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Use of IV iron in iron deficiency anemia in CKD with raised serum ferritin

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Abstract

Background: Many newer tests are now available to diagnose iron deficiency in CKD but these tests are not widely used in India as these tests are expensive and patients cannot afford these tests. Hence the traditional tests serum ferritin and transferrin saturation are needed to be studied more thoroughly to infuse IV iron to patients with iron deficiency anemia in CKD as many cannot afford ESAs and blood. Ferritin is an important indicator of iron overload as well as an acute phase reactant which increases in inflammatory conditions. Serum ferritin getting raised both in iron deficiency anemia and inflammatory states complicates our diagnosis. In this scenario TSAT plays important role in ruling out iron overload and inflammation is ruled out by inflammatory markers.
Objective: To study the effect of IV iron in patients with serum ferritin >1000ng/ml and TSAT <20%.
Methodology: This study was conducted at Department of Medicine, M.L.B. Medical College; Jhansi from March 2020 to November 2021, after seeking clearance from ethical committee and obtaining written informed consent from patient.
Result: It was seen than 18 patients showed improvement and had increase in Hb by 1g/dl. 1 patient had a reaction and transfusion was stopped immediately and 1 patient was lost to follow up.
Conclusion: Against the popular belief that infusion of iron in patients with raised serum ferritin should not be given, this study showed that after ruling out other causes of raised serum ferritin and iron overload by calculating TSAT, IV iron can be given to patients with raised serum ferritin as it shows improvement in anemia.

Keywords: Iron, anaemia, chronic kidney disease, ferritin

Introduction

Patients with inflammatory conditions such as chronic kidney disease (CKD), inflammatory

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bowel disease (IBD) and chronic heart failure (CHF), have high rates of iron deficiency with adverse clinical consequences [1]. Serum ferritin levels are normally a sensitive marker for iron status but as ferritin is also an acute-phase reactant that becomes elevated in response to inflammation and thus complicates inflammatory. Cytokines produced by inflammation also trigger an increase in hepcidin, which restricts uptake of dietary iron and promotes uptake of iron by ferritin within storage sites. Patients with inflammatory conditions thus have limited availability of iron for erythropoiesis due to increased hepcidin expression, despite normal or high levels of serum ferritin [2]. Two types of iron deficiency occur in CKD.

Absolute versus functional iron deficiency

We need to differentiate between absolute (or storage) iron deficiency and functional (or relative) iron deficiency.

The total body iron stores are depleted in absolute iron deficiency, limiting the production of RBCs. Factors which contribute to absolute iron deficiency are decreased gastrointestinal absorption in patients with CKD and increased blood loss [3].

Functional iron deficiency occurs due to inefficient utilization of iron stores. This occurs due to reticuloendothelial cell iron blockade in anemia of chronic inflammation. Reticuloendothelial cell iron blockade can be triggered by active infection or inflammation, hypoxia, or genetic deficiencies [4]. The other reason can be the use of exogenous EPO. The available iron may be used faster than the existing iron stores are able to release it, because RBC production increases in response to ESAs, leading to a supply/demand mismatch and a "relative" iron deficiency [5]. In these patients, the TSAT may be <20% as the bone marrow takes iron from the circulating transferrin faster than the transferrin can replenish it with iron released from stores. The serum ferritin thus may be normal or elevated [5].

The standard threshold for iron deficiency (<30 μg/L) therefore does not apply and transferrin saturation (TSAT), a marker of iron availability, should also be assessed [2].

Thus we determine the accuracy of serum ferritin and TSAT by their sensitivity and specificity. Sensitivity is the probability that a positive test will accurately identify iron status as deficient. Specificity is the probability that a negative test will accurately identify iron status as not deficient. It is seen that a TSAT of 20% seems to be good in terms of sensitivity, meaning that few patients are truly iron deficient with a TSAT much higher than 20%, but a ferritin cutoff of 100 or even 200 ng/ml miss majority of patients who ultimately may respond to intravenous iron [5].

Newer diagnostic test for detecting iron deficiency anemia in CKD are-

Reticulocyte Hb Content

The reticulocyte Hb content (CHr) is a measure of the amount of Hb in the reticulocytes, which are the RBC that are just 1 or 2 d old. Instead of examining the Hb content of the entire RBC population that may be anywhere between 1 and 120 d old, the CHr provides an idea of how much iron was available for RBC production in a clinically relevant timeframe. The CHr is the absolute amount in picograms of Hb in each reticulocyte. This theoretically should be a good marker, based on whether iron was available for RBC production.

Percentage of Hypochromic Red Cells

Another iron marker is percentage of hypochromic red blood cells (PHRC), which tests the concentration of Hb in RBC. PHRC is based on the Hb concentration in RBC and it takes into account the absolute amount of Hb as well as the size of the cell. The drawback to the use of this test is that the blood samples cannot be shipped because RBC tend to expand while they

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are stored.

Soluble transferrin receptor

Erythroblasts in the bone marrow increase the presentation of membrane transferrin receptor in the setting of iron deficiency. If there are no sufficient iron stores and erythropoiesis is being stimulated by an ESA, then increased transferrin receptors become expressed on the erythroblasts. Some of these receptors come off and qre detectable in the circulation. Thus sTfR correlates with this membrane expression of the transferrin receptor and also tends to be elevated in the presence of increased erythroid activity.

Hepcidin

Hepcidin is a peptide that is produced by the liver for iron homeostasis. It is a important mediator for iron absorption and mobilization. If storage iron is elevated, then the liver synthesizes hepcidin, which gives negative feedback to the gastrointestinal tract, preventing additional exogenous iron absorption. Hepcidin also inhibits the release of iron from the RE system to circulating transferrin. Under normal physiologic circumstances, when iron stores are replete, it plays an important role in protecting the organism from iron overload by preventing the entry of additional iron into the body and maintaining the appropriate balance of storage and circulating iron.
The aim of the present study is to give IV iron to patients with serum ferritin more than 1000ng/ml and TSAT <20% after inflammation and iron overload is ruled out.

Methodology
Venue

This prospective study will be conducted at Department of Medicine, M.L.B. Medical College; Jhansi from March 20120 to November 2021 after seeking clearance from ethical committee and obtaining written informed consent from the patients.

Study design: Prospective

Study period; 18 months

Sample size: 200 cases.

A follow up period of 6 weeks was kept.

Sample size is calculated by the formula n = Z2pq/e2 were n0 is the sample size, Z2 is the confidence level at 95% is the desired level of precision, p is the estimated proportion of an attribute that is present in the population, q is 1-p

Inclusion criteria

- Serum ferritin >1000ng/ml
- TSAT <20%
- ESR, CRP, PCT normal

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Exclusion criteria

- Serum ferritin <1000ng/ml.
- TSAT >20%
- ESR, CRP, PCT.

Data collection

Data was collected by withdrawing blood samples from patients after their consent. Samples were sent for central laboratory panel which included complete blood count, absolute reticulocyte count, general blood picture, parameters of iron metabolism: iron, ferritin, TIBC, and transferrin saturation index (TSAT), complete metabolic panel, vitamin B12 and folic acid levels and inflammatory markers like ESR, CRP and PCT.

Statistics

SPSS (Statistical Package for Social Sciences) and Graph Pad (online) for windows is used for data analysis. Paired t-test is used for comparing means of two dependent groups. P-value <0.05 is considered significant.

Results

The result of our study was that 18 patients showed improvement in hemoglobin and general condition after 6 weeks of follow up. 1 patient had reaction to IV Iron and infusion was stopped and 1 patient was lost to follow up.

Table 1: Serum Ferritin and TSAT

Serum Ferritin	TSAT <20%	TSAT <40%
<1000ng/ml	38	20
>1000ng/ml	50	22

Table 2: Rule out inflammation

Inflammatory markers	Normal	Raised
Serum ferritin >1000ng/ml with TSAT <20%	20	30

Discussion

The objective of the study was to transfuse IV iron in patients with serum ferritin >1000ng/ml but TSAT <20%. According to KDIGO 2012 guidelines IV iron is to be transfused only in patients with TSAT <30% and Serum Ferritin <500ng/ml. As serum ferritin is not a sole indicator of iron deficiency. It is also an acute phase reactant and is a marker of inflammation and hence is often increased in patients with infections, chronic inflammation and in iron overload. This was seen in Jay B Wish *et al.* [5] study of 2006 Assessing Iron Status: Beyond Serum Ferritin and Transferrin Saturation. The study concluded that increasing prevalence of multiple comorbidities among anemic patients with chronic kidney disease has made the use of serum ferritin and transferrin saturation more challenging in diagnosing iron deficiency. The scenario of patients with serum ferritin >800 ng/ml, suggesting iron overload, and transferrin saturation <20%, suggesting iron deficiency, has become more common.
Similar facts were seen in Karima Farrag *et al.*[2] study of 2018 which studied Limitations of Serum Ferritin in Diagnosing Iron Deficiency in Inflammatory Conditions which concluded that the standard threshold for iron deficiency (<30 μg/L) should not be applied and

transferrin saturation (TSAT), a marker of iron availability, should also be assessed.
Elizabeth Katherine Batchelor *et al.* [6] (2020) study on Iron Deficiency in Chronic Kidney Disease: Updates on Pathophysiology, Diagnosis, and Treatment also had similar conclusion. It said that the traditional biomarkers used for the diagnosis of iron-deficiency anemia (IDA) in patients with CKD have limitations, leading to persistent challenges in the detection and monitoring of IDA in these patients.
In my study we ruled out other causes of raised serum ferritin besides iron deficiency like active infections were ruled out by ESR, CRP and PCT reports in patients with serum ferritin >1000ng/ml and iron overload was ruled out by TSAT level >40%. After ruling out these conditions we transfused 100mg of IV iron sucrose for 5 days to the 20 patients eligible for this. After a period of 6 weeks a follow up was done and it was seen that out of 20 candidates, 1 patient had reaction so transfusion was stopped and 1 patient was lost to follow up. Rest all patients showed increase in Hb level by 1g/dl with increase in serum ferritin levels. This was in concordance with DRIVE1 and DRIVE 2 trials done by Daniel W Coyne *et al.* [7] in 2007 and Torois Kappin *et al.* [8] in 2018 respectively-Ferric Gluconate Is Highly Efficacious in Anemic Hemodialysis Patients with High Serum Ferritin and Low Transferrin Saturation: Results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. Administration of ferric gluconate (125 mg for eight treatments) is superior to no iron therapy in anemic dialysis patients receiving adequate epoetin dosages and have a ferritin 500 to 1200 ng/ml and TSAT ≤25%. In conclusion, ferric gluconate maintains hemoglobin and allows lower epoetin doses in anemic hemodialysis patients with low TSAT and ferritin levels up to 1200 ng/ml.

Conclusion

TSAT and serum ferritin have remained the favored markers for assessment of iron status through three iterations of the K/DOQI anemia guidelines because of their widespread availability, extensive literature base, and familiarity. Against the popular belief that infusion of iron in patients with raised serum ferritin should not be given, this study showed that after ruling out other causes of raised serum ferritin and iron overload by calculating TSAT, IV iron can be given to patients with raised serum ferritin.
Despite many concerns regarding the safety of intravenous iron since the first iteration of the K/DOQI anemia guidelines 9 yr ago, there have been few data in the literature from which to conclude that patient outcomes have been adversely affected by the use of intravenous iron within the original K/DOQI parameters.

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