in QOL with mean 5.1±1.85.

Table 11: Changes of systolic and diastolic blood pressure

Follow up (Weeks)	No. of Cases	SBP MmHg	DBP mmHg
0 day	46	121.54± 23.04	86.55± 14.89
4 weeks	40	124.30± 21.34	89.76± 12.02
8 weeks	40	138.94 ± 22.09	90.29± 10.10
12 weeks	40	141.94± 12.22	91.65 ± 11.80
24 weeks	40	146.34 ± 10.78	94.71± 13.09
P-value		**0.0001***	**0.0001***

***- Significance**

Adverse effects

A total of seven different type of adverse events are noted in study population, among them hypertension was recorded in 9 patients, headache in 2, seizure in 1, pain at injection site in 8, clotting of AV fistula, allergic reactions in 3 patients, respectively.

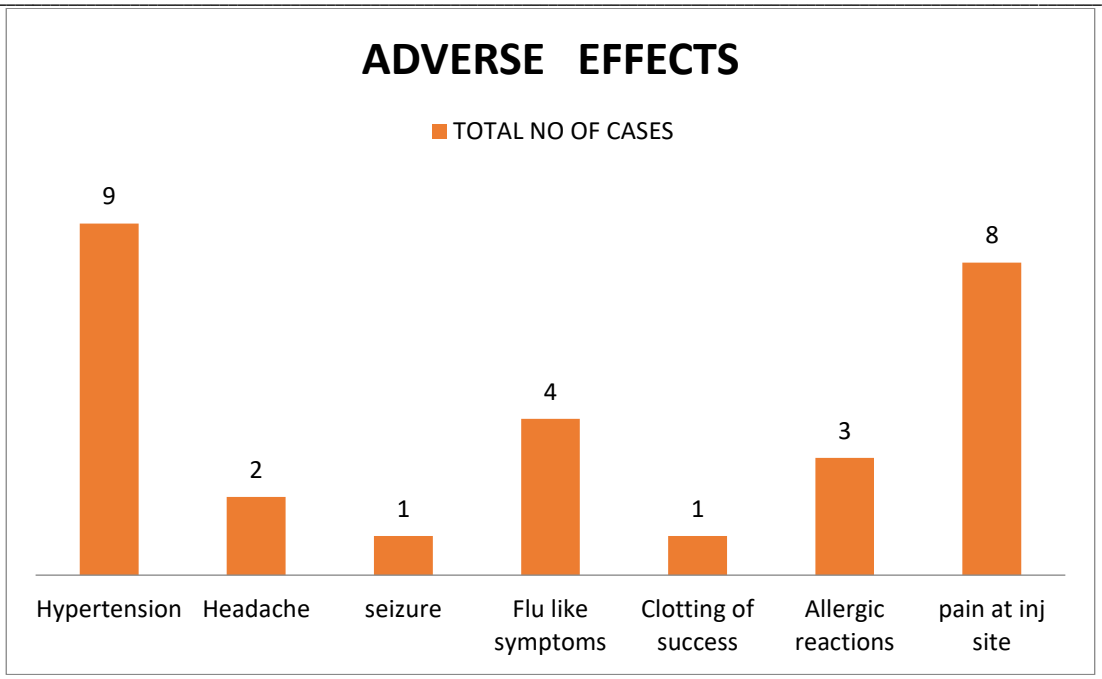

Fig. 1: Adverse effects

Discussion

Effective anaemia management is an essential component for the treatment of patients with CKD. Prior to the availability of recombinant erythropoietin, patients were subjected to repeated blood transfusions and generally remained profoundly anaemic. The advent of recombinant erythropoietin has revolutionized anaemia management in CKD patients.

Of the total 46 patients enrolled in the study, 31 patients required only regular conventional dose of 50 units /kg /dose and only 9 patients required incremental dose of erythropoietin 75 units/kg to achieve target haemoglobin level. In our study Haemoglobin increased progressively in 77% patients at 4 weeks and 23% patients at the end of 12 weeks. This result was in accordance with study (88%) done by Sanjay Agarwal et al in 2006[8], Eschbach JW et al[9].

Hypertension was a common side effect seen in 22.5%[9] patients in the study group and seizure in 2.5%[1]. In accordance, the CHOIR study by Singh et al. Which randomized non–dialysis-dependent CKD to once-weekly epoetin to achieve a target Hb concentration of 13.5 g/dl versus a target Hb concentration of 11.3 g/dl. The authors found that patients randomized to the higher Hb concentration had an increased risk of death, myocardial infarction, hospitalization for congestive heart failure, and stroke[10].

Similarly, in the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) trail also showed that 31.4% had high risk in reaching endpoint like stroke, MI, death[11].

References

1. Kalantari –Zadeh K arnoff GR .Hemoglobin variability in anemia of chronic kidney diseases. J Am Soc Nephrol. 2009;20:479.
2. Evans RG, Gardiner BS, Smith DW, et al. Intrarenal oxygenation: unique challenges and the biophysical basis o homeostasis. Am J Physiol Renal Physiol.2008;295: F1259.
3. Haase VH. Hypoxic regulation of erythropoiesis and iron metabolism. Am J Physiol Renal Physiol. 2010;299: F1.
4. Ng T, Marx G, Littlewood T, et al. Recombinant erythropoietin in clinical practice. Postgrad Med J. 2003;79: 367
5. Scho eld CJ, Ratcli e PJ. Oxygen sensing by HIF hydroxylases. Nat Rev Mol Cell Biol. 2004;5:343
6. Macdougall IC, Padhi D, Jang G: Pharmacology of darbepoetin alfa. Nephrol Dial Transplant 22[Suppl 4]: iv2–iv9, 2007
7. Effect of angiotensin converting enzyme inhibitors on erythropoietin concentrations in healthy volunteers**.** Br J Clin Pharmacol. 1992 Oct; 34(4): 363–365.
8. Sanjay K Agarwal, Sanjeev Saxena, Mita Nandy, Sanjay Gupta. Recombinant Human Erythropoietin in the Management of Anaemia in Chronic Kidney Disease Patients – An Indian Multicentre Experience.JIACM 2006;7(3):193-8.
9. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial**.** Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW, (N Engl J Med. 1990]
10. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators: Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 355: 2085–2098,2006.
11. Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT): Evolving the management of cardiovascular risk in patients with chronic kidney disease March 2005 Volume 149, Issue 3, Pages 408-413.

Conflict of Interest: Nil Source of support: Nil