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COMPARATIVE STUDY ON SAFETY AND EFFICACY OF REGULAR ERYTHROPOIETIN AND EPOIETIN BETA METHOXY POLYETHYLENE GLYCOL IN HAEMODIALYSIS PATIENTS

***[1]Dr. Manjula K., Pharma.D, [2]Dr. K. Swapna, Pharma.D, [3]Dr. E. Trivikram, Pharma.D, [4]Dr. Aqueela Masood and [5]Tahmina Sultana**

[1,2,3]Bharat Institute of Technology-Pharmacy, Mangalpally, Ibrahimpatnam, Telangana 501510, India.

[4]Clinical Pharmacist, Olive Hospital,Nanal nagar, Telangana, 500028, India.

[5]Assistant Professor, Department of Pharmacology, Nizam Institute of Pharmacy, Deshmukhi (V), Pochampally (M), Behind Mount Opera, Yadadri Bhuvanagiri (Dist)-508284, Telangana, India.

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***Corresponding Author**
Dr. Manjula K.
Bharat Institute of Technology-Pharmacy, Mangalpally, Ibrahimpatnam, Telangana 501510, India.

ABSTRACT

Chronic kidney disease (CKD) is the 12th and 17th leading cause of death and disability globally, respectively. Almost 60% of the deaths worldwide are due to CKD and ~80% of deaths occur in low and middle income countries. The kidney cells that make erythropoietin are sensitive to low oxygen levels in the blood that travels through the kidney. These cells make and release erythropoietin when the oxygen level is too low. A low oxygen level may indicate a diminished number of red blood cells (anemia), or hemoglobin molecules that carry oxygen through the body. Anemia can happen early in the course of kidney disease and grow worse as kidney fail and can no longer produce Erythropoeitin. Anemia in CKD Patients is commonly treated with Erythropoietin stimulating agents (ESAs), Erythropoietin (Conventional &Pegylated), Epoietin beta methoxy polyethylene glycol, Epoietin (alpha & beta), Darbapoeitin. A total number of 60 Patients with CKD were screened out of which, 30 patients with Anaemia receiving Regular Erythropoietin were compared with another 30 patients receiving Mircera. Out of 30 patients receiving mircera 76.6% of patients using mircera were males and 23.3% were females. The past medical history of the patients were recorded and found that 93.3% were with HTN, 70% were with DM and 70% were having both HTN and DM. 40% of

patients receiving mircera were recorded without any ADR's. The increase in haemoglobin value was found to be 1.55 % in patients using erythropoietin with 37% of no ADR's recordance compared to the patients using mircera whose increase in haemoglobin was 2.1% with 50 % of no ADR recordance. The ADR's of 30 patients receiving erythropoietin are 37% of patients were of no ADR and 23% with fever 17% with nausea 10% cough 7% vomiting others diarrhea and dizziness 6.6%.The ADR's of 30 patients receiving mircera are 50% of patients were of no ADR and 13.3% with HTN 10% with diarrhea 10% headache 6.6% cough others URTI and nasopharyngitis 10%.

KEYWORDS:- Chronic Kidney Disease, Regular Erythropoietin, Epoietin Beta Methoxy Polyethylene Glycol, Haemodialysis.

INTRODUCTION

Chronic kidney disease (CKD) is the 12th and 17th leading cause of death and disability globally, respectively. The number of deaths due to chronic disease in India was around 5.21 million in 2008 and was expected to be 7.63 million by 2020. Almost 60% of the deaths worldwide are due to CKD and ~80% of deaths occur in low and middle income countries. In 2015, US has seen a 30% increase in the CKD. In India, diabetes and hypertension account for 40-60 % cases of CKD. In India, not many studies have been carried out to estimate the prevalence of CKD.[1] A study in 2013 says that 17% of the urban Indians have kidney disease. The study found that 64.5% of patients suffering from CKD and hypertension, 31.6% from diabetes and surprisingly individuals who were diagnosed with different stages of CKD.[2]

Pathogenesis of Kidney

Kidney disease is caused by other conditions that put a strain on the kidneys: Once half of the total nephrons are lost, CKD progresses similarly irrespect to etiology. Initial hyperfiltration activates renin angiotensin aldorsterone system and Causes proteinuria. Angiotensin-2 and protein uptake at the tubules causes inflammation and fibrosis of the glomerulus and tubules. Progress decline in GFR and systemic complications occur.

Complication of CKD

The complications of CKD include:

Anaemia: The two most common causes of anemia in people with kidney disease are:

1) Not having enough iron in body (called iron deficiency);

2) Not having enough of a hormone called erythropoietin (EPO).

Hyperphosphatemia: kidneys are responsible to keep the right amounts of phosphorus and calcium in body. When kidneys are not working, too much phosphorus can build up in blood.

High potassium: The extra potassium that is not used by the body gets excreted by the kidneys. In kidney damage, kidneys cannot remove the extra potassium in blood, Instead it travels through your kidneys and back into bloodstream leading to more and more potassium in blood causing hyperkalaemia.[3]

ANAEMIA

Anaemia commonly occurs in people with chronic kidney disease (CKD)—the permanent, partial loss of kidney functions. Anaemia might begin to develop in the early stages of CKD, when someone has 20 to 50 percent of normal kidney function. Anemia tends to worsen as CKD progresses. Most people, who have total loss of kidney function, or kidney failure, have anaemia.

World Health Organization (WHO) criteria for anemia in men and women are <13 and <12g/dL, respectively.

Correlation of Anaemia and CKD

Anaemia might begin to develop in the early stages of CKD, when someone has 20 to 50 % of normal kidney function. Anaemia tends to worsen as CKD progresses. Most people, who have total loss of kidney function, or kidney failure, have anaemia. A hormone is a chemical produced by the body and released into the blood to help trigger or regulate particular body functions. EPO prompts the bone marrow to make red blood cells, which then carry oxygen throughout the body.

Causes of anaemia in chronic kidney disease

When kidneys are diseased or damaged, they do not make enough EPO. As a result, the bone marrow makes fewer red blood cells, causing anaemia. When blood has fewer red blood cells, it deprives the body of the oxygen it needs.[4]

ERYTHROPOIETIN STIMULATING AGENTS

1) Anaemia is a disorder that occurs when there is not enough hemoglobin in a person's blood. There are several different causes of anemia. For instance, anemia can be caused

by the body's inability to produce enough EPO to make red blood cells. If this is the case, the person may have to have a blood transfusion to treat anemia.

Recombinant Erythropoietin

1) In cases where transfusions are not an option—for example, when the patient cannot have, or refuses, a transfusion—it may be necessary to give the patient recombinant erythropoietin. Recombinant erythropoietin is a man-made version of natural erythropoietin. It is produced by cloning the gene for erythropoietin.
2) Recombinant erythropoietin drugs are known as erythropoietin-stimulating agents (ESAs). These drugs are given by injection (shot) and work by stimulating the production of more red blood cells. These cells are then released from the bone marrow into the bloodstream.

Mechanism of action of erythropoiesis

Erythropoietin (EPO) interacts directly with the EPO receptor on the red blood cell (RBC) surface, triggering activation of several signal transduction pathways, resulting in the proliferation and terminal differentiation of erythroid precursor cells and providing protection from RBC precursor apoptosis.[5,6]

Need for the study

Erythropoietin (EPO) is a hormone produced by the kidney that promotes the formation of red blood cells by the bone marrow. The kidney cells that make erythropoietin are sensitive to low oxygen levels in the blood that travels through the kidney. These cells make and release erythropoietin when the oxygen level is too low. A low oxygen level may indicate a diminished number of red blood cells (anemia), or hemoglobin molecules that carry oxygen through the body. Anemia can happen early in the course of kidney disease and grow worse as kidney fail and can no longer produce EPO.

Anemia in CKD Patients is commonly treated with:

Erythropoietin stimulating agents (ESAs)

1) Erythropoietin (Conventional &Pegylated)
2) Epoietin beta methoxy polyethylene glycol
3) Epoietin (alpha & beta)
4) Darbapoeitin

STATISTICAL ANALYSIS

Results are presented as mean ± S.D. The demographic and other baseline characteristics of the patients (e.g. age, gender, etc) are summarized.Change from baseline war calculated for haemoglobin Whenever change from baseline was calculated, only those patients for whom baseline and post- treatment assessment (at 3 months) are available were included in the analysis.Mean was used to compare the baseline and post-treatment values for each variable. Adverse events experienced by the patients during the course of the study were appropriately summarized.

RESULTS

Out of 30 patients receiving erythropoietin 53.3% are male 46.6% are female out of which the past medical history of patients were recorded and found that 86.6 % were with HTN, 60% were with DM and 53.3 % were having both HTN and DM. 37 % of patients receiving erythropoietin were recorded without any ADR's.(Table-1). Out of 30 patients receiving mircera 76.6% of patients using mircera were males and 23.3% were females. The past medical history of the patients were recorded and found that 93.3% were with HTN,70% were with DM and 70% were having both HTN and DM. 40% of patients receiving mircera were recorded without any ADR's.(Table-2). The ADR's of 30 patients receiving erythropoietin are 37% of patients were of no ADR and 23% with fever 17% with nausea 10% cough 7% vomiting others diarrhea and dizziness 6.6%.(Table-3)

The ADR's of 30 patients receiving mircera are 50% of patients were of no ADR and 13.3% with HTN 10% with diarrhea 10% headache 6.6% cough others URTI and nasopharyngitis 10%.(Table-4)

Table-1: Demographic and baseline characteristics of the patients receiving regular erythropoietin.

PARAMETERS		**MEAN ± S.D**
AGE		58.2±11.4
MALE		16 (53.3%)
FEMALE		14 (46.6%)
PAST MEDICAL HISTORY	HYPERTENSION	26 (86.6%)
	DIABETES	18 (60.0%)
	HYPERTENSION AND DIABETES	16 (53.3%)
	HAEMOGLOBIN	10.2±1.74

Table-2: Demographic and baseline characteristics of the patients receiving Mircera.

PARAMETERS		MEAN ± S.D
AGE		58.2±11.4
MALE		16 (53.3%)
FEMALE		14 (46.6%)
PAST MEDICAL HISTORY	HYPERTENSION	26 (86.6%)
	DIABETES	18 (60.0%)
	HYPERTENSION AND DIABETES	16 (53.3%)
	HAEMOGLOBIN	10.2±1.74

Haemoglobin value

At base line Haemoglobin value was 10.2±1.74 in patients receiving Regular Erythropoietin and at the end of 3 months it's value is 10.6±1.51.

At base line Haemoglobin value was 10.1± 1.93 in patients receiving Mircera and at the end of 3 months it's value is 10.7±1.7.

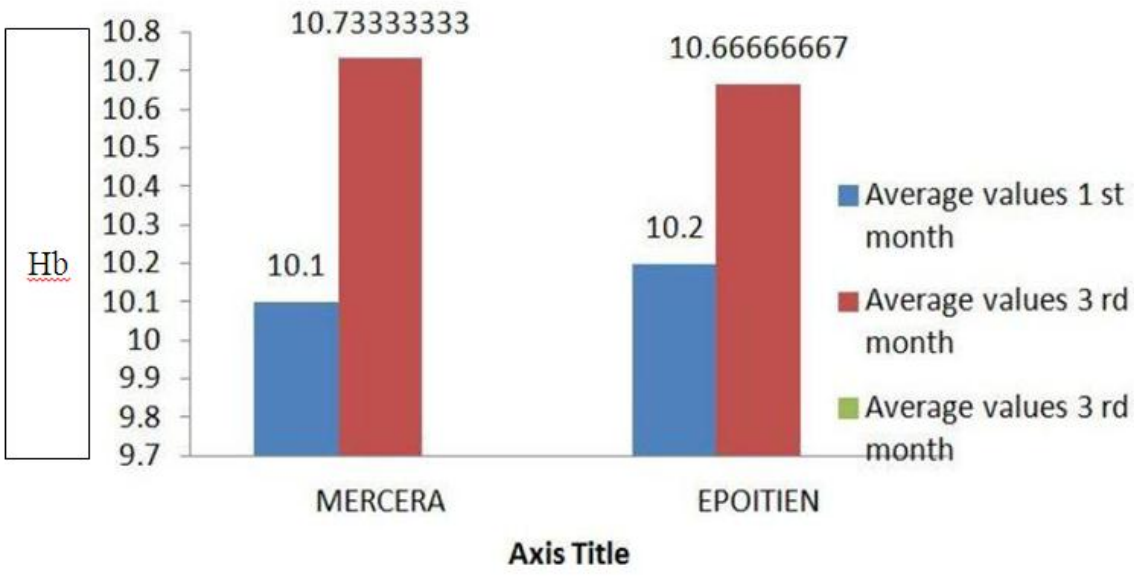

Fig. 1: Hb v/s Mircera and epoitin.

The ADR's observed during the study in patients receiving Regular Erythropoietin are figured in the below Table:3.

ADVERSE DRUG REACTIONS	NO OF PATIENTS
NO ADR'S	11 (37%)
FEVER	7 (23%)
NAUSEA	5 (16.66%)
COUGH	3 (10%)
VOMITING	2 (6.6%)

OTHERS: DIARRHOEA DIZZINESS	1 (6.6%) 1

REGULAR ERYTHROPOEITIN

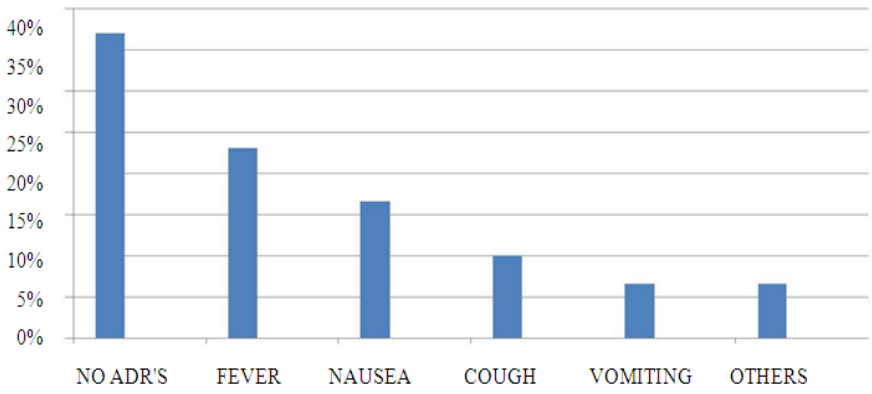

Fig. 2: Regular Erythropoeitin v/s Adverse drug reaction.

The ADR's observed during the study in patients receiving Mircera are figured in the below Table-4.

ADVERSE DRUG REACTIONS	NO OF PATIENTS
NO ADR'S	15 (50%)
HYPERTENSION	4 (13.33%)
DIAHORREA	3 (10%)
HEADACHE	3 (10%)
COUGH	2 (6.6%)
OTHERS: URTI NASOPHARYNGITIS	2 (10%) 1

MIRCERA

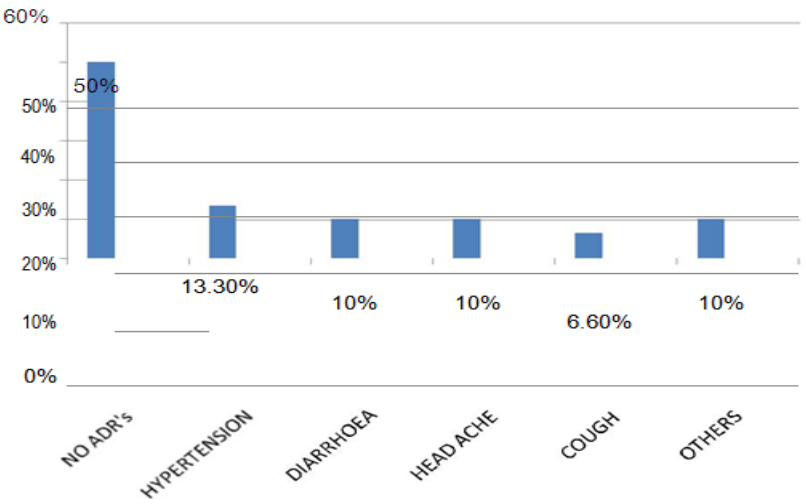

Fig. 3: Mircera v/s Adverse drug reaction and no ADR.

Patient Compliance

Patient characteristics	Patients	
	Erythropoietin	Mircera
Feeling Well	20 (66.6%)	24(80%)
Injection site pain	10(33.3%)	8(26.6%)
Injection site rash	5(16.6%)	4(13.3%)

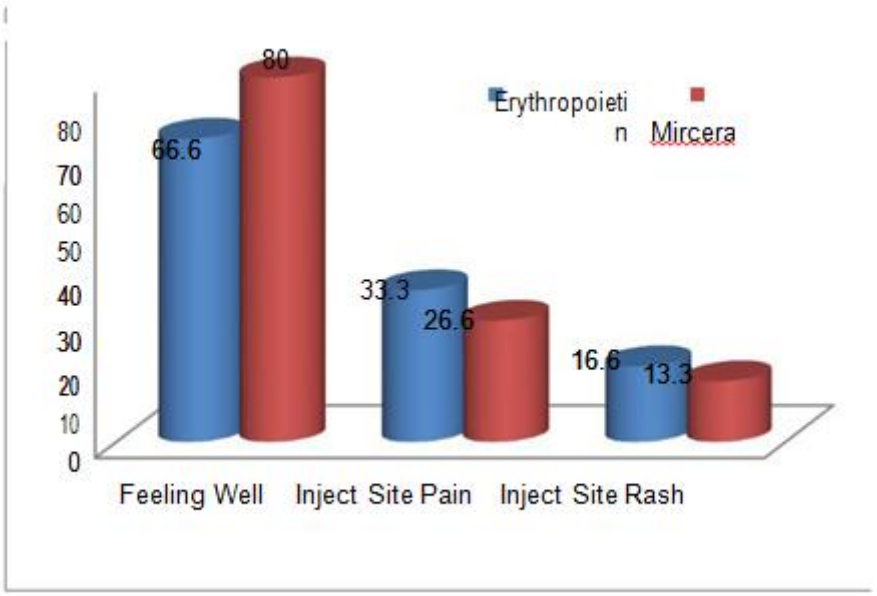

Fig. 4: Erythropoietin and Mircera Patient Compliance.

DISCUSSION

CKD is a major problem and its prevalence will continue to raise with increasing elderly population and the number of patients with diabetes, HTN. Prevalence of CKD is increasing in India. In our study, a total no. of 60 patients were enrolled of which 30 received inj Regular Erythropoietin 6000 IU once in a week and another 30 receive inj methoxy polyethylene glycol 100mcg twice a month.Patients received these drugs for 3 months to achieve significant increase in anaemia. Parameters such as haemoglobin, creatinine, iron are included in the study. This study was assessed statistically by using, mean ± standard deviation. Significant increase in haemoglobin shows the reduction of anaemia. After 3months of treatment with ESAs treatment haemoglobin was increased.

CONCLUSION

This study highlights the comparision of safety and efficacy of Regular Erythropoietin and Mircera in anaemic patients with CKD undergoing haemodialysis. The increase in haemoglobin value was found to be 1.55 % in patients using erythropoietin with 37% of no

ADR's recordance compared to the patients using mircera whose increase in haemoglobin was 2.1% with 50 % of no ADR recordance. In patient compliance study 66.6% of the patients receiving Erythropoietin were feeling well after taking the medication with 33.3% of them having injection site pain and 16.6% of them having injection site rash. In patients receiving Mircera 80% of the patients were feeling well after taking the medication with 26.6% of them having injection site pain and 13.3%of them having rash at injection site.

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