

## ASSESSMENT OF HAEMOGLOBIN RESPONSE TO INTRAVENOUS IRON THERAPY IN NON-DIALYTIC CHRONIC KIDNEY DISEASE PATIENTS WITH ANAEMIA

Murugesan V<sup>1</sup>, Shanmugasundaram A<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of Nephrology, Government Kilpauk Medical College, Chennai, Tamilnadu, India.

<sup>2</sup>Assistant Professor, Department of Nephrology, Government Royapettah Hospital, Government Kilpauk Medical College, Chennai, Tamilnadu, India.

### ABSTRACT

#### BACKGROUND

There is difficulty in assessing iron status in Chronic Kidney Disease (CKD) patients with anaemia, because of functional iron deficiency.

The aim of the study was to assess Haemoglobin (Hb) response to Intravenous (IV) iron therapy in CKD patients with anaemia and correlate Hb response with available iron indices.

#### MATERIALS AND METHODS

The study is a clinical, prospective, observational study. Forty newly detected CKD patients with GFR < 30 mL/min/1.73 m<sup>2</sup> and Hb < 10 g/dL were included in the study. Ten daily doses of 100 mg Intravenous (IV) iron sucrose injections were administered without erythropoietin when Transferrin Saturation (TSAT) was < 30% irrespective of serum ferritin levels. Their Hb and iron indices responses were assessed one month after the last dose of IV iron. The sample size required was taken for convenience.

#### RESULTS

There was a 0.8 g/dL Hb increase. Hb response was more when TSAT was less than 20%. There was Hb response even if serum ferritin was more than 500 ng/mL, when TSAT was less than 20% and when TSAT was 21 - 30% moderate. Hb response was present if serum ferritin was < 500 ng/mL and no Hb response if serum ferritin was > 500 ng/mL.

#### CONCLUSION

TSAT < 20% is a better predictor of Hb response in non-dialytic CKD patients with anaemia. Treatment with 1 g IV iron sucrose is beneficial in non-dialytic CKD patients with anaemia in spite of high serum ferritin levels when TSAT is < 20%. Further studies are needed in this regard.

#### KEY WORDS

Anaemia, CKD, Haemoglobin Response, Ferritin, TSAT.

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#### BACKGROUND

Anaemia is said to be uncommon in CKD stages 1 - 3 patients (GFR > 30 mL/min/1.73 m<sup>2</sup>), except in diabetic patients where Hb begins to fall even when GFR is 45 mL/min/1.73 m<sup>2</sup>.<sup>(1)</sup> In India Hb levels < 11 g/dL are 66.8%, 75% and 94.7% in stages 3, 4, 5 CKD patients respectively.<sup>(2)</sup> Survey in pre-dialysis patients in Europe revealed that only 32% CKD had Hb above 11 g/dL.<sup>(3)</sup> Treatment of anaemia early slows the progression of CKD.<sup>(4)</sup> Anaemia increases cardiovascular morbidity and mortality.<sup>(5)</sup> So evaluation and treatment of anaemia is important in pre-dialytic CKD patients. Erythropoietin deficiency, iron deficiency, deficiencies of vitamins B6, folic acid and B12, chronic inflammation and infections, marrow fibrosis due to uraemia and hepcidin excess are the causes of anaemia in CKD patients.<sup>(6)</sup> According to KDIGO guidelines, non-dialytic CKD patients with anaemia

should be given 3 months trial of oral iron or IV iron when serum ferritin level is < 500 ng/mL and TSAT is < 30%.<sup>(7)</sup> KHA-CARI guidelines prefer IV Iron in stage 1 - 3 CKD.<sup>(8)</sup> Shankar P Nagaraju demonstrated equal TSAT response between oral vs. IV Iron therapy and higher ferritin response with IV Iron group.<sup>(9)</sup> In dialytic CKD patients with anaemia, TSAT is a better predictor of Hb response and TSAT < 34% predicts the Hb response better.<sup>(10)</sup> Here, an attempt is made to find better predictor of Hb response in non-dialytic CKD patients.

#### MATERIALS AND METHODS

The study is a clinical, prospective and observational study which is conducted at Govt. Kilpauk Medical College Hospital, Chennai. Forty newly detected CKD patients with GFR < 30 mL/min/1.73 m<sup>2</sup> and Hb < 10 g/dL were included in the study. Nearly, 15 - 20 new CKD stages 4 and 5 patients attend our Nephrology OPD. One hundred patients were tested for Hb levels over a period of 6 months, of which 80% had Hb levels < 10 g/dL. After excluding patients with active infections/ active bleeding, recent myocardial infarction, congestive cardiac failure, on maintenance haemodialysis, already on iron or erythropoietin therapy sixty willing patients were tested for serum ferritin, serum iron, total Iron Binding Capacity (TIBC) and TSAT (calculated). To assess haemoglobin (Hb) response to intravenous (IV) iron therapy in CKD patients with anaemia and correlate Hb response with

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*Corresponding Author:*

*Dr. Shanmugasundaram A,*

*Department of Nephrology,*

*Government Royapettah Hospital,*

*Government Kilpauk Medical College,*

*Kilpauk, Chennai-600010, Tamilnadu, India.*

*E-mail: sddrshan@gmail.com*

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available iron indices. Twelve patients had TSAT > 30%. Finally, 48 patients were given 10 daily doses of 100 mg Iron sucrose infusion without erythropoietin. Hb response and Iron indices were analysed after 1 month. The sample size required was taken for convenience.

**Sampling Technique**

Convenient sampling method.

Quantitative determination of serum iron was done by colorimetric principle using ferrozine (spinreact), TIBC by saturation - precipitation with magnesium carbonate and serum ferritin by enzyme immunoassay using pathozyne ferritin (omega diagnostics).

TSAT is calculated by formula  $TSAT = \frac{\text{Serum Iron} \times 100}{TIBC}$

**Statistical Analysis**

For statistical analysis one-way ANOVA was used. This is an extension of the Wilcoxon Rank-Sum Test, used to compare population location parameters (mean, median etc.) among two or more groups including independent samples. It is based on the ranks of the data and for non-normal data were reported as median (Interquartile Range [IQR]). Means of 2 continuous normally distributed variables were compared by independent samples. Student's t-test and Mann-Whitney U test were used respectively to compare means of 2 and 3 or more groups of variables not normally distributed. Analysis of the data was done using a software SPSS system 16.0.

Microsoft Word and Excel had been used to generate graphs and tables.

**RESULTS**

The mean age was 55.82 years. Mean GFR was 13.3 mL/min/1.73 m<sup>2</sup> and mean pre-treatment Hb was 7.45 g/dL. There was a mean 0.8 g/dL increase in Hb post treatment.

1	Total number of stage 4 and 5 CKD patients	100
2.	Patients with Hb < 10 g/dL	80
3.	Unwilling and meeting exclusion criteria patients	20 + 12 (TSAT > 30%)
4.	Willing patients initially attended study	48
5.	Withdrawal due to allergic reactions	2
6.	Withdrawal due to personal reasons	2
7.	Missed follow-up	4
8.	Final study population	Median IQR
	40	48.2 86

**Table 1. Gives Details about Study Group Selection**

If we take Hb increase > 1 g/dL as adequate, 19 patients (47.5%) had adequate Hb response. Nearly, 45.8% of males and 50% of females had adequate Hb response. Nearly, 75% of age group < 40 years, 29% of age group of 41-50%, 41% of age group 51 - 60 years and 35% of age > 61 years had adequate Hb response. One had 3 g/dL Hb increase, 18 had 1-2 g/dL Hb response, 13 patients had < 1 g/dL Hb increase and 8 patients had reduced post treatment Hb.

Iron Indices		Pre-Treatment Levels	Post-Treatment Levels	P value
Serum Ferritin	Mean	213	236.6	0.05 (Wilcoxon signed-rank test)
	Median	233.55	318.4	
	IQR	343.05	270.25	
	Standard Deviation	217.2801	172.4157	
TSAT%	Mean	21.3	25.9	0.000
	Median	25.1	29	
	IQR	6.5	14.58	
	Standard Deviation	5.2734	9.30805	

**Table 2. Shows Individual Iron Indices Responses**

Since pre-test and post-test ferritin levels are not normally distributed, non-parametric t-test using Wilcoxon signed-rank test was done which shows statistical significance.

Ferritin Groups	Pre-Treatment Serum Ferritin	No. of Patients	Hb Response(g/dL)	Standard Deviation	F	P value
1.	< 200 ng/mL	17	1.1	.74117	4.248	0.022
2.	200 - 500 ng/mL	15	0.74	.86373		
3.	> 500 ng/mL	8	0.16	.53436		

**Table 3**

TSAT Groups	Pre-Treatment TSAT	No. of Patients	Hb Response (g/dL)	Standard Deviation	F	P value
1.	<20 %	7	1.34	.30472	4.34	0.044
2.	20-30%	33	0.66	.84549		

**Table 4**

**DISCUSSION**

Anaemia is diagnosed when Hb level is below 13 g/dL in men and below 12 g/dL in women.<sup>(7)</sup> In CKD patients, the desirable Hb is around 11 g/dL. Assessment of iron status in CKD patients with anaemia is difficult. TSAT and serum ferritin are favoured markers for assessment of iron status because of their widespread availability, extensive literature

base and familiarity. Ferritin is an acute phase reactant and has gender differences. Serum iron levels may be modified by diurnal variation and food intake. TSAT is also an acute phase reactant and may be falsely high in malnutrition and falsely low in inflammation. Serum ferritin > 250 ng/mL is associated with higher mortality in non-dialytic CKD patients. Lower TSAT < 17 is associated with higher mortality and

higher TSAT is associated with low mortality and higher chances of progression to ESRD.<sup>(11)</sup>

There is only one patient (2.5%) with absolute iron deficiency (serum ferritin < 100 ng/mL and TSAT < 20%) in our study. 4 patients (10%) have serum ferritin level less than 100 ng/mL and seven patients (17.5%) have TSAT < 20%. According to NHANES III absolute iron deficiency was present in 57.8% to 58.8% of men and 69.9% to 72.8% of women.<sup>(12)</sup> Of the 102 patients from New York, 28.4% had absolute iron deficiency and 54.9% had TSAT < 20% and 41.2% had ferritin < 100 ng/mL.<sup>(13)</sup>

There is 0.8 g/dL increase in Hb level one month after 1 gram of IV Inj. Iron sucrose. In a similar study, Vikrant observed 1.6 g/dL Hb response in 450 non-dialytic patients in northern India.<sup>(14)</sup> In similar studies, Agarwal has observed 0.4 g/dL Hb response in 75 patients.<sup>(15)</sup> Qunibi observed 1.16 g/dL Hb response in 188 patients,<sup>(16)</sup> Spinowitz 0.62 g/dL in 188 patients,<sup>(17)</sup> Van Wyck 0.7 g/dL in 188 patients,<sup>(18)</sup> Gotloib 1.8 g/dL in 47 patients.<sup>(19)</sup> Gabriel Mircescu observed 1.6 g/dL response in 160 Romanian patients.<sup>(20)</sup>

Nearly, 2.5% had > 2 g/dL Hb response, 45% had 1 - 2 g/dL response, 32.5% had < 1 g/dL Hb response and 20% had negative response in our study. In a similar study, Gotloib observed > 2 g/dL response in 48.9%, 1 - 2 g/dL in 19.1% and < 1 g/dL in 21.3%.<sup>(19)</sup> In our study, 47.5% had adequate Hb (> 1 g/dL) response. Vikrant observed that 72% had adequate Hb response.<sup>(14)</sup>

#### Drive Study

Dialysis patients' response to IV Iron with Elevated Ferritin (DRIVE) Study, a controlled, multicenter (37 centers) USA trial in which 134 haemodialysis patients were compared with 1 g of ferric gluconate therapy (68 patients) and no iron therapy (66 patients) if Hb is < 11 g/dl, serum ferritin of 500 to 1200 ng/mL, TSAT < 25% and were receiving adequate erythropoietin dosages. Hb response was higher after IV iron treatment than no iron therapy. This study disputed The 2006 Anaemia Clinical Practice Recommendations that there is insufficient evidence of responsiveness to iron when ferritin is > 500 ng/mL.<sup>(21)</sup>

Majority of patients in our study are from > 61 years of age group. This may be due to more conservative non-dialytic approach in older people compared to younger patients. Being a tertiary care centre, majority of patients are from CKD stage 5. Decreased response to IV iron in older age group may be due to age related cytopenias, but least percentage of adequate Hb response in the age group 41 - 50 years could not be explained, may be because of 80% of 41 - 50 years group were from CKD stage 5. In our study, females fared slightly better than their male counterparts. There are no statistically significant age, sex and CKD stage wise Hb responses.

In our study, mean serum ferritin increased from 211 ng/dL to 236.6 g/dL and TSAT from 21.3% to 25.9%. In a similar study by Gabriel Mircescu,<sup>(15)</sup> serum ferritin increased from 98 ng/mL to 156 ng/mL, 3 months after 600 mg IV iron sucrose and 442.5 ng/mL 1 year after 2400 mg IV iron sucrose. TSAT increased from 21.6% to 24.9% (3 months) and 33.6% (1 year).

There are statistically significant serum ferritin and TSAT responses. There are no correlation between Hb response and serum ferritin and TSAT responses.

When TSAT is < 20%, there is equal Hb response to IV iron therapy between serum ferritin levels of < 500 ng/mL and > 500 ng/mL in CKD patients with anaemia. When TSAT is 20 - 30%, there is moderate Hb response if serum ferritin is < 500 ng/mL and no Hb response if serum ferritin is > 500 ng/mL.

#### Limitations

Small sample size, absence of control group and follow-up, Hb variability and no assessment of inflammatory markers like CRP are some of the limiting factors of the study.

#### CONCLUSION

TSAT levels less than 20% is a better predictor of iron deficiency in non-dialytic CKD patients with anaemia. Further, RCTs are needed in this regard.

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