Original Article

TO COMPARE THE EFFECTIVENESS OF INTRAVENOUS WITH ORAL IRON IN NON-DIALYSIS DEPENDENT PATIENTS OF CHORONIC KIDNEY DISEASE.

Ijaz Nabi[1], Muhammad Sohail[2], Sumara Tabassam[3], Adeen Akram[4]
[1]Senior Registrar of Nephrology, Allied Hospital, Faisalabad.
[2]Assistant Professor of Urology, Madinah Teaching Hospital, Faisalabad.
[3]Assistant Professor of Anaehthesia, Madinah Teaching Hospital, Faisalabad.
[4]House Officer, Medicine, DHQ Hospital, Faisalabad.

ABSTRACT:

OBJECTIVE: To compare the efficacy of oral iron with intravenous iron in non-dialysis dependent patients of chronic kidney disease in terms of hemoglobin (Hb) increase of more than 1g/dl.
STUDY DESIGN: Randomized control trial.
PLACE AND DURATION OF STUDY: Department of Nephrology, Allied Hospital Faisalabad, from October 2015 to March 2016.
METHODOLOGY: 214 patients with chronic kidney disease who were not on dialysis and who fulfilled the criteria for iron deficiency anemia were included in the study. The population was randomized into two groups. Patients in the intravenous (i/v) iron group were given injection iron sucrose 1 gram in five divided doses while patients in the oral iron group were given tablet ferrous sulphate 200mg three times daily. Hb was checked after 40 days. Effect modifiers like age and gender were controlled by stratification. The Chi-square test was applied for categorical variable association. The Paired t-test was applied to compare the hemoglobin level before and after the treatment. P-value ≤ 0.05 was taken as significant.
RESULT: Minimum (min) age was 15 years and maximum (max) age was 80 years with mean age of 49.57± 15.89 years. Min Hb at baseline was 4.2 g/dl and max was 11.8 /dl with a mean Hb of 8.32±1.17 g/dl. Min Hb after 40 days of treatment was 5.5 g/dl and max Hb was 11.7 g/dl with a mean Hb of 9.007 ±1.20 g/dl. After 40 days of treatment 75 patients (35%) had an increase of Hb by 1g/dl. Out of these 75 patients 28(26.2%) were in the oral iron group and 47(43.9%) were in i/v group. The chi square value for efficacy was 7.410 and p-value was 0.006. In i/v iron group the mean Hb at baseline was 8.210±1.1363 g/dl and after 40 days it was 9.030±1.2014 g/dl with a p-value of 0.0001. In oral iron group mean Hb at baseline was 8.430±1.2008 g/dl and after 40 days it was 8.985±1.2211 g/dl with a p-value of 0.0001.
CONCLUSIONS: Iron replacement in ND-CKD patients increases the mean Hb levels significantly however i/v iron is more efficacious than oral iron in terms of Hb increase by 1g/dl till day 40.
KEY WORDS: Iron deficiency anemia, chronic kidney disease, non-dialysis dependent.

INTRODUCTION:

Anemia is one of the clinical manifestations of chronic kidney disease (CKD). It is defined as decrease in hemoglobin (Hb) to less than 13 g/dl in males and less than 12g/dl in females. Anemia develops when glomerular filtration rate (GFR) falls below 0.5 ml/sec or even below 0.75ml/sec in diabetics[1].
Anemia is associated with increased cardiovascular morbidity, mortality and also impaired quality of life[2,3]. Development of anemia in CKD is multifactorial. Erythropoietin and iron deficiency are two major causes. Other contributory factors include vitamin B12 and folate deficiency, hyperparathyroidism and inflammatory mediators (IL-6, IL-1, TNF alpha) which inhibit erythropoiesis[4].

Corresponding Author:
Muhammad Sohail
Assistant Professor of Urology,
Madinah Teaching Hospital, Faisalabad.
E.mail: drsohail195@hotmail

The estimated prevalence of iron deficiency anemia (IDA) in CKD is around 25-70%[5]. Iron deficiency may result from inadequate dietary intake, chronic iron loss from repeated gastrointestinal (GI) bleeding and decreased iron absorption[6]. The chronic inflammatory status of many CKD patients induces increased hepcidin synthesis. Increased hepcidin levels are known to block iron absorption from intestine as well as its release from iron stores[6,7]. Iron status should be evaluated in patients of CKD with anemia before embarking on erythropoietin stimulating agents (ESA)[8]. Different tests available for evaluation of iron status include serum iron level, total iron binding capacity, serum ferritin and transferrin saturation.

Kidney disease Improving Global Outcomes (KDIGO) recommends Iron replacement for adult CKD patients if serum ferritin is less than 500ng/ml and transferrin saturation level of less than 30%[9].

For non-dialysis dependent CKD (NDCKD) patients who require iron supplementation, route of iron administration depends on severity of iron deficiency, availability of venous access, response to prior oral therapy, side effects with prior therapy, patient compliance and cost. Oral iron is less expensive, easier to administer, and more safe. The main side effects are GI tract related and limit adherence and dose. With i/v iron larger dose can be given with better results, however adverse reactions are feared[10]. In one study, patients achieving primary outcome (Hb increase of more than or equal to 1 g/dl) was greater in i/v iron treatment group than oral iron treatment group (44.3% vs 28.0%) by day 42[11].

In hemodialysis (HD) patients several different studies are available which show superiority of i/v iron,[12] however in NDCKD patients the evidence is less convincing. Rationale of this study is to compare the safety and effectiveness of oral vs i/v iron in NDCKD patients.

METHODOLOGY:

214 patients fulfilling the selection criteria were enrolled in the study from nephrology department (both outpatient as well as inpatient) of Allied Hospital, Faisalabad. Informed consent was taken. Demographic information (name, age, gender and address) was recorded. Patients were randomly divided in two groups. Patients in the i/v iron group were given 1 gram intravenously iron sucrose in five divided doses. Each dose was administered as injection Bisleri 200 mg intravenous over 5 minutes on different days from day 0-14. Patients in the oral iron group were given tablet Ferrous Sulphate 200 mg, one tablet three times daily with eight ounces of tap water one hour before meals from day 0 until day 30. Patients were followed up to 40 days of treatment by taking their contact numbers. Hb level was measured on day 40 by the pathologist by Drabkin's method. All the data was recorded on the proforma and SPSS Windows software (version 23.0) was used for data analysis. Numerical data, i.e. age, Hb at baseline and after 40 days of treatment was presented by calculating mean and standard deviation, whereas qualitative data e.g. gender and efficacy was presented in the form of frequency and percentage. Effect modifiers like age and gender were controlled with stratification. Chi-square test was applied for categorical variable association. The Paired t-test was applied for comparing the hemoglobin level before and after the treatment. P-value $\leq$0.05 was taken as significant.

RESULTS:

A total of 214 patients with CKD meeting the inclusion criteria were included in the study. The patients were randomized into two major groups. 107 patients were given intravenous iron and 107 were given oral iron.

Minimum (min) age was 15 years (yrs) and maximum (max) age was 80 yrs with mean age of 49.57± 15.89 yrs. (table 1). Min Hb at baseline was 4.2 g/dl and max was 11.8 /dl with a mean Hb of 8.32±1.17 g/dl (table 1). Min Hb after 40 days of treatment was 5.5 g/dl and max Hb was 11.7 g/dl with a mean Hb of 9.007 ±1.20 g/dl (table 1).

The study population was divided into three age groups (table 2). Max number of patients were in the age group of 40-65 yrs i.e., 128 (59.8%) and min number of patients were in group of >65 yrs i.e., 26 (12.1%).The Chi square value for this age distribution was 0.879 and p-value was 0.644.

Total number of patients was 214 in which 102 were male and 112 were female. Out of the male patients 52 were in the i/v group and 50 were in the oral group. Out of the female patients 55 were in the i/v group and 57 were in the oral group. The chi-square value of this gender distribution was 0.075 and p-value was 0.784 (table 3).

Out of 214 patients 75 patients (35%) had an increase of Hb by 1g/dl after 40 days of treatment. Out of these 75 patients 28(26.2%) were in with the oral iron group and 47(43.9%) were in the i/v group. The chi-square value for efficacy was 7.410 and p-value was 0.006 (table 4).

Out of 102 male patients, 39 had an increase in Hb of 1g/dl while 63 didn't. Amongst the 39 patients 16 (32.0%) were in the oral group and 23 (44.2%) were in i/v group with a p-value of 0.204. Out of 112 female patients 36 had an increase in Hb of 1g/dl. Amongst these 12 (21.1%) were in the oral group and 24 (43.6%) were in i/v group with a p-value of 0.011 (table 5).

In the age group of 14-40 yrs 29 out of 60 patients had an increase of Hb by 1g/dl. In these 29 patients 8 (29.6%) were in the oral group and 21(63.6%) were in an i/v group with a p-value of 0.009. In the age group of 41-60 yrs 34 out of 124 patients had an increase of Hb by 1g/dl. Among these 34 patients 14 (21.2%) were in the oral group and 20 (32.3%) were in i/v group with a p-value of 0.157. In the age group of >65 yrs 12 out of 26 patients had an increase in Hb by 1g/dl. Out of these 12 patients 6 (42.9%) were in the oral group and 6 (50.0%) were in the an i/v group with a p-value of 0.716 (table 6).

In an i/v iron group the mean Hb at baseline was 8.210±1.1363 g/dl and after 40 days it was 9.030±1.2014 g/dl with a p-value of 0.0001. In the oral iron group mean Hb at baseline was 8.430±1.2008 g/dl and after 40 days it was 8.985±1.2211 g/dl with a p-value of 0.0001 (table 7).

Table 1: Age and Hb distribution

	n	Minimum	Maximum	Mean	Std. Deviation
Age	214	15	80	49.57	15.895
Hb at baseline	214	4.2	11.8	8.320	1.1714
Hb after 40 days	214	5.5	11.7	9.007	1.2086

Table 2: Age distribution

		Group		
		i/v iron	oral iron	Total
Age distribution	14-40 years	33	27	60
		30.8%	25.2%	28.0%
	41-65 years	62	66	128
		57.9%	61.7%	59.8%
	> 65 years	12	14	26
		11.2%	13.1%	12.1%
	Total	107	107	214

Chi-square 0.879
p-value 0.644

Table 3: Gender distribution

		Group		
		i/v iron	oral iron	Total
Gender	Male	52 48.6%	50 46.7%	102 47.7%
	Female	55 51.4%	57 53.3%	112 52.3%
	Total	107	107	214

Chi-square 0.0755
p-value 0.784

Table 4: Efficacy of i/v and oral iron

		Group		
		i/v iron	oral iron	Total
Efficacy	no	60 56.1%	79 73.8%	139 65.0%
	yes	47 43.9%	28 26.2%	75 35.0%
	Total	107	107	214

Chi-square value 7.410
p-value 0.006

Table 5: Efficacy in relation to gender

			group			p-value
Gender			i/v iron	oral iron	Total	
Male	efficacy	no	29 55.8%	34 68.0%	63	0.204
		yes	23 44.2%	16 32.0%	39	
Female	efficacy	no	31 56.4%	45 78.9%	76	0.011
		yes	24 43.6%	12 21.1%	36	

Table 6: Efficacy in different age groups

age distribution			group			
			i/v iron	oral iron	Total	p-value
14-40 years	efficacy	no	12 36.4%	19 70.4%	31	0.009
		yes	21 63.6%	8 29.6%	29	
41-65 years	efficacy	no	42 67.7%	52 78.8%	94	0.157
		yes	20 32.3%	14 21.2%	34	
> 65 years	efficacy	no	6 50.0%	8 57.1%	14	0.716
		yes	6 50.0%	6 42.9%	12	

Table 7: Mean Hb at baseline and after 40 days

Group		Mean	Std. Deviation	p-value
i/v iron	Hb at baseline	8.210	1.1363	0.0001
	Hb after 40 days	9.030	1.2014	
oral iron	Hb at baseline	8.430	1.2008	
	Hb after 40 days	8.985	1.2211	0.0001

DISCUSSION:

Kidney is one of the most highly differentiated organs in human body. It has excretory and metabolic functions. Endocrine function, regulation of blood pressure, solute and water transport, acid base balance and removal of metabolites are accomplished by an intricate renal process. Normal renal function can be maintained until 50% of the nephrons are functional.

GFR is the rate of plasma flow filtered across the glomerular basement membrane. CKD is defined by the abnormal measurements of GFR for at least 3 months. CKD is also labeled when GFR is normal, but other kidney pathology is there in the form of structural abnormality or proteinuria. The most common cause of CKD in adults is diabetes mellitus followed by hypertension and chronic glomerulonephritis.

CKD has emerged as a global health problem. The number of patients is increasing with high risk of progression to end stage renal disease and increased mortality. During the coming decades the expanding financial burden of CKD will be difficult to meet even by the developed nations. In US the annual burden of end stage renal disease is expected to rise by 52 billion dollars[10,6].

CKD is usually asymptomatic in early stages. So early diagnosis is important to retard the progression and prevent the complications. With the exception of hypertension the complications of CKD usually start when eGFR is < 60ml/min/1.73m[2]. The various complications of CKD include anemia, mineral bone disease, acidosis, fluid and electrolyte disturbance, cardiovascular complications,

endocrine and neurological disturbances etc[13].

Anemia is common in CKD. It is defined as Hb of <13g/dl in males and <12g/dl in females. [1] Claims data from the 2010 united states renal data registry system include a diagnosis of anemia in 43% of patients with stages 1-2 and 57% of those in stages 3-5[14]. African Americans have a higher prevalence of 48% and 64% in stages 1-2 and 3-5 respectively. In contrast anemia was present in 12-14% of subjects at risk for kidney disease (Kidney Early Evaluation Program) and only 5-6% of general population[15].

KDIGO has developed recommendations for testing for anemia. In patients without anemia KDIGO recommends testing at least annually in CKD 3, twice per year in non-dialysis dependent patients of CKD 4-5 and every three months in those on peritoneal or HD. In patients with anemia not being treated with ESA, measure Hb concentrations every 3 months in non-dialysis dependent CKD patients on stage 3-5 and patients with CKD 5 on peritoneal dialysis. For patients on HD measure Hb at least monthly[9].

Anemia is increasingly being recognized as a cause of some symptoms which were previously attributed to uremia such as fatigue, lethargy, dizziness, shortness of breath, reduced exercise capacity and reduced quality of life. Anemia is also associated with increased cardiovascular mortality, left ventricular hypertrophy, congestive heart failure, progression to end stage renal disease. In a cohort of 1300 men without a history of congestive heart failure, the presence of both Hb of 13g/dl and GFR of 60ml/min/1.73m2, compared to either anemia or CKD alone, was associated with a significantly higher rate of previously unrecognized left ventricular dysfunction. Rates of congestive heart failure related hospital admissions and death were 3-5 times higher in group with anemia. In the European HD patients the relative risk of hospitalization and death increased by 4% and 5% respectively, with each 1g/dl fall in Hb within 10-13g/dl range. Similarly in a recent study from the UK the relative hazard for death increased nearly 3 fold with each 1g/dl fall in Hb in the range of 9-13g/dl[16].

Anemia in CKD is multifactorial, erythropoietin deficiency being the major culprit. Deficiency of nutrients, iron, and blood loss are other major contributory factors. Iron deficiency is the major cause of erythropoietin hypo responsiveness and must be looked for before embarking upon ESA therapy. About 50% of patients of pre dialysis CKD 3-5, who are not on ESA or iron therapy show depleted iron stores in the bone marrow. With iron supplementation the dose of ESA can be decreased, reducing the cost and decreasing the cardiovascular mortality associated with high dose erythropoietin. However, precise estimation of iron deficiency is challenging and requires invasive procedures such as bone marrow or liver biopsies. Measurement of serum ferritin levels and TSAT are reasonable alternatives and most guidelines recommend their measurement to label iron deficiency. However target levels of serum ferritin and TSAT are different in different guidelines. KDIGO 2012 states," for adult CKD patients with anemia not on ESA iron, we suggest a trial of iron therapy if an increase in Hb is desired without ESA and TSAT is ≤30% and serum ferritin is ≤500ng/l. in contrast the KDOQI, Kidney Health Australia Caring for Australians with Renal Impairment and European Renal Best Practice aims for lower TSAT and ferritin levels. Japan is even more conservative in this regard[17].

The route of iron administration is an issue which is still debatable in the light of existing data. Generally oral iron has been associated with limited efficacy and frequent gastrointestinal side effects, whereas an i/v iron demonstrates higher efficacy but had been associated with side effects like acute anaphylactic reactions. Anaphylactoid reactions may occur because of immunologic interactions with the carbohydrate coating of an i/v iron preparations especially dextran. Other acute reactions are likely due to labile plasma iron released from iron products. Recently developed i/v iron preparations minimize the release of labile iron permitting higher dose infusions but at same time increasing the cost of treatment[18,19]. In dialysis patients an i/v iron administration is recommended however the evidence is still not convincing in ND-CKD population. KDIGO also allows a trial of oral iron for 2-3 months in ND-CKD patients[17].

This study was done on 214 non dialysis

dependent CKD patients with anemia, TSAT <20%, serum ferritin <100ng/l and who were not on iron or ESA therapy. The study population was randomized into two groups, one given i/v iron and other oral iron. Both groups showed insignificant variation in terms of age and gender. 43.9% patients in the i/v group and 26.2% in oral group showed improvement in Hb of 1g/dl. This difference was statistically significant (p-value 0.006). The mean concentration of Hb increased significantly from baseline to 40 days of treatment in both groups.

Similar findings were noted by Van Wyck et al in the United States Iron Sucrose Clinical Group. They found that 44.3% of patients in the i/v group and 28% in the oral group achieved the increase in Hb by 1g/dl. The mean increase in the Hb at day 42 was higher in the i/v group than the oral group (0.7 vs 0.4, p-value 0.029). The patients in the oral iron group had a greater decline in GFR than the i/v group. However the study population was different from our study in terms of TSAT and serum ferritin levels at baseline. They also permitted the use of oral iron prior to enrollment in the study[11].

A local study by Moorani KH et al also had similar findings. They observed an increase in mean Hb levels from 7.38g/dl to 9.22g/dl with i/v iron sucrose. These findings were true for both males and femals. However the study population was different from our study in terms of age. [4]

A study by Agarwal et al also noted similar findings as our study. They included 75 ND-CKD patients. Mean Hb increase was 0.4±0.8 in the i/v group and 0.2±0.9 in the oral group. The difference was statistically significant. However the i/v iron formulation was different from that used in our study. They used sodium ferric gluconate as an i/v iron[20].

In the FIND-CKD trial Mcdougal et al also found greater benefit of an i/v iron as compared to oral iron. Their study size was larger and duration was longer as compared to my study.[21]

Quinibi et al in a multicenter trial also noted significant increase in mean Hb with an i/v iron as compared to oral iron at day 42 (p-value 0.005). They also found 60.4% of study population achieving Hb increase of ≥1g/dl in the i/v group as compared to 34.7% in oral iron group. However their study population was already on stable doses of ESA.[22] The mean Hb level in this study population was 8.3g/dl which was similar to that observed in two other local studies[4,23].

Data from Randomized Trial to Evaluate Intravenous and Oral Iron in Chronic Kidney Disease (REVOKE) trial does not favour the findings in our study. In REVOKE i/v iron sucrose was compared with oral ferrous sulfate. The difference in Hb increase in both groups was not statistically significant at 3, 6 and 12 months. Moreover population in the i/v group encountered significantly higher rates of infection and cardiovascular events. The difference can be due to longer study duration, and different study population[24].

A study by Nagaraju SP et al also found contradictory results to our study. They randomized their study population to groups. Oral iron group was given heme iron polypeptide and i/v iron group was given iron sucrose. After 60 days of treatment the increase in Hb in both groups was not significantly different (p-value 0.37). The difference in results can be explained by the fact that they used different oral iron formulation and sample size was smaller as compared to ours[5].

This study does not exclude the possibility that greater efficacy could be achieved by increasing the dose of i/v iron or prolonging the use of oral iron. Secondly the compliance in the oral iron group could not be guaranteed as it was totally based on patient's description.

CONCLUSION:

The use of iron replacement in ND-CKD patients increases the mean Hb levels significantly however an i/v iron is more efficacious than oral iron in terms of Hb increase by 1g/dl till day 40. These findings need to be confirmed by further randomized controlled trials of longer duration.

REFERENCES:

1. Zardazil J, Horak P. Pathophysiology of anemia in chronic kidney disease. A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014; Jan
2. Johansen KL, Finkelstein FO, Revicki DA,

Gitlin M, Evans C, Mayne TJ. Systematic review and meta-analysis of exercise tolerance and physical functioning in dialysis patients treated with erythropoiesis stimulating agents. Am J Kidney Dis 2010;55:535-48.
3. Patel TV, Singh Al. Anemia in chronic kidney disease: new advances. Heart Fail Clin 2010;6:347-57.
4. Moorani KN, Asim S. Parentral iron sucrose in iron deficiency anemia of paediatric chronic kidney disease. J Ayub Med Coll Abottabad. 2011;23:47-50.
5. Nagaraju SP, Cohn A, Akbari A, Davis JL, Zimmerman DL. Heme iron polypeptide for the treatment of iron deficiency anemia in non-dialysis chronic kidney disease patients: a randomized controlled trial. BMC Nephrology 2013;14:64.
6. Macdougall IC, Geisser P. Use of intravenous iron supplementation in chronic kidney disease. Iran JKidney Dis. 2013;7:9-22
7. Ganz T, Nemaeth E. Hepcidin and Disorders in Iron Metabolism. Annu Rev Med. 2011;18:347-60.
8. Locatelli F, Aljama P, Canaud B, Covic A, De Francisco A, Macdougall IC et al. Target haemoglobin to aim for with erythropoeisi-stimulating agents: a position statement by ERPB following publication of the Trial to reduce cardiovascular events with Aranesp therapy (TREAT) study. Nephro Dial Transplant. 2010;25:2846-50.
9. Kliger AS, Foley RN, Goldfarb DS, Goldstein SL, Johansen K, Singh A, Szczech L. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guidelines for Anemia in CKD. Am J Kidney Dis. 2013;62:849-59.
10. Darshan D, Frazer D, Anderson GJ. Molecular basis of iron loading disorders. Expert Rev Mol Med. 2010;12:e36.
11. Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurry S; for the united states iron sucrose (venofer) Clinical Trials Group. A randomized controlled trial comparing IV iron sucrose with to oral iron in anemic patients with nondialysis-dependent CKD. Kidney Int. 2005;68:2846-56.(for sample size only)
12. Yessayan L, Sandhu A, Besarb A, Yessayan A, Friank S, Zasuwa G et al. Intravenous Iron Dextran as a Component of Anemia Management in Chronic Kidney Disease: A Report of Safety and Efficacy. Int J Nephrol. 2013;2013:703038.
13. Tomlinson LA, Wheeler DC. Clinical evaluation and management of chronic kidney.
14. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney diseasein the United States. JAMA. 2007;298:2038.
15. McFarlane SI, Chen SC, Whaley-Connell AT, Sowers JR, Vassalotti JA, Salifu MO et al; Kidney Early Evaluation Program Investigators.Prevalence and associations of anemia of CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004.Am J Kidney Dis. 2008 ;51:S46-55.
16. Novak JE, Yee J. Anemia in chronic kidney disease.In: Coffman TM, Falk RA, Molitoris BA, Neilson EG, Shrier RWeditors Schrier's diseases of the kidney. 9th ed Lipincot 2013 p 2238-56.
17. Tanaka S, Tanaka T. How to supplement iron in patients with renal anemia. Nphron. 2015;131:138-44.
18. Larson DS, Coyne DW. Update in intravenous iron choices. Curr Opin Nephrol Hypertens. 2014;23:186-191.
19. Auerbach M, Macdougall IC. Safety of intravenous iron formulations: facts and folklore. Blood Transfus. 2014;12:296-300.
20. Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehay DJ, Besarab A. A randomized control trial of oral versus intravenous iron in chronic kidney disease. Am J Nephrol. 2006;26:445-54.
21. Macdougall IC, Bock AH, Carrera F, Eckardt KU, Gaillard C, Van Wyck D et al; FIND-CKD study investigators: FIND-CKD: a randomized control trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anemia. Nephrol Dial Transplant. 2014;29:2075-84.
22. Qunibi WY, Martinez C, Smith M, Benjamin J, Mangione A, Roger SD. A randomized control trial comparing intravenous ferric

carboxymaltose with oral iron for treatment of iron deficiency anemia of non-dialysis-dependent chronic kidney disease patients. Nephrol Dial Transplant. 2001;26:1599-607.
23. Akhter N, Tahir MM, Kiran S. recombinant human erythropoietin therapy in predialysis patients of chronic kidney disease. Nephrol Reviews. 2010;2:43-6.
24. Agarwal R, Kusek JW. Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. 2015;88: 905-14.

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""WHEN THE WORLD PUSHES YOU TO YOUR KNEES, YOU'RE IN THE PERFECT POSITION TO PRAY""

Hazrat Ali (Karmulha Wajhay)