The Egyptian Journal of Hospital Medicine (Oct. 2015) Vol. 61, Page 514- 521

Comparison of Efficacy of Continuous Erythropoietin Receptor Activator (CERA) In Chronic Kidney Disease Patients versus Patients on Hemodialysis, Single Center Experience.

Ayman Aly Seddik

Department of Medicine, Faculty of Medicine Ain Shams University, Cairo, Egypt and Nephrology Department, Dubai Hospital, Dubai Health Authority.

Corresponding author: Dr Ayman Aly Seddik ,Internal Medicine & Nephrology, Faculty Of Medicine Ain Shams University, cairo , Egypt P011588,Dubai hospital, Dubai health authority, Dubai, UAE ,email: Seddik500@gmail.com

ABSTRACT

Background : prior to the availability of recombinant human erythropoietin (r-EPO, epoetin), patients on dialysis frequently demanded blood transfusions and excessive iron therapy, exposing them to the risks of iron overload, transmission of viral hepatitis, and sensitization, which reduced the chances of successful transplantation . Recombinant human erythropoietin has been used for more than 20 years for the treatment of renal anemia, Epoetin-Alfa and -beta representing the common traditional preparations. By the modification of the molecule's carbohydrate moiety or structure a longer duration of erythropoietin receptor stimulation was achieved. The continuous erythropoietin receptor activator C.E.R.A. once or twice a month was found sufficient to achieve serum hemoglobin target levels.

This study was aimed to identify the efficacy of C.E.R.A (Methoxy polyethylene glycol-epoetin beta in achieving and maintenance of hemoglobin level in patients with chronic kidney disease and patients on regular Hemodialysis therapy.

Patients and methods: 145 patients with either CKD stage 4 & 5 (e GFR < 45 ml/min) on follow up in nephrology outpatient department or on regular Hemodialysis in nephrology unit Dubai hospital. In this center, the CERA approved by the local pharmacy authority was used for treatment of anemia in chronic kidney disease monthly dose of (100 mg for 70 kg patient) and adjusted according to monthly HB level during the trial period for reaching and maintaining target HB level of 11-12.5 g/dl.

Results : Patients on HD 78 patients (53.8%) and CKD patients 67 patients the mean HB level at the end of study period showed statistically significant rise in whole patient cohort with HB START (8.882 ±1.272 g/dl) and at the end of 24month (11.119±1017 g/dl) With *P-value* (< 0.001). HB at start was (9.013±1.298 g/dl) and (8.769±1.246) g/dl for CKD and HD respectively slightly higher in CKD group however without statistical difference (P-value 0.250). HB level at the 24 month period (end of trial period) was found statically higher in HD group (11.305±1.197g/dl) than CKD group (10.903±1.116g/dl) again without statistical significance *P-value* (0.038).

Conclusion: It could be concluded that the long acting erythropoietin stimulating therapy using continuous erythrpoeitin receptor activator (CERA) as once monthly dose is effective and safe in maintaining target HB level in both CKD patients and patients on maintenance hemodialysis and there was no recorded side effects of its use either by intravenous or subcutaneous use.

Key words: Anemia, CKD, Hemodialysis, Continuous Erythropoietin Receptor Activator (CERA)

INTRODUCTION

The definition of anemia is controversial. The WHO defines anemia as hemoglobin (HB) <13 g/dL for men and <12 g/dL for women. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, defines anemia in adult men and postmenopausal women as HB<12 g/dL, or <11 g/dL in a premenopausal woman the recently launched. [1,2]

HB levels starts to fall early in course of chronic kidney disease (CKD), at an estimated glomerular filtration rate (e-GFR) of less than 75 ml/min per 1.73 m2 in men and 45 ml/min per 1.73 m2 in women. [3]. Among patients under regular care and known to have CKD, the prevalence of anemia was found to be much greater, with mean HB levels of 12.8 ± 1.5 g/dl (CKD stages 1 and 2), 12.4 ± 1.6 g/dl (CKD

Received:2/5/2015
Accepted:9/5/2015

DOI: 10.12816/0018755

stage 3), 12.0 ± 1.6 g/dl (CKD stage4), and 10.9 ± 1.6 g/dl (CKD stage 5). [4]

Prior to the availability of recombinant human erythropoietin (r-EPO, epoetin), patients on dialysis frequently demanded blood transfusions and excessive iron therapy , exposing them to the risks of iron overload, transmission of viral hepatitis, and sensitization, which reduced the chances of successful transplantation. [5]

It is of outmost importance to identify anemia in CKD patients as it may signify nutritional deficits, systemic illness, or other conditions that warrant attention, and even at modest degrees, anemia reflects an independent risk factor for hospitalization, cardiovascular disease, and mortality. [6]

Renal anemia is a multifactor process and its treatment has to focus on stepwise approach targeting all factors involved in this process notably iron deficiency should be treated before adding more expensive therapies such as (r-EPO) therapy. [7]

Erythropoietin is a complex physiologic process through which delivering sufficient oxygen levels in the body is maintained. It is primarily regulated by EPO, a 30-kD, 165–amino acid hematopoietic growth factor that is produced primarily by renal tubular and interstitial cells. Under normal conditions, endogenous EPO levels change according to O2 tension. [8]

Recombinant human erythropoietin has been used for more than 20 years for the treatment of renal anemia, revolutionizing its treatment in patients with CKD when it was approved for use in the United States in 1989 .[9]

Epoetin-Alfa and -beta representing the common traditional preparations. By the modification of the molecule's carbohydrate moiety or structure a longer duration of erythropoietin receptor stimulation was achieved. The continuous erythropoietin receptor activator C.E.R.A. once or twice a month was found sufficient to achieve serum hemoglobin target levels. [10]

Our study aim at identifying the efficacy of continuous erythropoietin receptor activator C.E.R.A (Methoxy polyethylene glycol-epoetin beta (MPG-EPO; Mircera®, Roche, Basel, Switzerland) in achieving and maintainenance of hemoglobin level in patients with chronic kidney disease and patients on regular Hemodialysis therapy .

PATIENT AND METHODS

Observational open labeled follow up trial including 145 patients with either CKD stage 4 & 5 (e GFR < 45 ml/min) on follow up in Nephrology Outpatient Department (67 patients) or on regular Hemodialysis in nephrology unit Dubai hospital (78 patients), after patient informed consent and approval from ethical committee, Patient records confidentiality was assured follow up period of 24 months with primary end point achievement of the target hemoglobin level (11- 12.5 g/dl) at end of the study period .Patients who refused to sign the consent or who fail to comply with administration instructions were excluded from trial .

The CERA approved by the local pharmacy authority was used for treatment of anemia in chronic kidney disease(CKD) a monthly dose of 1.2 mg/kg body weight (100 mg for 70 kg patient) and adjusted according to monthly Hb level during the trial period for reaching and maintaining target HB level of 11-12.5 g/dl , dose reduction if target HB reached was done by reducing the frequency of administration to a maintenance once every 6 – 8 weeks and increasing dose to achieve the target HB for those who fail to achieve adequate response was made by increasing dose to 150 mg up to 200 mg each month which was the highest dose administered throughout the trial period .

Dose was given intravenous in HD patient group through the dialysis venous line at end of dialysis, and Subcutaneously in CKD patient group , compliance was followed up through administration injection cards given to patients enrolled and signed by the administering nurse at the injection clinic .

Data regarding age sex and stage of CDK collected , HB level measured monthly during the study period and for ease of statistical analysis measures every 3rd month was taken as referral points start , 3 month , 6 month , 12 month , 15 months , 18 months 21 months and 24 months (end of study period)

Data was then tabulated, computerized and statistical analysis done using SPSS 16 software.

RESULTS

Current data showed as illustrated in table (1) and figure (1) that age among the group was 65.8±13.66 years and the gender distribution was 84 female patients (57.9%) and 61 male (42.2%) the patients on HD 78 patients (53.8%) and CKD patients 67 patients (46.2%) .

As shown in table (2) and figure (2) the mean HB level at the end of study period showed statistically significant rise in whole patient cohort with HB at START (8.882 ±1.272g/dl) and at 24month(11.119±1017g/dl) With *P*-value (< 0.001) .

Table (3) showed the analysis of the patients subgroups, we found that there was insignificant difference between groups at the start and end of the study confirming the homogeneity of action and the significant changes found by the use of CERA in the patients at both groups as mentioned above. HB at start was (9.013±1.298g/dl) and (8.769±1.246)g/dl for CKD and HD respectively insignifant higher in CKD group than HD group *P-value **(0.250).***

On the other hand HB level at the 24 month period (end of trial period) was found higher in HD group (11.305±1.197g/dl) than CKD group (10.903±1.116g/dl) again without statistical significance *p-value**(0.038)*** still insignificant .

TABLE (4) analysis of the changes in HB level through the study period, showed an initial significant rise in HB level 3 months in the whole patient groups (8.882±1.272g /dl) at start and (10.443±1.250 g/dl) after 3 months.

Another significant rise at interval 12 and 18 months of the trial with HB level (10.430±1.014 g /dl) at 12 months and (11.312±1.534g/dl) at 18 month *P– value* (<0.001) .

No intergroup differences in CKD and HD groups was maintained throughout the study period as shown in table (5) .

figure (3) showed the distribution of results of HG at start and 24 months of the study with clear demonstration of not only the significant rise in HB values but also the achievement of target hemoglobin in most of the patients in study group mostly all cross the reference line at 10g /dl .

patient compliance to CERA was satisfactory especially with monthly single dose for patients in CKD group with good compliance and, no recorded side effects through the study period including less recorded pain at the injection side, we also did not report any case of of thrombocytopenia, gastrointestinal bleeds, or pure red cell aplasia identified in our center during the 24 month folw up period of the trial.

DISCUSSION

The result of our study showed a significant rise in HB level in all patients cohort and the efficacy of the CERA (continuous erythropoietin stimulating agents) in maintaining HB level within target range both in the CKD and HD groups.

Our results come in accordance with results achieved by ***Ohashi et al,*** who proved that Once-monthly CERA therapy maintains stable Hb values with low intra-individual variability and few dose adaptations in CKD patients when administered entirely according to local practice, and the regimen is well tolerated . **(11)**

Weinreich et al, demonstrated similar results on a cohort of Hemodialysis patients with achievement of target HB in studied patient . **(11)**

Macdougall et al, studied the pharmacokinetics and drug metabolism of CERA in CKD patiens and showed the efficacy and safety of once monthly admisinsteration in maintating serum level of the drug and continuous receptor activation .**(12)**

We found no difference between efficacy of CERA compound in both the HD and the CKD groups and regarding the dose of admisstration either IV or SC this comes in accordance with the results achieved by ***Leypoldt et al*** , who confirms that intravenous administration of CERA drug is as effective as subcutaneous route in Hemodialysis And Hemodiafilteration Patients .**(13)**

Luc Frimat et al , conducted a multicenter longitudinal observational trial on patients with chronic kidney disease and found proven efficacy of once monthly administration of CERA in those patients without recorded side effects this goes with the obseravation of our study .**(14)**

A recent trial by Abeer et al , in Baghdad university , Iraq studied the efficacy and safety of CERA (EPOEITIN BETA) versus epoeitin alfa in 46 hemodialysis patients and concluded that methoxy polyethylene glycol-epoetin beta

every two week effectively corrected chronic kidney disease (CKD) related anemia and was well tolerated and it is efficacy and safety is comparable to twice weekly epoetin alfa for anemia correcting in hemodialysis patients. This less frequent dosing schedule of methoxy polyethylene glycol-epoetin beta may offer clinicians and patients a simplified anemia management as compared to traditional erythropoietin (epoetin Alfa). [15]

Although once monthly admisistration of CERA is the widely encountered practice, some trials have tested the efficacy and safety of using a lower initial dose of 0.6 mg/kg every two month with acceptable safety and efficacy profiles. [16, 17]

Arecent trial by ***Locatelli et al*** , in italy demoestrated the effectiveness and safety of once monthly CERA in maintating HG level in patients with chronic kidney disease on conservative measures which goes in accordance with the result of our trial on the CKD group .[18]

Our trial result is largely supported by the recent K-DIGO (kidney disease initiatives for global outcome) guidelines on management OF anaemia in chronic kidney disease and the position statement of EUROPEAN best practice guidelines on anemia of chronic kidney disease which both showed the importance of use of erythrocyte stimulating agents in their protocols and demonstrated the efficacy and safety of the long acting continuous erythropoietin stimulating agents (CERA) in management of anemia both in CKD and HD patients. [19, 20]

Weak points of our trial include that it was open labeled as the investigator and patients knew the administered drug , that we did not compare the efficacy against a standard erythropoietin therapy(erythropoietin Alfa) to compare efficacy and safety profiles and we did not study the effects of co administered standard drugs that were used concomitantly as part of anemia management protocol in our center (iron , vitamin B , folic acid) .

CONCLUSION

We can conclude that the long acting erythropoietin stimulating therapy through using CERA (CONTINOUS ERYTHROPOEITIN RECEPTOR STIMULATOR) once monthly use is effective and safe in maintaining target HB level at the recommended target by the current practice guidelines K-DIGO and European best practice guidelines and there was no recorded side effects of its use either by intravenous or subcutaneous use .

REFFERENCES

1. **Robinson B E (2006):** Epidemiology of chronic kidney disease and anemia. J Am Med Dir Assoc., 9 quiz S17-21 [PMID: 17098633 S1525-8610(06)00457-9 [pii] 10.1016/ j.jamda.2006.09.004, 7, 3-6.
2. **Macdougall C ,Iain EK-U(2010):** : Anemia in Chronic Kidney Disease. In: Jurgen Floege RJ, John Feehally., editor Comprehensive Clinical Nephrology. Fourth ed. St. Louis, Missouri: Elsevier Saunders, 951-958.
3. **Astor B C ,Muntner P, Levin A, Eustace J A & Coresh J(2002):** Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med., 162(12), 1401-1408, PMID: 12076240, ioi10526.
4. **Mc Clellan W, Aronoff S L, Bolton W K, Hood S, Lorber D L, Tang K L, Tse T F, Wasserman B & Leiserowitz M(2004)** : The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin., 20(9), 1501-1510, PMID: 15383200 X2763.
5. **Adamson JW & Eschbach JW (1998):** Erythropoietin for end-stage renal disease. N Engl J Med., 339(9), 625-627, PMID: 9718384, NEJM199808273390910
6. **Locatelli F, Pozzoni P & Del Vecchio L (2005):** Anemia and heart failure in chronic kidney disease. Semin Nephrol PMID: 16298261, S0270-9295(05)00103-8[pii]10.1016/ j.semnephrol.2005.05.008 , 25(6), 392-396.
7. **Lankhorst C E & Wish J B (2010)** :Anemia in renal disease: diagnosis and management. Blood Rev. S0268-960X(09)00054-X, 24(1), 39-47, PMID: 19833421[pii]10.1016/j.blre.2009.09.001.
8. **Mohini R (1989) :** Clinical efficacy of recombinant human erythropoietin in hemodialysis patients. Semin Nephrol., 9(11), 16-21, [PMID: 2648516].
9. **Carrera F, Lok CE, de Francisco A, Locatelli F, Mann J F, Canaud B, Kerr P G, Macdougall IC, Besarab A, Villa G, Kazes I, Van Vlem B, Jolly S, Beyer U, & Dougherty F C (2010)** : Maintenance treatment of renal anaemia in haemodialysis patients with methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa administered monthly: a randomized comparative trial. Nephrol Dial

Transplant, 25(12):4009-4017, PMID: 20522670 PMCID: 2989790, 10.1093.

10. **Ohashi N, Sakao Y, Yasuda H, Kato A & Fujigaki Y (2012) :** Methoxy polyethylene glycol-epoetin beta for anemia with chronic kidney disease., Int J Nephrol Renovasc Dis., 5, 53-60, [PMID: 22536082 PMCID: 3333806, 10.2147/ IJNRD.S23447ijnrd-5-053.
11. **Weinreich T, Leistikow F, Hartmann H G, Vollgraf G & Dellanna F (2012) :** Monthly continuous erythropoietin receptor activator treatment maintains stable hemoglobin levels in routine clinical management of hemodialysis patients,. Hemodial Int., 16(1), 11-19, [PMID: 22098689, 10.1111/j.1542-4758.2011.00608.x.
12. **Macdougall I C, Robson R, Opatrna S, Liogier X, Pannier A,Jordan P, Dougherty FC & Reigner B (2006):** Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (C.E.R.A.) in patients with chronic kidney disease ,. Clin J Am Soc Nephrol., 1(6): 1211-1215, [PMID: 17699350, 10.2215/C JN.00730306.
13. **Leypoldt J K, Loghman-Adham M, Jordan P& Reigner B (2012)**: Effect of hemodialysis and hemofiltration on plasma C.E.R.A. concentrations, Hemodial Int., 16(1): 20-30, [PMID: 22098670, 10.1111/j.1542-4758.2011.00634.x.
14. **Luc Frimat, Christophe Mariat, Paul Landais(2013):**Anaemia management with C.E.R.A. in routine clinical practice: (CohorteMircera patients non-dialysés), OCEANE a national, multicenter, longitudinal, observational prospective study, in patients with chronic kidney disease not on dialysis., BMJ Open ,2013; 3.
15. **Abeer K Jumaa1, Hassan M Abbas Al Temimi, May S Alsabbagh, Jawad I Rasheed(2015)** :Efficacy and Safety of Methoxy Polyethylene Glycol Epoetin - Beta versus Epoetin Alpha for Treatment of Chronic Renal Anemia in Hemodialysis Patients. , *American Journal of Pharmacological Sciences, 3(4):87-93.*
16. **Spinowitz B, Coyne DW, Lok CE, Fraticelli M, Azer M, Dalal S (2008)** : CERA Maintains Stable Control of Hemoglobin in Patients with Chronic Kidney Disease on Dialysis when Administered Once Every Two Weeks., Am J Nephrol ., 28:280–289.
17. **Klinger M, Arias M, Vargemezis V(2007):** Efficacy of intravenous methoxy polyethylene glycol-epoetin beta administered every 2 weeks compared with epoetin administered 3 times weekly in patients treated by hemodialysis or peritoneal dialysis: a randomized trial. ,Am J Kidney Dis., 50(6): 989-1000.
18. **Francesco Locatelli, Salvatore Mandolfo, Massimo Menegato Adorati(2013) :** Efficacy and safety of once-monthly continuous erythropoietin receptor activator in patients with chronic renal anemia. , JNEPHROL., 26(6): 1114-1121.
19. **KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease (2012) :**kidney-international , 2 (4) :279-335.
20. **Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease(2013)**: a European Renal Best Practice position statement. , Nephrol. Dial. Transplant**. ,** doi: 10.1093-1099.

FIGURES AND TABLES

TABLE (1) Descriptive Statistics Of The Patient Enrolled In The Study

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	**145**	**36**	**87**	**65.8**	**13.6685**
HB START	**145**	**6.3**	**11.8**	**8.8821**	**1.27157**
HB 3MONTH	**145**	**7.5**	**13.3**	**10.4434**	**1.2501**
HB 6MONTH	**145**	**9**	**12.8**	**10.7759**	**1.19857**
HB 9MONTH	**145**	**8.5**	**13.1**	**10.7559**	**1.1726**
HB 12MONTH	**145**	**8.1**	**12.4**	**10.4297**	**1.01353**
HB 15MONTH	**145**	**7.4**	**13.6**	**11.1428**	**1.65889**
HB 18 MONTH	**145**	**8.5**	**13.9**	**11.3117**	**1.53399**
HB 21 MONTH	**145**	**8.4**	**13**	**10.9759**	**1.28794**
HB 24 MONTH	**145**	**9.1**	**13.9**	**11.1193**	**1.17375**

***P -VALUE < 0.05 SIGNIFICANT ** P- VALUE < 0.001 HIGLY SIGNIFICANT**

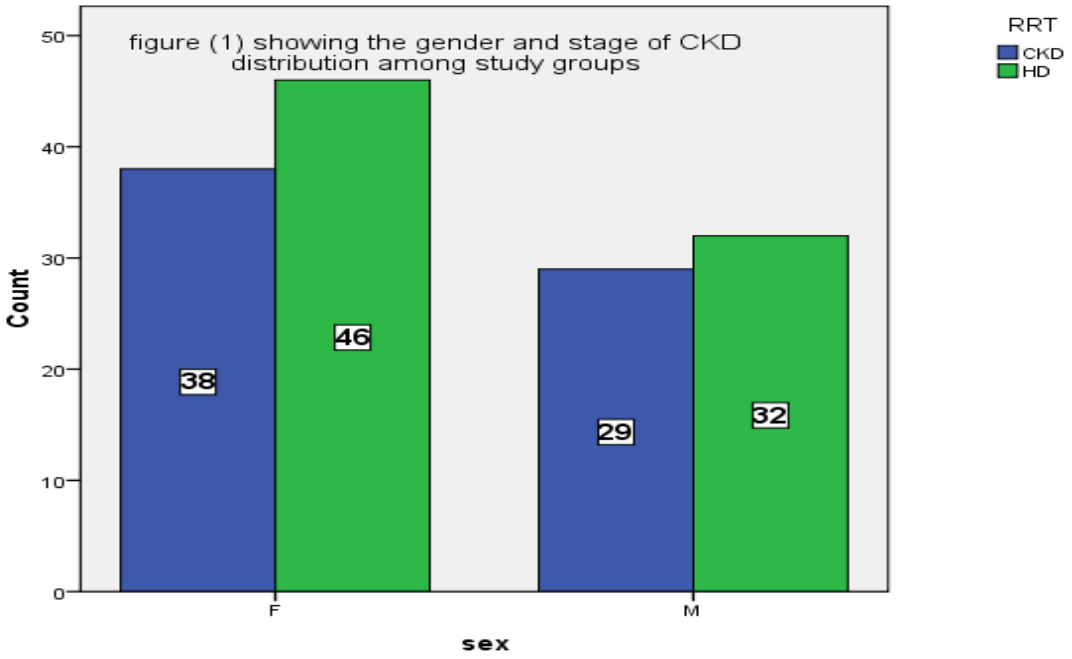

FIGURE 1 (Demographics Of Study Group Regarding Stage Of Ckd Or Hd , Gender Dyistribution)

TABLE(2) T-TEST COMPARING HG G/DL AT START AND END OF STUDY PERIOD ALL PATIENT GROUPS

		Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)
	HBSTART	8.882	1.272	0.106	-16.179	**<0.001
	HB24MONTH	11.119	1.174	0.097		

*P -VALUE < 0.005 SIGNIFICANT ** P- VALUE < 0.001 HIGLY SIGNIFICANT

TABLE (3) T- TEST COMPARISON BETWEEN HB LEVEL AT START AND 24 MONTHS BETWEEN CKD AND HD GROUPS

	CKDSTAGE	N	Mean	Std. Deviation	t	Sig. (2-tailed)
HB START	CKD	67.000	9.013	1.298	1.154	0.250
	HD	78.000	8.769	1.246	1.151	0.252
HB24MONTH	CKD	67.000	10.903	1.116	-2.081	0.039
	HD	78.000	11.305	1.197	-2.092	0.038

***P -VALUE < 0.005 SIGNIFICANT ** P- VALUE < 0.001 HIGLY SIGNIFICANT**

THE TWO GROUPS

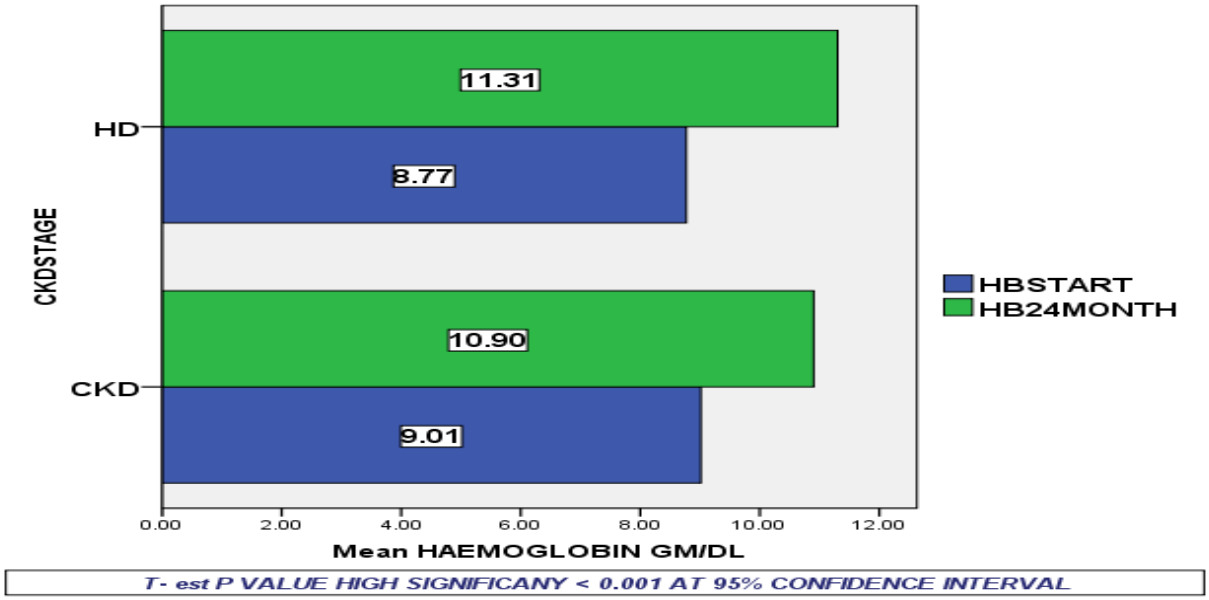

FIGURE (2)HB AT START AND 24 MONTH OFF THE STUDY GROUPSBETWEEN

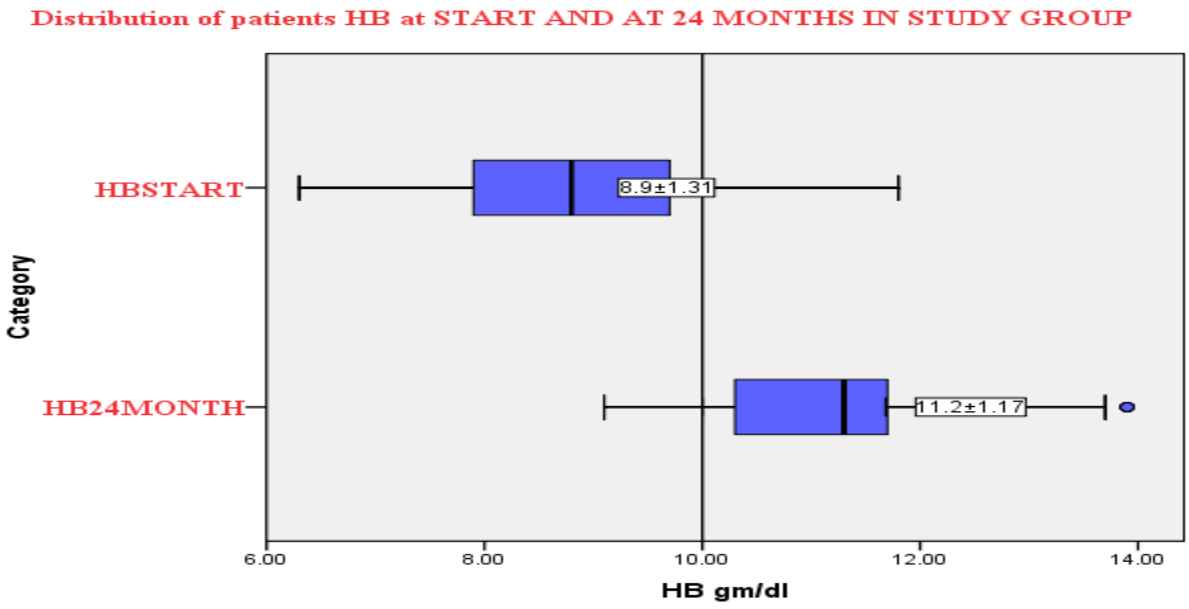

FIGURE (3) comparison between HB distribution at start and 24 moth of trial period

TABLE(4) T-Test Comparing Hg G/Dl During The Study Period In All Patients Groups(Ckd And Hd)						
		Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)
Pair 1	HB START	8.882	1.272	0.106	-15.170	**<0.001
	HB 3MONTH	10.443	1.250	0.104		
Pair 2	HB 3MONTH	10.443	1.250	0.104	-2.985	*0.003
	HB 6MONTH	10.776	1.199	0.100		
Pair 3	HB 6MONTH	10.776	1.199	0.100	0.146	0.884
	HB 9MONTH	10.756	1.173	0.097		
Pair 4	HB 9MONTH	10.756	1.173	0.097	2.526	0.013
	HB 12MONTH	10.430	1.014	0.084		
Pair 5	HB 12MONTH	10.430	1.014	0.084	-6.092	**<0.001
	HB18MONTH	11.312	1.534	0.127		
Pair 6	HB18MONTH	11.312	1.534	0.127	1.313	0.191
	HB 24MONTH	11.119	1.174	0.097		

***P -VALUE < 0.005 SIGNIFICANT ** P- VALUE < 0.001 HIGLY SIGNIFICANT**

TABLE (5) Independent Sample T-Test For Comparison HG Level Between CKD And HD Groups							
	CKD - STAGE	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)
HBSTART	CKD	67	9.013	1.298	0.159	1.154	0.25
	HD	78	8.769	1.246	0.141		
HB 3MONTH	CKD	67	10.361	1.275	0.156	-0.733	0.465
	HD	78	10.514	1.232	0.140		
HB 6MONTH	CKD	67	10.687	1.139	0.139	-0.831	0.408
	HD	78	10.853	1.249	0.141		
HB 9MONTH	CKD	67	10.643	1.225	0.150	-1.072	0.286
	HD	78	10.853	1.125	0.127		
HB12MONTH	CKD	67	10.308	1.023	0.125	-1.349	0.179
	HD	78	10.535	1.000	0.113		
HB18MONTH	CKD	67	11.096	1.646	0.201	-1.581	0.116
	HD	78	11.497	1.415	0.160		
HB 21MONTH	CKD	67	10.945	1.231	0.150	-0.268	0.789
	HD	78	11.003	1.342	0.152		
HB 24MONTH	CKD	67	10.903	1.116	0.136	-2.081	0.039
	HD	78	11.305	1.198	0.136		

*P -VALUE < 0.005 SIGNIFICANT ** P- VALUE < 0.001 HIGLY SIGNIFICANT