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IRON STATUS IN ANEMIA OF CHRONIC KIDNEY DISEASE (CKD) STAGE-V AND ITS IMPROVEMENT WITH INTRAVENOUS IRON SUPPLEMENTATION

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ABSTRACT

89 cases of chronic renal failure CKD stage-V were materials for the study. All the cases (100%) had severe degree of anemia. 41 cases had iron deficiency with a mean TSAT 10.71 ± 3.10% and serum iron 20.95 ± 4.78µg/dl which was significantly lower than the control group and from patients who did not have iron deficiency. However serum ferritin was higher than the control which was due to the reason that all these cases had severe degree of inflammation (CRP +ve) and serum ferritin is known to be an acute phage reactant. After intravenous iron sucrose administration for 4 weeks the serum iron and TSAT increased to 89.40 ± 3.56 µg/dl and 24.11 ± 1.78 % respectively which were statistically significant $p<0.01$. But the hemoglobin rise was from 6.80 ± 0.150 to 7.80 ± 0.125gm%. The increase was not statistically significant. This indicates that other factors like erythropoietin deficiency is the main cause of anemia.

KEY WORDS-: Chronic Kidney Disease (CKD) stage –V, Hemodialysis, Anemia, Transferrin Saturation (TSAT), Iron Sucrose.

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INTRODUCTION

Anemia is one of the most common complications in patients of chronic renal failure (CRF). A clear association exists between declining kidney function and presence of anemia which is nearly universal by the time the patient reaches end stage renal failure. The most common cause of anemia in these patients is erythropoietin deficiency[1], but iron deficiency also plays an important role in the causation of anemia. Iron depletion and iron deficiency usually results from blood loss from gastrointestinal tract. Hemodialysis patients are subject to repeated blood loss due to retention of blood in the dialyzer and the blood lines. Other contributing causes in these patients include frequent blood sampling for laboratory test and blood loss from surgical procedures such as creation of vascular access. The management of anemia in CKD patients requires an appropriate balance between stimulating the generation of erythroblast (erythropoiesis) and maintaining sufficient iron levels for optimum hemoglobin production. Thus assessing iron status is integral for anemia management in Chronic Kidney Disease (CKD) patients as iron is essential for hemoglobin (Hb) formation. Correction of iron deficiency can reduce the severity of anemia in patients of CRF. However in these patients oral iron supplementation is not sufficient as iron absorption is reduced due to inflammation of the gastrointestinal tract. Iron absorption can also be reduced due to simultaneous administration of gastric acid inhibitors[2] and phosphate binders which are frequently taken by CKD patients. Untreated iron deficiency is an important cause of hyporesponsiveness to erythropoietin.[3,4] Keeping this in mind the study has been undertaken to determine the iron status in these patients of CKD stage-V with anemia.

MATERIALS AND METHODS

89 cases of chronic irreversible end stage renal failure (CKD stage-V) who were undergoing hemodialysis in the dialysis unit of IMS & SUM Hospital, Bhubaneswar were taken as materials for the study. 20 normal healthy persons were taken as controls. CKD stage-V was defined when Glomerular Filtration Rate (GFR) was less than 15ml/minute and duration of the illness was more than 3 months and there was no reversible cause of renal failure in this patients. Anemia was defined when hemoglobin was less than 13gm% in males and less than 12 gm% in females as per WHO recommendation. Care was taken to exclude other causes of anemia like sickle cell disease, thalassemia and malignancy. These patients had not received Intravenous (IV) iron or erythropoietin before the study. During the study erythropoietin was not given to the patients until their status was corrected.

INVESTIGATIONS

After a thorough clinical examination, the following investigations were done:-

(i)CBC (complete blood count),(ii) Serum Urea,(iii) Serum Creatinine,(iv) Serum Electrolytes, (v) FBS, PPBS,(vi) Serum Protein,(vii) Serum Albumin, (viii)Serum Phosphorous ,(ix) Serum Calcium

To know the iron status, serum ferritin, serum iron and Transferrin saturation (TSAT) were estimated. CRP was done to find out the presence of inflammation/infection. Serum ferritin was estimated by chemiluminescent immunoassay (CLIA).[5] Serum iron and total iron binding capacity were estimated by spectrophotometry.[6] Transferrin saturation was calculated from serum iron and Total Iron Binding Capacity (TIBC) values.

$$\text{TSAT} = \frac{\text{serum iron} \times 100}{\text{TIBC}}$$

When TSAT is below 20% patient is thought to have iron deficiency. The serum ferritin should also be less than 100 ng/ml but its value may be high in presence of inflammation (CRP +ve). However when serum ferritin is above 500 ng/ml, no iron supplementation was advocated and serum ferritin level above 800 ng/ml was taken as iron overload. Patients who had documented iron deficiency were given IV iron supplementation till TSAT was above 20% and serum ferritin was kept between 200-500 ng/ml. The IV iron preparation used was iron sucrose. The dose

was as follows- 100 mg in 100 ml Normal Saline (NS) as first dose, subsequent doses were 200 mg in 100 ml NS two to three times per week during each hemodialysis. This was continued till TSAT was more than 20%. Serum ferritin and TSAT were measured every week along with hemoglobin. Any untoward reaction to iron supplementation was recorded.

OBSERVATION

Table 1

Age and sex distribution of cases. Maximum number of cases (73%) was in the range of 30-60 years. 75.3% cases were males and 24.7 % were females.

Age in years	CKD patients stage-V		
	Male	Female	Total
11-20	0	0	0
21-30	5	1	6
31-40	9	4	13
41-50	16	5	21
51-60	23	8	31
61-70	11	4	15
71-80	3	0	3
Total	**67**	**22**	**89**

Table 2

Biochemical parameters in these patients of CKD stage-V

Groups	S.Urea (mg%)	S.Creatinine (mg%)	S.Protein (gm%)	S.Albumin (gm%)	S.Potassium (mEq/L)	S.Phosphorous (mg%)	S.Calcium (mg%)
Patients	150.421	10.498	6.288	3.476	5.508	4.87	8.57
	±4.21	±0.35	±0.071	±0.05	±0.058	±0.165	±0.133

Table 3

Glomerular filtration rates

Patients(n=89)	S. Creatinine (mg%)	GFR (ml/min)
	10.49	8.12
	±0.35	±0.21

Table 4

Initial Hb and PCV in CKD stage-V patients on hemodialysis.

Patients	Initial Hb (gm %)	Initial PCV (%)
	6.959	28.811
	±0.102	±0.370

Table 5

Percentage of CRP +ve cases.

CRP	NO. OF PATIENTS	PERCENTAGE
+ve	51	57.30
-ve	38	42.70
TOTAL	89	100

Table 6
Reticulocyte response.

	Hb(gm%)	Reticulocyte(%)
Patients (n=89)	6.959 ±0.102	1.735 ±0.020

Table 7
Iron status in 20 healthy controls and CKD stage-V patients

Groups	Serum Iron (microgram/dl)	TSAT(%)	Serum Ferritin(ng/ml)
(patients)	59.021	18.598	465.714
	±4.446	±0.92	±41.629
(Control)	59.6	25.112	223.55
	±5.789	±0.729	±4.78

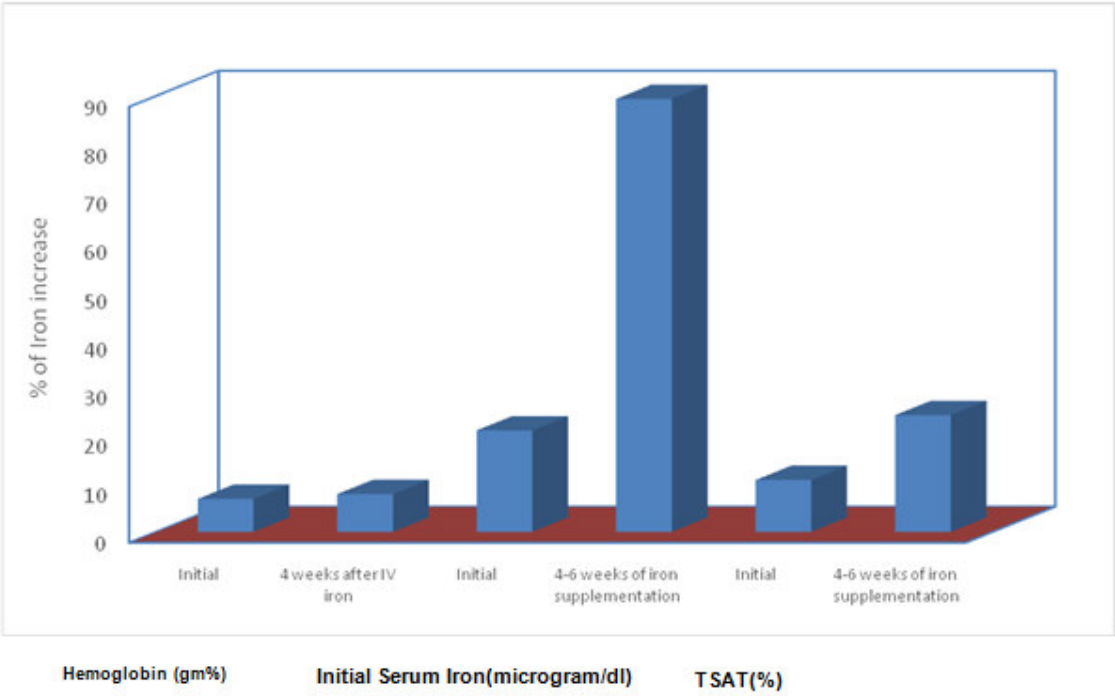
Table 8
Iron status and serum ferritin levels in the control, iron deficient group and patients with no iron deficiency.

	Serum Iron (µg/dl)	TSAT (%)	Serum Ferritin(ng/ml)
Control (n=20)	59.6 ± 5.789	25.112±0.729	223.55±4.78
Iron Deficient Group Patients (n=41)	20.95±4.78	10.71±3.10	421.02±349.54
Non-Iron Deficient Group Patients (n=48)	91.54±29.78	25.33±4.85	503.94±426.30

Out of these 89 cases, 41 cases had iron deficiency with TSAT 10.71 ± 3.10% and serum iron 20.95 ± 4.09microgram/dl.

Table 9
Initial Hb, initial serum iron and initial TSAT and their improvement 4-6 weeks after IV iron sucrose supplementation in the iron deficient group.

Patients	Hemoglobin (gm%)			Initial Serum Iron(microgram/dl)			TSAT(%)		
	Initial	4 weeks after IV Iron	T value	Initial	4-6 weeks of Iron supplementation	T value	Initial	4-6 weeks of Iron supplementation	T value
Iron Deficient Group (n=41)	6.80	7.80	1.24^{NS}	20.95	89.40	10.33^{**}	10.71	24.11	11.08^{**}
	±0.160	±0.125		±4.78	±3.56		±3.10	±1.78	



DISCUSSION

Chronic kidney disease is a prevalent worldwide condition and the number of patients affected continues to increase. In United States, by the end of 2010, more than 2 million people have been affected with CKD.[7] AS the most severe form of CKD is end stage renal failure and here there arises the need for renal replacement therapy. As per KDOQI guidelines, end stage renal failure (CKD stage-V) is defined when GFR is below 15 ml/minute/1.73 sq meter body surface area. As per WHO definition[8], anemia is defined when Hb is < 13 gm% in males and 12gm% in females. As per NICE guidelines in patients receiving hemodialysis, the target Hb level is 11 gm% in women and 12 gm% in men. There is an inverse relationship between GFR and prevalence of anemia. In patients with GFR 60ml/minute prevalence of anemia is 1%, at GFR 30ml/minute prevalence is 9 % and at GFR < 15ml/minute the prevalence of anemia is 33% for males and 67 % for females[9]. The reduction in Hb level in CKD occurs for a variety of reasons. The hormone erythropoietin (around 90%) is produced in the kidney. Under normal physiological conditions, hypoxia in the kidney leads to an increase in the production of erythropoietin (EPO) which subsequently stimulates erythropoiesis. In CKD, this hormone is not produced in sufficient amount and hence there is anemia. Iron deficiency is also an important factor for anemia in CKD[10]. In CKD there is platelet dysfunction which leads to increased GI bleeding. This may be one of the causes of iron deficiency. Moreover in patients on hemodialysis there is chronic blood loss from blood in the dialysis tubings and dialyzers after each hemodialysis. A substantial amount of blood is also lost from frequent blood testings and operative procedures like vascular access surgery[10,11]. Now uremic toxins can also lead to hemolysis with a shortened RBC life span. Other factors like malnutrition, deficiencies of folic acid and Vit.B12 have been found to be the cause of reduction in Hb concentration.

Before 1989 correction of anemia was done mostly by multiple blood transfusions. However after the discovery of recombinant human erythropoietin, the treatment has been revolutionised. Most centres prescribe recombinant human erythropoietin with target Hb level of 11 to 11.5 gm%[12]. But it has been found that unless other factors like iron deficiency, malnutrition, inflammation, Vit.B12 and folic acid deficiencies are taken care of, the response to recombinant human

erythropoietin is poor and unsatisfactory. Among these factors, iron deficiency is the most important factor which if untreated produces hypo responsiveness to EPO. In the present series, 89 cases in CKD stage-V have been taken as materials for the study. Maximum numbers of cases were in the age range of 30 to 60 years. 75.3 % were males and 24.7 % were females. 100 % of these cases were severely anemic with mean Hb of 6.959 ± 0.102 gm%. There was no reticulocyte response in these cases. Other causes of anemia like sickle cell disease, thalassemia and malignancy were excluded from this group. Iron status was evaluated in all these patients. 57.30 % of cases were found to have severe degree of inflammation/ infection (CRP +ve). Serum iron, TSAT and serum ferritin were estimated in all these cases. Absolute iron deficiency is defined when serum ferritin level is < 100 ng/ml, but serum ferritin is an acute phase reactant (inflammatory marker) hence its value may be high when there is infection and inflammation even if there is iron deficiency. Hence the ideal parameters to diagnose iron deficiency in these cases are to measure.

(i) % of hypochromic red cells (the test is not available in most of the centres)

(ii) TSAT below 20 % and a low serum iron level. [13,14]

In the present series 41 cases (46.07 %) had iron deficiency and the other 48 cases (53.93 %) did not show any evidence of iron deficiency. In this iron deficient group, the serum iron was 59.021 ± 4.446 µg/dl which was significantly lower than the control $p<0.01$ and from the patients who did not have iron deficiency $p<0.01$. The TSAT in this group was 18.598 ± 0.092 % which was significantly lower than the control $p< 0.01$ and from the patients who did not have iron deficiency $p<0.01$. But the serum ferritin level was high because most of the cases were CRP +ve. In the DOPPS study[9], 31 to 38 % cases of CKD with anemia had iron deficiency. 5 cases had folic acid and Vit.B12 deficiency. They were given oral folic acid and IV Vit.B12 supplementation. Then these 41 cases were given IV iron supplementation two times per week till the TSAT increased above 20%. After TSAT was above 20% IV iron sucrose was given at dose of 50 mg at an interval of 4 weeks to maintain adequate iron level. Table 8 shows the rise of Hb, serum iron and TSAT values after IV iron sucrose supplementation for 4 to 6 weeks. There was a significant rise in the serum iron and TSAT values. Although there was rise of Hb from 6.80 ± 0.160 to 7.8 ± 0.125 gm%, it was not statistically significant. This shows that iron deficiency is a common feature in CKD with anemia and iron status is improved with IV iron sucrose supplementation. But only correction of iron deficiency cannot reach the target Hb level for which recombinant human erythropoietin supplementation is necessary after correction of iron deficiency. In these 41 cases, no adverse effect was noted with IV iron supplementation. Care was taken not to give IV iron supplementation when serum ferritin was above 500 ng/ml.

CONCLUSION

Severe degree of anemia is prevalent in almost all cases of CKD stage-V on hemodialysis. Iron deficiency is one of the causes of anemia and its correction is needed by IV iron supplementation. But this will not increase the hemoglobin to target level as the most important cause of anemia in these cases is erythropoietin deficiency. But correction of iron status is needed to get good response to erythropoietin.

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