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Comparison of Erythropoietin and Darbepoetin in Chronic Kidney Disease Patients in a Tertiary Care Hospital

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ABSTRACT

Chronic kidney disease (CKD), is a progressive loss of kidney function over several months to years and cause complications like anaemia. Erythropoiesis stimulating agents (ESAs) such as erythropoietin and darbepoetin are widely used as a first-line treatment for the management of renal anaemia in CKD patients. Treatment of anaemia with ESAs could reduce the need for red blood cell transfusion and improve outcome and quality of life (QOL). The objective of this study is to compare the effect of erythropoietin and darbepoetin by measuring serum haemoglobin and creatinine in CKD patients. It concluded after statistical analysis darbepoetin is more effective in increasing haemoglobin and reducing creatinine levels than erythropoietin in a mean difference. Darbepoetin is a unique erythropoietic agent with an approximately threefold longer half-life than erythropoietin, allowing less frequent dosing than erythropoietin.

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INTRODUCTION

Chronic kidney disease (CKD), also known as chronic renal disease, is progressive loss in kidney function characterized by gradual replacement of normal kidney architecture with interstitial fibrosis over a period of months or years. The most common recognized cause of CKD is Diabetes mellitus. Others include hypertension, glomerulonephritis, congenital abnormalities and idiopathic. Swelling, uremia, high BP, drowsiness, fatigue, chest pain, itching etc are common symptoms of CKD. Anaemia is associated with worsening of cardiovascular morbidity and is an independent predictor of mortality in patients with chronic kidney disease (CKD). Anemia is a condition in which the body has fewer red blood cells than normal. Red blood cells carry oxygen to tissues and organs throughout the body and enable them to use energy from food. With anemia, red blood cells carry less oxygen to tissues and organs—particularly the heart and brain—and those tissues and organs may not function as well as they should. Anemia commonly occurs in people with chronic kidney disease (CKD)—the permanent, partial loss of kidney function. Anemia 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 anemia. Healthy kidneys produce a hormone called erythropoietin (EPO). This 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. When kidneys are diseased or damaged, they do not make enough Erythropoeitin. As a result, the bone marrow makes fewer red blood cells, causing anemia. When blood has fewer red blood cells, it deprives the body of the oxygen it needs. In anaemic CKD, Haemoglobin (Hb) levels are decreased and if blood tests indicate kidney disease as the most likely cause of anemia, hence treatment with erythropoietin and darbepoetin done to bring it to normal ranges.

Patients who receive EPO should have regular blood tests to monitor their hemoglobin so the health care provider can adjust the EPO dose when the level is too high or too low.Health care providers should discuss the benefits and risks of EPO with their patients.

Many people with kidney disease need iron supplements and EPO to raise their red blood cell count to a level that will reduce the need for red blood cell transfusions. In some people, iron supplements and EPO will improve the symptoms of anemia.

The objectives of this stuy is to estimate the effect of erythropoietin and darbepoetin on serum Haemoglobin and creatinine in CKD patients in a tertiary care hospital with comparing the side effect profile and to determine medication adherence in CKD patients using MMAS-4.

REVIEW OF LITERATURES

1**. Jeffrey Patton**[1] ***et al*** ;(2004)conducted a study on "Effectiveness of Darbepoetin Alfa Versus Epoetin Alfa in Patients with Chemotherapy Induced Anemia Treated in Clinical Practice" .The objective of this retrospective observational cohort study was to compare the effectiveness of darbepoetin alfa with that of epoetin alfa in patients with chemotherapy-induced anemia using data from non-contemporaneous chart audits conducted at a community-based oncology practice.For the first chart audit, data were collected from consecutive patients with nonmyeloid malignancies with diagnoses of chemotherapy-induced anemia and hemoglobin levels ≤10.5 g/dl who were receiving concurrent chemotherapy and had at least 5 weeksof visits from July-September 2000. After therapeutic substitution of darbepoetin alfa for epoetin alfa for all patients with chemotherapy-induced anemia, data were collected from consecutive darbepoetin alfa-treated patients with diagnoses of chemotherapy-induced anemia and at least 8 weeks of visits from June-October 2002 (darbepoetin alfa was approved in July 2002). The results of the study shows Darbepoetin alfa, 100 µg once weekly or 200 µg every 2 weeks,appears to be as effective as epoetin alfa, 40,000 U once weekly, for the treatment of chemotherapy-induced anemia in the clinical practice setting. The mean change in hemoglobin level was 1.1 g/dl for the darbepoetin alfa patient group and 1.0g/dl for the epoetin alfa patient group.

2**. Wanic Kossowska**[3]**M.*et al***; (2010) conducted a study on "Results of anemia treatment with darbepoetin alfa and erythropoietin beta in patients with chronic kidney disease". The aim of study was to analyze the results of anemia treatment with darbepoetin alfa and erythropoietin beta in patients with chronic kidney disease (3,5stage of CKD) in predialysis period. In the study were analyzed 35 and 20 patients during 11 months,and also measured blood pressure.During 11 months of observation blood pressure was not changed but a creatinine serum level was stable in females and increased in males. Erythropoietin beta was well tolerated and injection pain was smaller compared to darbepoetin alfa.

3**. John Glaspy**[4] ***et al***;(2006)conducted a study on "Randomized Comparison of Every-2-Week Darbepoetin Alfa and Weekly Epoetin Alfa for the Treatment of Chemotherapy-Induced Anemia". This non inferiority study systematically compares efficacy and safety of DA and EA using common doses and schedules used in clinical practice. Of 1,220 patients randomly assigned, 1,209 received greater than or equal to one dose of the study drug. Patients were randomly assigned 1:1 to DA 200 micro gram every two weeks (Q2W) or EA 40,000 units every week (QW) for up to 16 weeks with identical dose adjustment rules. This large, phase III study demonstrates comparable efficacy of DA Q2W and EA QW. Less frequent dosing offers potential benefits for patients, caregivers and health care providers.

4**. Can C**[5] ***et al***;(2013)conducted a study on "Comparison of recombinant human erythropoietin and darbepoetin alpha in children". The aim was to compare the clinical efficacy of recombinant human erythropoietin (rHuEPO) and darbepoetin alpha (DA) in the treatment of anemia in children with chronic kidney disease (CKD). Thirty four (13 female, 21 male) CKD patients were enrolled in the study. Mean age was11.42 ± 4.05 years. Nine patients were on hemodialysis, 18 were on peritoneal dialysis and seven patients were in CKD stage 4. Seventeen patients received rHuEPO and the remaining 17 patients received DA. Hemoglobin (Hb) was not significantly different between the two groups during monthly follow up and at the end of 6 months ($P > 0.05$), but there was a significant increase within each group at the end of 6 months ($P = 0.01$ for rHuEPO; $P = 0.02$ for DA). Hb was not different between the patients on and not on dialysis in both groups at the end of the study ($P > 0.05$). The efficacy of the s.c. and i.v.routes was similar within each group ($P > 0.05$). Systolic hypertension was observed in only one patient in the DA group, no other adverse effect was observed in either groups. Result shows that DA is a reasonable alternative to rHuEPO in the treatment of anemia in pediatric CKD patients, due to its clinical efficacy, convenience of use, patient compliance and tolerability.

5**. Voils A**[6] ***et al*;**(2007) conducted a study on "Comparison of darbepoetin alfa and epoetin alfa in the management of anemia of critical illness". It was a retrospective, descriptive study conducted on intensive care unit with seventy-two patients who spent at least 3 days in the cardio-thoracic, medical, or surgery-trauma intensive care units and received at least one weekly dose of epoetin alfa 40,000 units (33 patients) or darbepoetin alfa 100 µg (39 patients). Number of epoetin alfa and darbepoetin alfa doses, hemoglobin concentrations, and cumulative number of transfusions were recorded for up to 28 days after the first dose was

given, and the data were statistically analyzed. Patients receiving darbepoetin alfa 100 micro μg/week and those receiving epoetin alfa 40,000 units/week for anemia of critical illness achieved similar rates of transfusion independence and increases in hemoglobin concentrations from baseline at 28 days. Compared with previously published studies, erythropoietic agents were administered late in the course of critical illness in response to low hemoglobin concentrations**.**

MATERIALS AND METHODS

This prospective comparative experimental study was conducted in the department of Nephrology, Pushpagiri Medical College, Thiruvalla and Pushpagiri Pharmacy College, Thiruvalla to find out the Comparison of erythropoietin and darbepoetin in chronic kidney disease patients in a tertiary care hospital. In 6 months study, a total of 60 CKD patients with anaemia were enrolled as per inclusion and exclusion criteria from IP and OP department of Nephrology, Pushpagiri Medical College. In which 30 patients were upon Erythropoietin and other 30 patients on Darbepoetin. Inclusion Criteria were both male and female patients,patients on age group above 18 years ,both OP & IP patients, patients diagnosed as CKD based on radiological and biochemical parameters,patients with Hb less than 10 gm/dl. Exclusion Criteria were patients on dialysis/End Stage Renal Disease, patients undergone kidney transplantation, patients taking any Bone Marrow suppression medicine, patients with other diagnosed cause of anaemia, patients with evidence of ongoing chronic blood loss, patients who are not taking either Erythropietin or Darbepoetin in 1 month, patients who are not willing to participate in the study. Patient's demographic details were collected, residual blood sample were analysed for finding Haemoglobin and creatinine using semi auto analyser. Medication adherence was assessed using MMAS 4 (Morisky Medication Adherence Scale). Side effect profile were analysed by interacting with patients.

STATISTICAL ANALYSIS

All statistical analysis were performed by using SPSS software. Mean and standard deviation were used for the variables of the study. A various test like ANOVA, chi-square test were used. The significant association between the variables under consideration were found out if the p-value is less than 0.05.

RESULTS AND DISCUSSION

In 6 months study, a total of 60 CKD patients with anaemia were enrolled as per inclusion and exclusion criteria from IP and OP department of Nephrology, Pushpagiri Medical College. In which 30 patients were upon Erythropoietin and other 30 patients on Darbepoetin.

DEMOGRAPHIC DETAILS

4.1. AGE CATEGORIZATION

TABLE 1: DISTRIBUTION OF PATIENTS BASED ON AGE

Age groups	ERYTHROPOIETIN	DARBEPOETIN	Total
< 50	8	2	10
	26.7%	6.7%	16.7%
50 – 60	5	5	10
	16.7%	16.7%	16.7%
61 – 70	5	15	20
	16.7%	50.0%	33.3%
> 70	12	8	20
	40.0%	26.7%	33.3%
Total	**30**	**30**	**60**
	100.0%	**100.0%**	**100.0%**

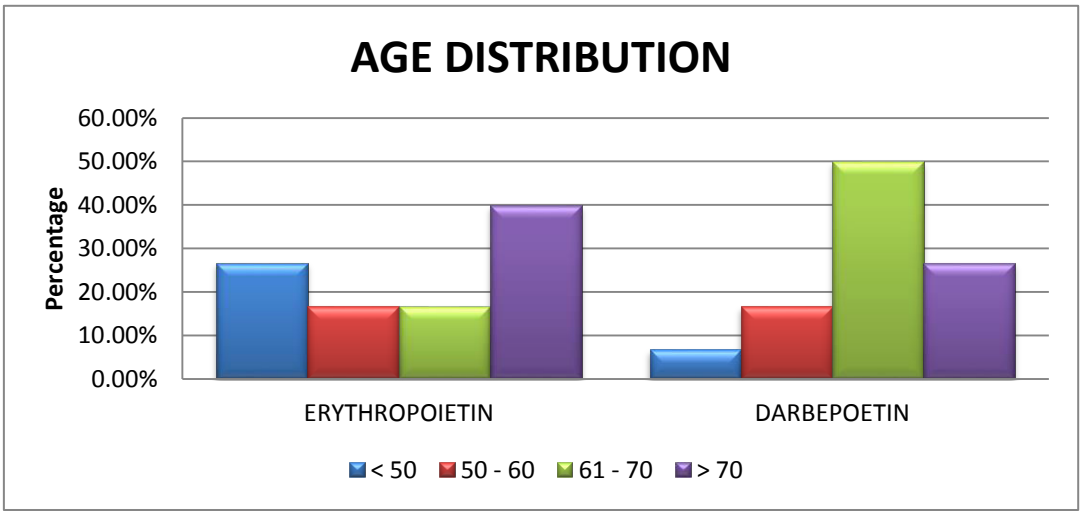


FIGURE 1: DISTRIBUTION OF PATIENTS BASED ON AGE

The study population belongs to 30-78 age group and the mean age is 62.12 years (59.6 for Erythropoietin and 64.63 for Darbepoetin in years).

4.2. GENDER

TABLE 2: DISTRIBUTION OF PATIENTS BASED ON GENDER

Gender	ERYTHROPOIETIN	DARBEPOETIN	Total
Male	16	23	39
	53.3%	76.7%	65.0%
Female	14	7	21
	46.7%	23.3%	35.0%
Total	**30**	**30**	**60**
	100.0%	**100.0%**	**100.0%**

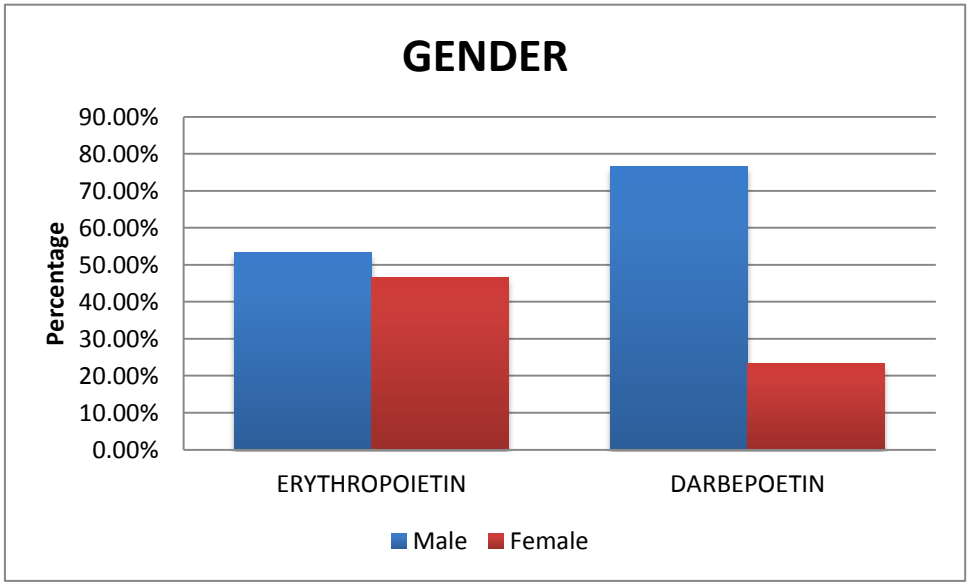


FIGURE 2: DISTRIBUTION OF PATIENTS BASED ON GENDER

In this study out of 30 patients under Erythropoietin therapy 53.3% are males and 46.7% are females. Other 30 Patients under Darbepoetin 76.7% are males and 23.3% are females.

4.3. FAMILY HISTORY OF CHRONIC KIDNEY DISEASE

TABLE 3: DISTRIBUTION OF PATIENTS BASED ON FAMILY HISTORY OF CHRONIC KIDNEY DISEASE

FAMILY HISTORY OF CKD	ERYTHROPOIETIN	DARBEPOETIN	Total
Yes	13	6	19
	43.3%	20.0%	31.7%
No	17	24	41
	56.7%	80.0%	68.3%
Total	**30**	**30**	**60**
	100.0%	**100.0%**	**100.0%**

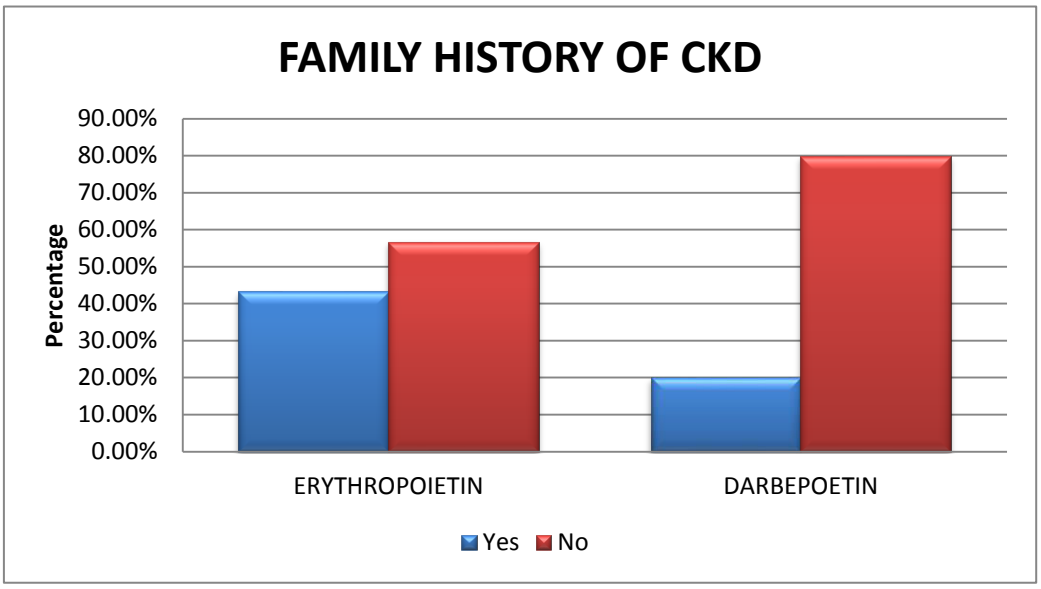


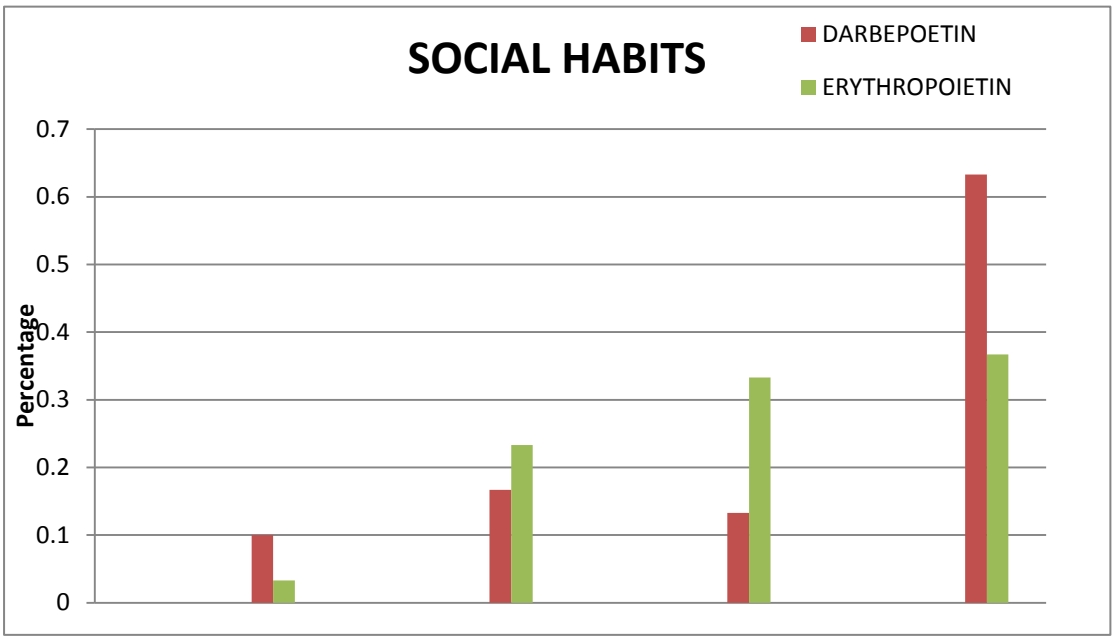
FIGURE 3: DISTRIBUTION OF PATIENTS BASED ON FAMILY HISTORY OF CHRONIC KIDNEY DISEASE

In the study population 43.3% upon erythropoietin and 20.0% on darbepoetin have family history of CKD. Remaining 56.7% on erythropoietin and 80.0% on darbepoetin shows no family history.

4.4 SOCIAL HABITS,

TABLE 4: DISTRIBUTION OF PATIENTS BASED ON SOCIAL HABITS

Social Habits	DARBEPOETIN	ERYTHROPOIETIN	Total
Smoking	3	1	4
	10.0%	3.3%	6.7%
Alcoholic	5	7	12
	16.7%	23.3%	20.0%
Alcoholic and smoking	4	10	14
	13.3%	33.3%	23.3%
Nil	19	11	30
	63.3%	36.7%	50.0%
Total	30	30	60
	100.0%	100.0%	100.0%



FIQURE 4: DISTRIBUTION OF PATIENTS BASED ON SOCIAL HABITS

Patients on Darbepoetin therapy 10.0% with smoking, 16.7% with alcoholic and 13.3% with both habits. But 63.3% patients shows no habits.

Patients on Erythropoietin therapy 3.3% with smoking, 23.3% with alcoholic and 33.3% with both the habits. But 36.7% shows no habits.

4.5 SIDE EFFECTS

TABLE 5: DISTRIBUTION OF PATIENTS BASED ON SIDE EFFECTS

SIDE EFFECTS	DARBEPOETIN	ERYTHROPOIETIN	Total
Myalgia	1	2	3
	3.3%	6.7%	5.0%
Hypertension	2	4	6
	6.7%	13.3%	10.0%
Headache	3	1	4
	10.0%	3.3%	6.7%
Nil	24	23	47
	80.0%	76.7%	78.3%
Total	**30**	**30**	**60**
	100.0%	**100.0%**	**100.0%**

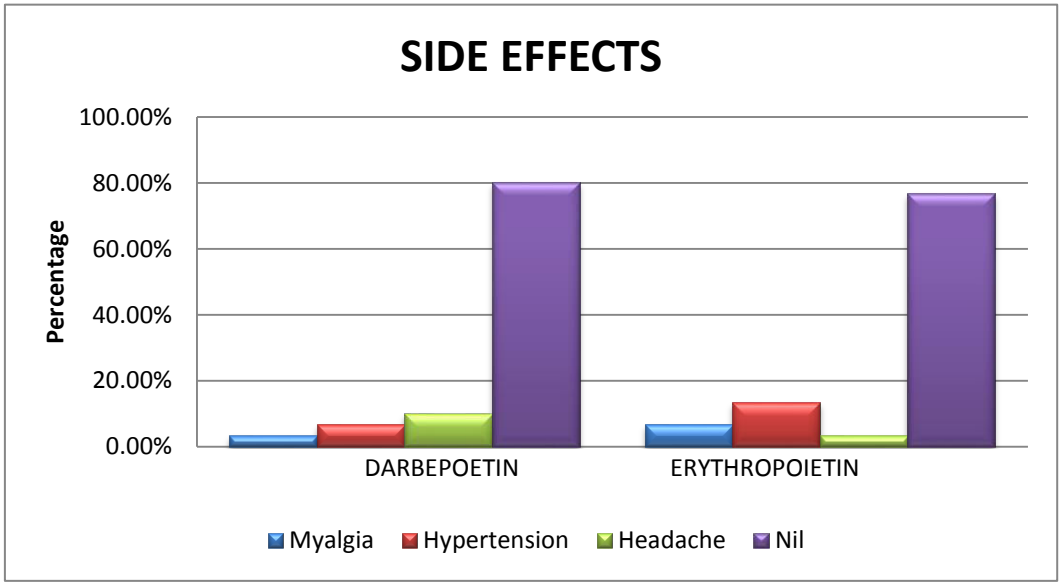


FIGURE 5: DISTRIBUTION OF PATIENTS BASED ON SIDE EFFECTS

Out of 30 patients on Darbepoetin, Myalgia was seen in 3.3%, Hypertension in 6.7% and 10.0% with Headache.

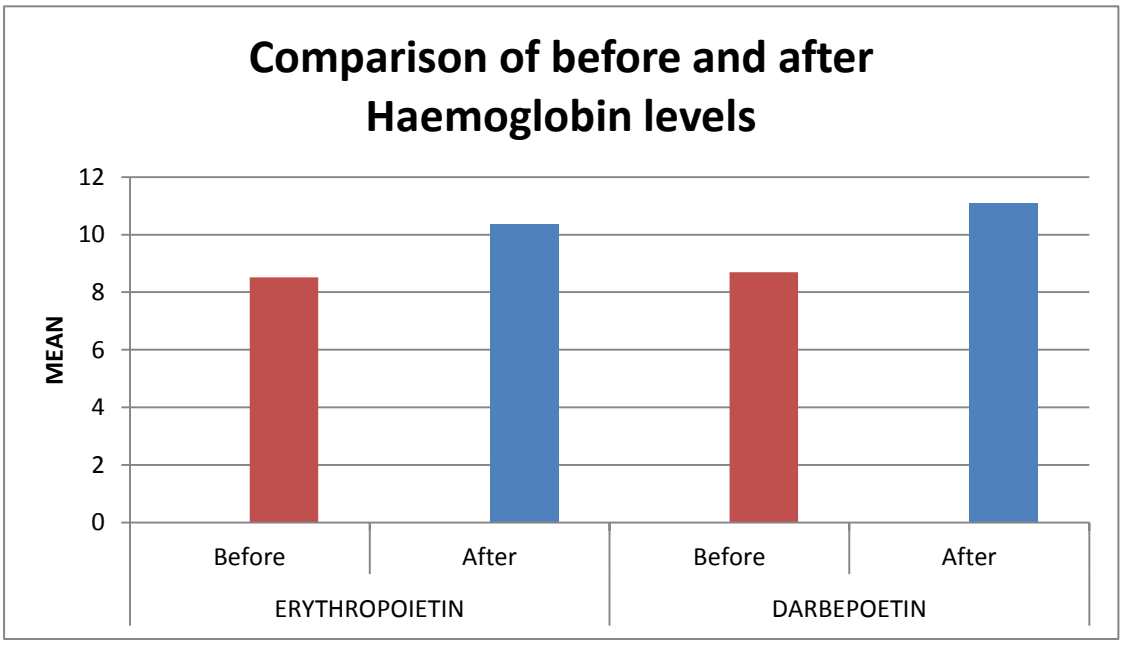
Among 30 patients on Erythropoietin, Myalgia was seen in 6.7%, Hypertension in 13.3% and 3.3% with Headache.

4.6 COMPARISON OF BEFORE AND AFTER HAEMOGLOBIN VALUES

TABLE 6: DISTRIBUTION OF PATIENTS BASED ON BEFORE AND AFTER HAEMOGLOBIN VALUES

DRUG	HAEMOGLOBIN	N	Mean	SD	Mean difference	P value
ERYTHROPOIETIN	Before	30	8.52	0.86	1.96	P< 0.001*
	After	30	10.48	0.84		
DARBEPOETIN	Before	30	8.59	1.09	2.51	P< 0.001*
	After	30	11.1	0.86		

* Significant at 1% level of significance



FIQURE 6: DISTRIBUTION OF PATIENTS BASED ON BEFORE AND AFTER HAEMOGLOBIN VALUES

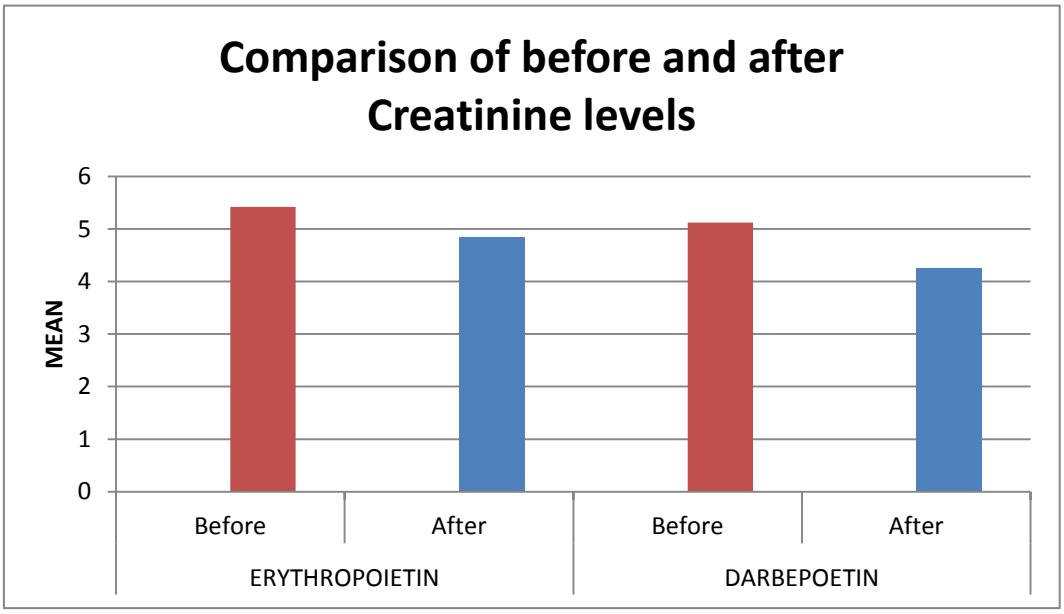
Erythropoietin increases Haemoglobin levels from mean value of 8.52g/dl to 10.48g/dl. Darbepoetin increases Haemoglobin levels from mean value of 8.59g/dl to 11.1g/dl. Both erythropoietin and darbepoetin increases Hb level to target range 10-12gm/dl. Darbepoetin increases Haemoglobin levels with a mean difference of 2.51mg/dl than erythropoietin with mean difference of 1.96mg/dl.

4.7 COMPARISON OF BEFORE AND AFTER CREATININE VALUES

TABLE 7: DISTRIBUTION OF PATIENTS BASED ON BEFORE AND AFTER CREATININE VALUES

DRUG	CREATININE	N	Mean	SD	Mean difference	P value
ERYTHRO POIETIN	Before	30	5.12	2.1	0.67	P< 0.001*
	After	30	4.45	2.2		
DARBEPO ETIN	Before	30	4.99	2.3	0.84	P< 0.001*
	After	30	4.15	1.8		

* Significant at 1% level of significance



FIQURE 7: DISTRIBUTION OF PATIENTS BASED ON BEFORE AND AFTER CREATININE VALUES

Patients upon Erythropoietin therapy, Creatinine decreases from mean value of 5.12 to 4.45 mg/dl. Patients upon Darbepoetin therapy, Creatinine decreases from mean value of 4.99 to 4.15 mg/dl.

Darbepoetin decreases creatinine level with a mean difference of 0.84mg/dl than erythropoietin with mean difference of 0.67mg/dl.

4.8. MEDICATION ADHERENCE

TABLE 8: DISTRIBUTION OF PATIENTS BASED ON MEDICATION ADHERENCE IN DARBEPOETIN BEFORE AND AFTER PHARMACIST INTERVENTION

MEDICATION ADHERENCE	Before		After		P value
	Frequency	Percent	Frequency	Percent	
High	7	23.4	20	66.7	0.003*
Medium	16	53.3	7	23.3	
Low	7	23.3	3	10.0	
Total	**30**	**100.0**	**30**	**100.0**	

* Significant at 1% level of significance

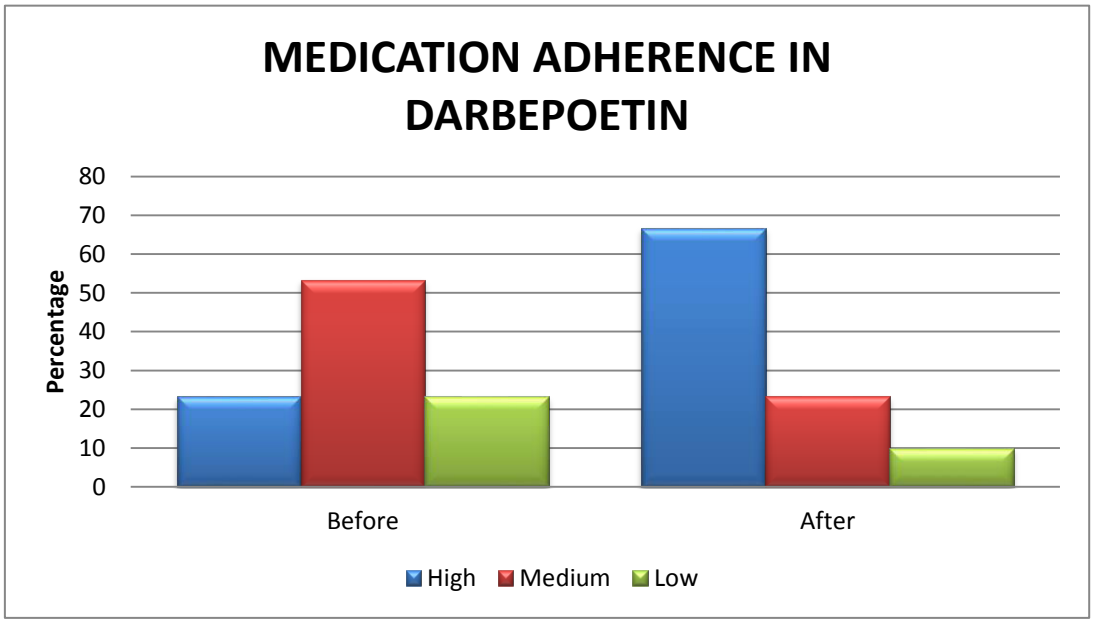


FIGURE 8: DISTRIBUTION OF PATIENTS BASED ON MEDICATION ADHERENCEBEFORE AND AFTER PHARMACIST INTERVENTION

Before pharmacist intervention, 23.4% of the patients were high adherent to medication, 53.3% medium and 23.3% low adherent respectively.

After pharmacist intervention 66.7% of the patients were high adherent to medication and 23.3% medium and 10.0% low adherent to medication.

TABLE 9: DISTRIBUTION OF PATIENTS BASED ON MEDICATION ADHERENCE IN ERYTHROPOIETIN BEFORE AND AFTER PHARMACIST INTERVENTION

MEDICATION ADHERENCE	Before		After		P value
	Frequency	Percent	Frequency	Percent	
High	6	20.0	19	63.3	0.003*
Medium	17	56.7	8	26.7	
Low	7	23.3	3	10.0	
Total	**30**	**100.0**	**30**	**100.0**	

* Significant at 1% level of significance

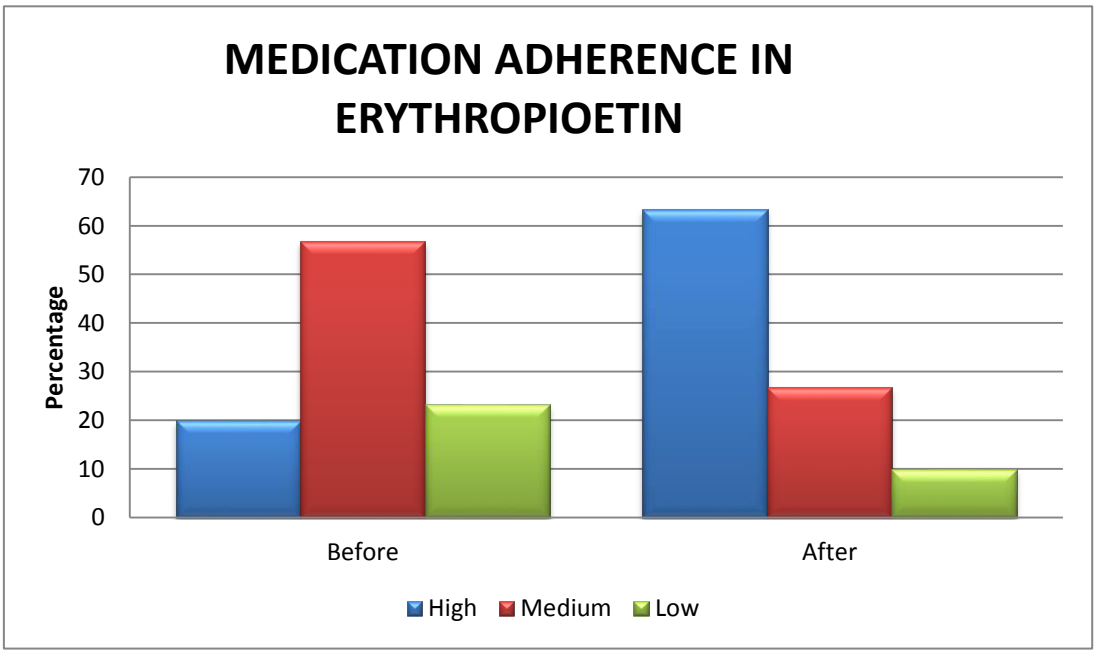


FIGURE 9: DISTRIBUTION OF PATIENTS BASED ON MEDICATION ADHERENCE BEFORE AND AFTER PHARMACIST INTERVENTION

Before pharmacist intervention, 20.0% of the patients were high adherent to medication, 56.7% medium and 23.3% low adherent respectively.

After pharmacist intervention 63.3% of the patients were high adherent to medication and 26.7% medium and 10.0% low adherent to medication.

CONCLUSION

From this study it concluded that both erythropoietin and darbepoetin increases haemoglobin to the target range (10-12g/dl) while decreases creatinine than the value before drug treatment. But comparatively darbepoetin is more efficant in increasing haemoglobin and decreasing creatinine than erythropoietin in mean difference. Mostly seen side effect is hypertension, and on comparison hypertension is more common in erythropoietin and headache is common in darbepoetin. On analysing demographic details CKD increases with advanced age, male gender, family history and social habits. Medication adherence among Chronic kidney disease patients were found to be medium adherent in both the drugs and after pharmacist intervention got increased to high adherence level.

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