Section: General Medicine

Original Research Article

COMPARISON OF RETICULOCYTE HAEMOGLOBIN CONTENT WITH SOLUBLE TRANSFERRIN RECEPTOR/LOG FERRITIN RATIO AND TRADITIONAL MARKERS OF IRON DEFICIENCY IN EVALUATION OF IRON STATUS AMONG HEMODIALYSIS PATIENTS

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Abstract

Background: Most common cause of anemia in chronic Kidney disease is 'relative 'erythropoietin deficiency and Second most common cause is iron deficiency anemia. Various serum markers have been searched and studied since last 2 decades that can clearly detect iron deficiency in dialysis patients. The aim of the study was to understand the significance of newer markers like Reticulocyte haemoglobin content and soluble transferrin receptor and its index in evaluation of iron status in haemodialysis patients. **Materials and Methods:** This prospective, descriptive and observational study was carried out in dialysis unit of Kokilaben Dhirubhai Ambani Hospital and Medical Research Centre, Mumbai, Maharashtra. Total 100 CKD stage5 D patients (patients on maintenance hemodialysis) with anemia were selected randomly. Present analysis includes diagnosing absolute and functional iron deficiency in our dialysis unit, to evaluate sensitivity and specificity of traditional and newer markers to diagnose iron deficiency in hemodialysis patient and compare them. **Result:** Out of 100 anemic patients 14% of patients had absolute iron deficiency and 18% of patients had functional iron deficiency. Sensitivity and specificity of Transferrin saturation (TSAT) at 20% was 76.2% and 52.9% respectively. Sensitivity and specificity of ferritin at 100ng/ml cut-off level was 28.60% and 91.11% respectively which suggest very low sensitivity but high specificity. Reticulocyte Haemoglobin (Ret He) seems to be as comparable marker of iron deficiency as TSAT. In addition to the traditional markers Ret He can provide additional diagnostic power with better specificity at lower levels. **Conclusion:** Functional iron deficiency is common in dialysis patients and need to be detected by markers which are not affected by inflammation. Prevalence of iron deficiency in dialysis centre depends on many factors and it varies from 20-45%. STfr and sTfr/log ferritin ratio are not reliable marker of iron deficiency in dialysis patients when they are receiving erythropoietin therapy.

INTRODUCTION

Iron deficiency is the main cause of hyporesponsiveness to erythropoietin therapy in dialysis patients. Its detection is of value as it is easily corrected by intravenous iron therapy. Hemodialysis patients on maintenance erythropoietin therapy frequently develop iron-deficient erythropoiesis due to accelerated erythropoiesis coupled with ongoing dialysis related blood loss. Iron deficiency can be absolute-means true iron deficiency or functional-means failure to deliver iron to red blood cell precursors in spite of apparently appropriate iron stores.[1,2]

Most common cause of anemia in chronic Kidney disease is 'relative 'erythropoietin deficiency, which means that erythropoietin production is less in proportion to the anemia as compared to the general population. Second most common cause is iron deficiency anemia.[3,4]

Anemia is found in 70-75% of dialysis patients. Dialysis patients have frequent cardiovascular complications mainly acute left ventricular failure and acute coronary syndrome which get precipitated

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by anemia. The response to intravenous iron can be monitored by an increased erythropoeitic response at a constant rate of Epo or a decrease Epo needs.[5,6] Anemia of chronic disease complicates the pathophysiology of iron deficiency anemia in CKD. In CKD patients traditional markers of iron deficiency get deranged in presence of inflammation. So, ferritin and transferrin saturation (TSAT) have less sensitivity and specificity in predicting iron-deficient erythropoiesis in dialysis patients as described in many studies.[7-9]

In dialysis patients, the pathophysiology is further complicated by erythropoietin injections. Immediately after the injections, erythroid marrow activity gets increased which further consumes the iron and lower down the TSAT. Absolute iron deficiency anemia in dialysis patients is considered when serum TSAT is less than 20% and serum ferritin is less than 200 ng/ml. For non-dialysis patients serum ferritin should be less than 100ng/ml. In clinical practice, when serum ferritin levels are more than 200 ng/ ml and TSAT is less than 20%, a scenario called functional iron deficiency, real confusion arises. In this type of patients, whether to give iron supplementation or not is confusing as excessive iron supplementation is hazardous. Overall sensitivity and specificity of traditional parameters of iron deficiency is also not impressive.[10,11]

Various serum markers have been searched and studied since last 2 decades that can clearly detect iron deficiency in dialysis patients. Reticulocyte hemoglobin content/equivalent (CHR/Ret He) is one of the promising markers in this setting. Ret He levels does not get affected by inflammation or erythropoietin therapy. Also as it is a reticulocyte marker, Ret He is first to increase following iron therapy and helps in showing response to iron therapy. Many studies have compared Ret He with the traditional markers in detecting iron deficiency in dialysis patients.[10,12]

Sensitivity and specificity of Ret He/ CHr was established at various cut-off levels. However, still there is controversy regarding exact cut-off of Ret He that can accurately diagnose iron deficiency. Whether Ret He can be used as an isolated marker of iron deficiency without monitoring ferritin or TSAT levels is also controversial. Recommendations of Ret He regarding monitoring of those patients who received iron therapy are also lacking. There is lack of proper standardization and availability regarding Ret He all over the world at present. So regarding Ret He there are many areas in which requirement of clear cut guidelines is highly recommended.[13,14]

In recent years, the measurement of soluble transferrin receptor levels (sTfR) in serum has been proposed as an indicator of adequacy of iron therapy. It has shown some promising results in anemia of chronic disease as it does not change with inflammation. Some of the studies have shown that sTfR including sTfR/log ferritin ratio is a reliable marker for diagnosing and monitoring of iron therapy in patients with anemia of chronic disease. However, soluble transferrin receptor kit is expensive and not widely available. Its levels are also changed with erythropoietin therapy, which makes it controversial and less reliable marker for hemodialysis patients who are on erythropoietin therapy.[15]

So, it is still controversial which parameter is accurate in detecting iron deficiency anemia in hemodialysis patients. The parameter which is cheap, easily available, has high sensitivity and specificity to detect iron deficiency is still being evaluated in multiple studies. Ret He seems to be accurate parameter, particularly when used with the traditional parameter but it requires standardization in terms of cut-off values for diagnosis and monitoring in hemodialysis patients.

This study was done on 100 patients on maintenance hemodialysis who are on erythropoietin therapy. Prevalence of absolute and functional iron deficiency of all 100 patients was noted. Comparison was made between Ret-He, sTfr/log ferritin ratio, TSAT and serum ferritin levels. 38 patients who are eligible for iron therapy have received IV iron sucrose 100mg every dialysis for 10 dialysis. Iron responders and non-responders numbers were noted. According to the results sensitivity and specificity of each parameter noted and evaluated. The aim of the study was to understand the significance of newer markers like Reticulocyte haemoglobin content and soluble transferrin receptor and its index in evaluation of iron status in haemodialysis patients.

MATERIALS AND METHODS

This prospective, descriptive and observational study was carried out in dialysis unit of Kokilaben Dhirubhai Ambani Hospital and Medical Research Centre, Mumbai, Maharashtra.

Total 100 CKD stage5 D patients (patients on maintenance hemodialysis) with anemia were selected randomly. Anemia was defined as Hb < 11 gm/dl for both male and female. All patients were receiving erythropoietin injections also. The study duration was 1 year from April 2016 to April 2017. It was a prospective, descriptive and clinical study.

Based on the literature, it is found that prevalence of iron-deficiency anemia in hemodialysis patient is variable. It usually varies from 20-60% in various studies. Hukic et al did study in hemodialysis patients and found the prevalence of iron deficiency in dialysis patients approximately 50%. 61 Using prevalence of disease at 5% level of significance with desired precision +/-10%, estimated sample size was 96 and considering ~5% dropout rate; Total 100 patients were enrolled in the study to achieve the objective.

Inclusion Criteria

- Hb < 11gm/dl.

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- Hemodialysis patients on erythropoietin therapy

Exclusion Criteria

- Patients with recurrent bleeding episodes
- Those who received recent blood transfusions
- Known hemoglobinopathies
- Associated infections or malignancies
- Allergy to IV iron
- Vitamin B12 deficiency

Methods

Total 100 CKD stage 5D (hemodialysis) patients with anemia, defined by Hb <11gm/dl were selected for the study after all inclusion and exclusion criteria were applied. All patients were receiving erythropoietin injections.

Informed consent was taken from the patients willing to take part in the study. Ethics Committee approval was taken from Institutional Scientific and Ethics Committee (ISEB) of Kokilaben Dhirubhai Ambani Hospital and Medical Research Centre.

The study was carried out in two steps.

Step 1

Blood samples were taken before dialysis into plain and EDTA bulb and immediately sent for the process. In each patient CBC, iron studies, serum ferritin, Ret-He and sTfr level was done. For sTfr levels, blood was stored at -20^0 C. Results were noted. Patients who were eligible for IV iron therapy according to KDIGO guidelines were calculated. Absolute iron deficiency and functional iron deficiency was calculated.

Absolute Iron deficiency has been defined as – TSAT <20% and serum ferritin level <200 ng/dl.

Functional iron deficiency has been defined as – TSAT <20% and serum ferritin levels >200ng/dl.

Step 2

Second step was done in those who were eligible for IV iron therapy. 40 patients were eligible for iron therapy but 2 patients left the study. So, iron was given to 38 patients Iron was given to following patients - (according to KDIGO recommendation) TSAT <30% and serum ferritin <500 ng/dl, TSAT <20% and serum ferritin between 500-800ng/dl. No iron was given to anyone with TSAT >30% or Ferritin > 800ng/dl.

Those 38 patients, who were eligible for IV iron therapy, received IV iron sucrose 100mg post dialysis for consecutive 10 dialysis sessions. (Total 1gm dose). In 38 patients who received IV iron, blood sample was taken again after 1 month of the last dose of IV iron. CBC, iron studies, serum ferritin, sTfr and Ret He was sent.

Outcome of interest

Those who received iron, if Hb was raised by 1gm or more they were considered as iron responder, in other terms iron deficient and for those patients whose hemoglobin didn't raised by 1gm were considered as iron –nonresponders or in other terms as iron replete patients.

Following statistics were done and evaluated in the study.

- Total number of patients with absolute iron deficiency and functional iron deficiency.
- Total numbers of patients who were iron responders and non iron responders.
- Mean value with standard deviation of Ret-He in functional iron deficient patients, Absolute iron deficient patient and in iron replete patients was noted. (Other remaining patients).
- Mean value with standard deviation of sTfr and sTfr / log ferritin ratio in functional iron deficient patients, Absolute iron deficient patient and with iron replete patients (other remaining patients).
- Sensitivity and specificity of traditional markers to detect iron deficiency was determined.
- Sensitivity and specificity of Ret-He at different values in detecting iron deficiency was determined.
- Sensitivity and specificity of sTfr was determined at cut-off value 3 for iron deficiency.
- Sensitivity and specificity of sTfr/log ferritin ratio was determined at cut-off value 1.4 for iron deficiency.

Statistical Analysis

Data were analysed using the SPSS statistical package (version 21). The numeric data is summarised by descriptive statistics like; N, mean ± SD, median, minimum, maximum (e.g. Age, Hb, ferritin and Ret-He). Two t-tests were performed to compare the difference between Mean value of Ret He, sTfr and sTfr/log ferritin ratio in iron responders and non-responders. The categorical data is summarized by frequency count and percentage (e.g. Age group, Gender distribution and Number of patients received IV iron etc.). The Pearson correlation analysis was done for numeric data between Ret-He vas TS, Ret-He vs. Hb and Ret-He vs. ferritin etc.

RESULTS

This prospective observational study was conducted from April 2016 to April 2017 in the dialysis unit of Kokilaben Dhirubhai Ambani Hospital, Mumbai. Total 100 dialysis patients with anaemia who were receiving erythropoietin therapy were included in the study.

The study was carried out in two steps- in the first step, the hemogram and the complete iron profile along with the newer parameters were analysed while in the second step IV iron was administered to those patients who were eligible for it. Total 40 patients were eligible for IV iron out of which 2 patients left the study. So 38 patients received iron therapy. All the data after step 1 and step 2 were collected and noted into excel spread sheet.

Age and sex distribution was noted. Results were divided into 2 sections. In 1st section data from all 100 patients was noted and evaluated. In 2nd section data was evaluated from those 38 patients who

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received IV iron therapy. Iron responders and nonresponders were noted. Sensitivity and specificity of each parameter for diagnosis of iron deficiency in a background of chronic kidney disease were evaluated.

So this study has included patients of all ages in dialysis unit. Mean age of the patients was 60.4 years. 63% of patients were between 40-70 years of ages. Gender distribution analysis shows that 43% patients were female and 57% were male which shows that male were slightly higher than females. Overall, patients from both sexes have taken part in significant proportions which will help the results to be applied without any discrimination. As per the KDIGO guidelines 40 patients were eligible for IV iron therapy but 2 patients left the study, so total 38 patients received iron therapy.

In our study, the range of age distribution of patients was wide with minimum of 27 to maximum of 87yrs. Hemoglobin ranged from 6.3gm/dl to 11gm/dl. 11gm/dl was highest Hb level in inclusion criteria. Mean value for TSAT in our dialysis unit was 28.64. Many patients were receiving maintenance iron therapy, so highest TSAT levels of 89% also noted. Mean ferritin level was 827ng/ml which showed that it is important to differentiate anemia of chronic disease from iron overload. Newer markers like Ret He and sTfR/log ferritin ratio have also shown wide range. Mean Ret He was 31.23 and mean sTfr/log ferritin ratio was 1.36 in our dialysis unit.

This table 1 is showing category of all patients according to the results of TSAT and ferritin levels. (According to KDIGO guidelines)

- 18 patients were classified as having functional iron deficiency as their TSAT were less than 20% and ferritin levels were more than 200ng/ml.
- 14 patients were classified as having absolute iron deficiency as their TSAT were less than 20% and ferritin were less than 200ng/ml.
- 13 other patients who were not in the category of functional or absolute iron deficient. But they were still eligible for IV iron as their TSAT were less than 30% and ferritin was less than 500ng/ml.

Table 1: Division of all patients according to their iron status

Category	Numbers (out of 100)
Functional iron deficiency	18
Absolute iron deficiency	14
Iron replete patients	55
Other patients eligible for iron	13

The table 2 is showing Mean Ret He levels along with standard deviation in functional iron deficiency patients, in absolute iron deficiency patients and in those patients who did not have iron deficiency. Mean Ret He is around 28.7 in absolute iron deficiency patient and 29.7 in functional iron deficiency patients (p value 0.498). In iron replete patients it was 32.47.

Table 2: Mean Ret He in functional iron deficiency, absolute iron deficiency and in iron replete patients

Types of patients	Ret He (Mean ± SD)
Functional iron deficiency	29.69 ± 3.86
Absolute iron deficiency	28.74 ± 3.92
Iron replete patients	32.47± 3.43

[Table 3] is showing mean sTfr in all the three categories described before. It is slightly higher in absolute iron deficiency but in functional iron deficiency and in iron replete patients it is not much different. (p value 0.098) Those patients whose hemoglobin increased more than 1gm/dl after iron therapy were considered as 'iron responders' or in other words they were true iron deficient.

Category	STfr (Mean + SD)
Functional iron deficiency	3.29 ± 1.10
Absolute iron deficiency	4.20 ± 1.61
Iron replete patients	3.13 ± 0.89

The rest were considered as 'iron non responders' or in other words they have enough iron in the body. According to KDIGO guidelines 38 patients received IV iron, out of which 21 (52.75%) responded and 17 (47.25%) have not responded. So, prevalence of iron deficiency in our hemodialysis unit is 21%.

Mean values of all the parameters are noted in iron responders and nonresponders. Hemoglobin in iron responders and non-responders shows mean of 8.84g/dl and 9.27 g/dl respectively. For Ret He, mean value of 28.35pg and 30.75pg is noted for absolute and functional iron deficiency. STfr/log ferritin ratio shows 1.8 for responders and 1.54 for nonresponders.

TSAT shows mean of 16.55% in responders and 19.94 % in non responders. Mean value of sTfr was 3.98mmg/l and 3.32mg/l in responders and non responders respectively. However, none of the values showed statistically

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significant difference in iron responders and in iron nonresponders. It suggests that none of the parameters is very accurate to differentiate whether patient will respond to iron or not.

[Table 4] shows minimum, maximum and mean value with standard deviation of all the parameters in those patients who received IV iron (n=38). All the parameters show statistically significant change post iron therapy

Table 4: Pre-and post-result of IV iron taken by patients (n=38)

Parameters		Mean	Std. Deviation	P-value
Pair 1	Hb	9.04	1.05	< 0.001
	Hb2	10.24	1.27	
Pair 2	TSAT	18.09	6.33	< 0.001
	TSAT2	26.22	7.77	
Pair 3	FERRITIN	273.89	200.35	< 0.001
	FERRITIN2	496.45	394.8	
Pair 4	STfr	3.69	1.31	< 0.001
	STfr2	3.17	0.72	
Pair 5	Ret He	29.43	4.05	< 0.001
	Ret_He2	31.60	2.86	
Pair 6	sTfr/logferritin	1.69	0.82	0.038
	sTfr/logferritin2	1.48	0.57	

DISCUSSION

Iron deficiency anemia is the second most common cause of anemia in dialysis patients. Early and accurate detection of iron deficiency can prevent short- term and long-term morbidities and mortality. It is necessary to detect ideal marker of iron detection in hemodialysis patients as traditional markers are not very sensitive and specific. This study was done with the same intentions.[16,17]

In our single centre prospective observational study, a total of 100 dialysis patients with anemia were enrolled. Each patient was also taking erythropoietin injections on maintenance basis. Male patients were 57% and female were 47% in our study. Mean age of the patients was 60.4 years. However 63% of patients were between 40-70 years of ages.

Prevalence of iron deficiency anemia in our study.

Total of 40 patients were eligible for IV iron according to current KDIGO recommendations. 2 patients left the study. So, according to KDIGO recommendations 38% of patients received IV iron therapy. Out of 38 patients, 21 were iron responders and 17 were nonresponders. So according to that criterion prevalence of iron deficiency anemia was 21% in our study population. We found 14% of patients had absolute iron deficiency and 18% of patients had functional iron deficiency. 55% of patients were iron replete in our study. Overall there are wide variations in the prevalence of iron deficiency anemia in different studies and centres.

Overall prevalence of iron deficiency varies from 20% to 60% in various studies. The reason behind different prevalence is different races and ethnicity of patients, different food habits of patients, different pattern of maintenance iron treatment for dialysis patients. Fishbane et al in 1996 studied 47 hemodialysis patients and found that 66% of patients were iron deficient. One Indian study by Talwar et al in 27 late stage CKD patients found that prevalence of anemia was as high as 94% out of which iron deficiency anemia was in 60% of patients.

Malyszko et al.[18] reported incidence of functional iron deficiency in 200 hemodialysis patients as 21% which is closer to our study group. Kalantar-Zadehet al did the study in 23 patients, the proportion of iron deficiency was 40% using an extremely rigorous bone marrow criterion.[19]

Editorials by Szu-chun hung.[20] in 2010 concluded that prevalence of iron deficiency by bone marrow staining ranging from 23.5% -40%. Rehman et al studied bone marrow characteristics In 52 end stage kidney patients with mean creatinine of 8.5mg/dl and found that prevalence of iron deficiency was 23%.

One possibility of relatively low levels of iron deficiency in our dialysis unit is many of them were receiving once or twice a month maintenance iron injections. Overall blood loss during dialysis procedure was also kept minimal as possible and regular monitoring of iron parameters and regular correction might be the possible factors for relatively low prevalence of iron deficiency in our dialysis centre.

We found sensitivity and specificity of Ret He as comparable to TSAT in diagnosing iron deficiency. Ret He can be easily done along with CBC and it is cheaper also (cost of an automated CBC). In addition, low levels of Ret He have very high specificity in diagnosing iron deficiency anemia. In our study mean value of Ret He in functional iron deficiency is 29.6pg. It has very high specificity (>90%) at low levels (25-26pg). So in some patients when TSAT was less than 20% and ferritin was more than 200ng/ml, Ret He can provide an additional diagnosing strength. It is better to do Ret He along with traditional markers to improve the sensitivity and specificity in diagnosing iron deficiency in hemodialysis patients.

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CONCLUSION

Evaluation of iron deficiency in dialysis patients is different from general population as traditional markers of iron deficiency are affected by anemia of chronic disease. They seem to be moderately accurate in diagnosing iron deficiency in dialysis patients. Functional iron deficiency is common in dialysis patients and need to be detected by markers which are not affected by inflammation. Prevalence of iron deficiency in dialysis centre depends on many factors and it varies from 20-45%. STfr and sTfr/log ferritin ratio are not reliable marker of iron deficiency in dialysis patients when they are receiving erythropoietin therapy. Reticulocyte hemoglobin content/equivalent seems to be promising marker in diagnosing iron deficiency in hemodialysis patients even if they are receiving erythropoietin therapy. Addition of Ret He along with the traditional markers will improve accuracy for diagnosis iron deficiency in dialysis patients.

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