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RECOMBINANT HUMAN ERYTHROPOIETIN IN THE MANAGEMENT OF ANEMIA IN CHRONIC KIDNEY DISEASE (NON-DIALYSIS) PATIENTS

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ABSTRACT
The present study was conducted to evaluate the efficacy of recombinant human erythropoietin (EPO-alpha) in the treatment of anemia in rural patients having stage-3 and stage-4 of Chronic Kidney Disease (CKD). Moreover To check the level RBCs, hemoglobin/haematocrit (markers of anaemia) and to evaluate patients on chronic kidney function tests. A descriptive observational cross-sectional study was conducted among 50 patients of anemia in chronic kidney disease in the Nephrology department of Shree Krishna Hospital, Karamsad. Cross sectional is a type of observational study that involves the analysis of data collected from the patients (before and after treatment). The present study included 50 patients as the total number of patients, out of which 18 were females and 32 were males. 92% patients had hypertension, 60% had diabetes mellitus. The average blood pressure is 138/83.68 mmHg and 73.80/min is pulse rate. After taking EPO-alpha, the hematological parameters were increased and significant clinical improvement was seen in chronic kidney disease patients. From present study, The hematological parameters (Hb, RBCs, Hct, % transferrin saturation, ferritin and TIBC) were increased and have significant clinical improvement after 3 months. Based on the results, treatment of recombinant human erythropoietin was helpful in the patients of anemia in CKD stage-3 and stage-4. They do not require blood transfusion. It shows that the role of EPO is important armamentarium for the management of anemia in CKD. In our study, we took 50 patients and all of them have CKD (non-dialysis).

KEYWORDS: Recombinant Human Erythropoietin, chronic kidney disease, anaemia.

INTRODUCTION
Chronic kidney disease[1] Chronic kidney disease is defined by a reduction in the glomerular filtration rate and/or urinary abnormalities or structural abnormalities of the renal tract.

Stages of CKD: The severity of chronic kidney disease is classified from 1 to 5 depending upon the level of glomerular filtration rate.

Complications Of CKD: Fluid retention, which could lead to swelling in your arms and legs, high blood pressure, or fluid in your lungs (pulmonary edema), Heart and blood vessel (cardiovascular) disease, Hyperkalaemia, Weak bones and an increased risk of bone fractures.

Anemia[1] The condition having lower than normal number of red blood cells or quantity of haemoglobin [<12 g/dL (female) or <13.5 g/dL (male)] and oxygen carrying capacity to tissues and organs throughout the body is known as anemia in chronic kidney disease.

Pathophysiology[1,5] When kidneys are diseased or damaged, they do not make enough erythropoietin (EPO). As a result, the bone marrow makes fewer red blood cells, causing anemia. Other common causes of anemia in people with kidney disease include blood loss from hemodialysis and low level of nutrients found in food. Decrease in RBCs, Hb or Hct level, Diminished O2 carrying capacity, Hypoxia and hypoxia induced effects on vital organ function.

Causes and Risk Factors[1] Blood loss**,** Lack of red blood cell production**,** High rates of red blood cell destruction**,** Diet**,** Hormones**,** Pregnancy.

Signs and Symptoms[1] Fatigue or feeling tired, Weakness**,** Headaches**,** Problems with concentration, Paleness**,** Dizziness, Difficulty in breathing or shortness of breath, Chest pain.

Diagnosis[4] A health care provider diagnoses anemia based on,
Markers of chronic kidney disease: Albuminuria (ACR≥30mg/g), Urine sediment abnormalities, Electrolyte and other abnormalities due to tubular

disorders, Abnormalities detected by histology, Structural abnormalities detected by imaging, History of kidney transplantation) and glomerular filtration rate.

Medical history: It is based on symptoms of the patients.

Physical examination: During a physical exam, a health care provider usually examines a patient's body including skin colour.

Hematological parameters: RBCs, Hb, Hct, MCHC, MCV, % transferrin saturation, ferritin, folate/B12.

Treatment and management[4] Iron supplements, Eating, Diet, and Nutrition, Vitamin B12 and Folic Acid Supplements, Red Blood Cell Transfusions.

Erythropoietin (EPO) is a hormone produced by the kidneys. EPO is the best treatment for the patient's anemia in CKD. It raise their red blood cell count to a level that will reduce the need for red blood cell transfusions.

Types of Erythropoietin

EPO-alfa is manufactured and marketed by Amgen under the trade name Epogen.

EPO-beta is a synthetic, recombinant form of erythropoietin, a protein that promotes the production of RBCs and trade name is Betapoietin.

Darbepoetin is a re-engineered form of erythropoietin containing 5 amino acid changes resulting in the creation of 2 new sites for N-linked carbohydrate addition and trade name is Aranesp.

MATERIALS AND METHODS

Study Design

The study was conducted at Nephrology department of Shree Krishna Hospital after getting approval of the research project from Institutional Ethics committee (IEC).

Study Population

Inclusion Criteria

1. Patient who is a known case of CKD which is based on renal tests.
2. Patients who had a baseline blood haemoglobin value of < 10.0 g/dl.
3. Patient who were medically stable with CKD in pre-dialysis period while undergoing therapy for at least 3months.

Exclusion Criteria

1. Patients with uncontrolled severe hypertension (systolic blood pressure persistently more than 160 mm Hg and/or diastolic blood pressure persistently greater than 100 mm Hg).
2. Patient with history and presence of malignancy.

Procedure of The Study

Pre Study: Initiation of Study- Selection of dissertation topic, Literature review, Protocol was prepared and submitted to IEC & approval from IEC was obtained.

During study: Demography, Medical history, and Physical examination were performed at screening, before initiating treatment with the test drug.

Haematological parameters: RBC, Haemoglobin, Haematocrit, MCV, MCHC, % Transferrin saturation, Ferritin and B12.

Measures of hypertension: Systolic blood pressure and Diastolic blood pressure.

Markers of chronic kidney disease: Albuminuria (ACR≥30mg/g), Urine sediment abnormalities, Electrolyte and other abnormalities due to tubular disorders, Abnormalities detected by histology, Structural abnormalities detected by imaging, History of kidney transplantation) and glomerular filtration rate.

After Study: Statistical analysis was done. Result and Conclusion was drawn from data obtained.

Statistical Analysis

Descriptive analysis was done depending on variable suitable as per respective formula and for independent samples T test was used to compare the data between patients.

RESULTS AND DISCUSSION

Total 50 patients of CKD were included in the study. Among of them, 64% (32) were males and 36% (18) were females.

Table 1: Patient characteristics and data.

CHARACTERISTIC	TOTAL NO. OF PATIENTS			PERCENTAGE
GENDER				
Male	32			64%
Female	18			36%
AGE				
<40	0			0%
41-60	25			50%
61-80	22			44%
>80	3			6%
MEDICAL HISTORY CKD	100			100%
Hypertension	46			92%
Diabetes mellitus	30			60%
Anemia	10			20%
PHYSICAL HISTORY		**AVERAGE**		
Blood pressure	50	138/83.68mmHg		100%
Pulse rate	44	73.80/min		88%
HEMATOLOGICAL PARAMETERS	**TOTAL NO.OF PATIENT**	**BEFORE TREATMENT (MEAN)**	**AFTER TREATMENT (MEAN)**	**P-VALUE**
Hb	46	10.16957	10.77848	*0.0043
RBC	37	3.68	4.133243	*0.0321
Hct	34	31.85882	33.82059	*0.0004
MCV	37	83.28405	86.46838	0.0581
MCHC	37	32.10838	31.91514	0.2202
%transferrin saturation	6	10.75	13.34	*0.0047
Ferritin	10	107.16	257.63	*0.00001
TIBC	10	124.4	196.1	*0.00001
MARKERS OF CKD	**TOTAL NO. OF PATIENT**	**BEFORE TREATMENT (MEAN)**	**AFTER TREATMENT (MEAN)**	**P-VALUE**
Creatinine	46	3.624783	3.730652	0.3656
Urea	24	85.66667	83.52083	0.7524
Protein	13	1.923077	1.769231	0.4363
Na+	30	135.5367	135.8933	0.7006
K+	43	4.766512	4.8	0.8041
Ca+2	17	2.135882	2.944706	0.1769
PO4-	8	3.845	3.74	0.7455

The majority 50% of patients were in the age range between 41-60 years, 44% of them were in the age range between 61- 80 years and 6% were in above 80 years.

Out of 50 patients of anemia in chronic kidney disease, 100% were CKD, 92% were HTN, 60% were Diabetes mellitus.

Physical history

Out of 50 patients of anemia in chronic kidney disease, 100% (138/83.68mmHg) were measures hypertension and 88%(73.80/min) were pulse rate.

Hematological parameters

The hematological parameters are increased and only MCHC were decreased. It shows that, there is significant clinical improvement.

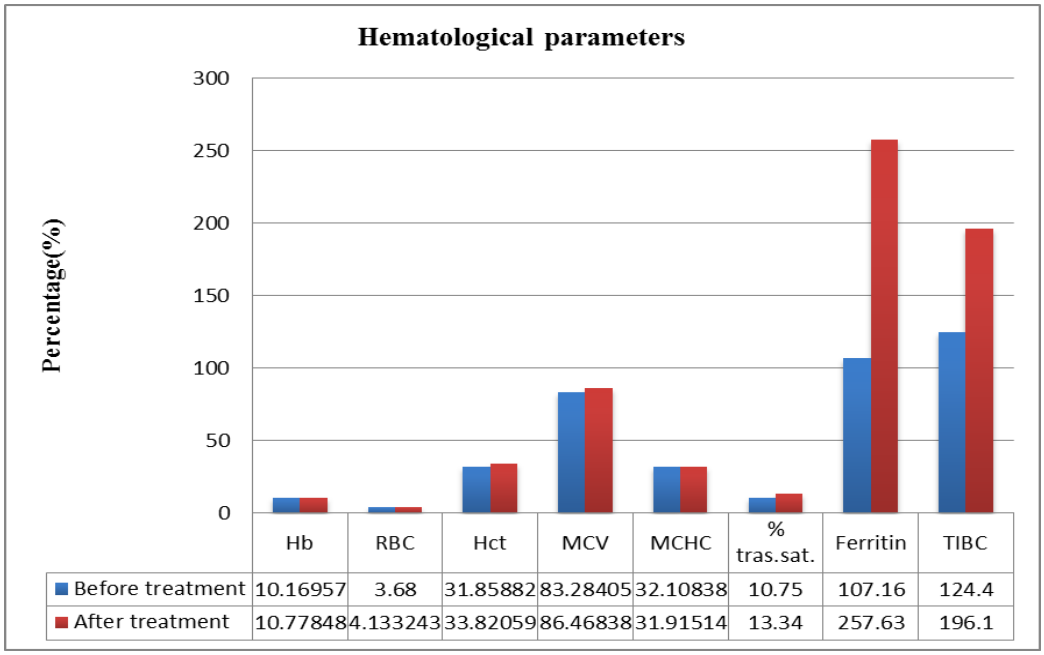

Fig. 1: Hematological Parameters.

Markers of chronic kidney disease

According to the data collection, the level of creatinine, Na+, K+ and Ca+2 were increases and the level of urea, protein and PO4- were decreases.

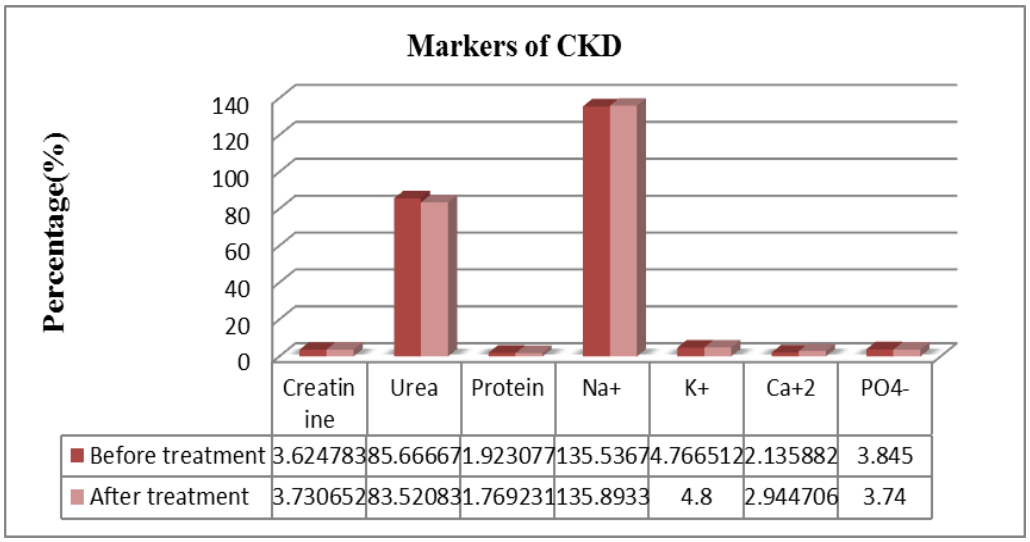

Fig. 2: Markers of chronic kidney disease.

In this study, majority of the patients belonged to the age group of 41-60 years and 61-80 years (50% and 44% respectively) and 6% are age group >80. According to age group, 41-60years peoples are more vulnerable to chronic kidney disease.

Out of 50 patients, 46 (92%) patients had hypertension and 30 (60%) had diabetes mellitus and 10(20%) had anemia. Based on medical history, majority of patients had hypertension and diabetes mellitus. The average blood pressure is 138/83.68 mmHg and 73.80/min is pulse rate. After giving EPO-alpha, the hematological parameters are increases and only MCHC is decreases. MCHC is an estimated of the amount of Hb in a given number of RBCs. It carries oxygen to the cells in the body from the lungs. It shows that RBCs do not have enough hemoglobin and production of hemoglobin decreases.

In this study, it has been observed that the MCHC is decreased in CKD ($P<0.0001$, highly significant). Primary cause of decrease MCHC in CKD is an iron rich protein and a lack of it may indicate anemia.

Hb level is also increase because RBCs production also increases. RBCs are also increase due to transport

oxygen from the lungs to tissues throughout the body. MCV is the complete blood count which is used for RBCs indices to help classify the cause of anemia based on red cell morphology.

% Transferrin saturation is increases and it is the value of serum iron divided by total iron-binding capacity. According to the result, % transferrin saturation is 13.34%, it means the value is normal. Before treatment the level of ferritin is 107.16 and after giving EPO, the level of ferritin is 257.63. It shows that the ferritin level is normal range and it is the cellular storage protein for iron. There is no effect in the body. TIBC is the capacity to bind iron with transferrin. The normal range of TIBC is 240-450 (mcg/dl) and the results of before treatment are 124.4 and after treatment are 196.1. It indicates that TIBC is low compared with normal range because the iron stores are elevated.

During the study it was observed that Hb, RBCs, Hct, MCV, % transferrin saturation, ferritin and TIBC values have shown an increase in their mean values in the second test when compared with their values in the first test which was done during the study period and showed statistically significant increase in their mean values.

During the study, out of 50 patients, 46 patients were observed creatinine and before treatment the mean value is 3.624783 and after giving drugs in the patients, the level of creatinine was increases (3.730652). It shows that waste product found in the blood and indicates kidney damage.

The level of Na+, K+ and Ca+2 was increases after treatment and the level Na+ and K+ are normal as compared with normal range, there is no effect in the body. The level of Ca+2 is too low from the normal range after giving drugs because it may cause hypocalcemia and problem with parathyroid glands, as well as from diet, kidney disorder and certain drugs.

Based on the results, the level of urea, protein and phosphorus are decreases after giving the drugs. The urea level also high due to kidneys are not working well and elevated nitrogen can also due to congestive heart failure and urinary tract obstruction.

The result of protein level also too low as compared with normal range. It shows that patients have liver disorder and protein are not digested or absorbed properly. According to results, phosphorus level is normal as compared with normal range and it is depends on age.

CONCLUSION

Treatment of recombinant human erythropoietin was helpful in the patients of anemia in CKD stage 3 and stage 4. They do not require blood transfusion. It shows that the role of EPO is important armamentarium for the management of anemia in CKD.

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