Efficacy of IV Iron Compared to Oral Iron for Increment of Haemoglobin Level in Anemic Chronic Kidney Disease Patients on Erythropoietin Therapy

Adhikary L, Acharya S
Department of Medicine, Kathmandu Medical College Teaching Hospital, Kathmandu, Nepal.

ABSTRACT

Introduction: Anemia is the most common finding in chronic kidney disease patients. Iron supplements are commonly prescribed for these patients with or without erythropoietin therapy by means of oral and intravenous iron. Both oral and intravenous irons have their own advantage and disadvantage, and the efficacy is also different. The objective of the study is to analyze the efficacy of oral and intravenous iron in chronic kidney disease patients on erythropoietin therapy, an erythropoiesis stimulating agents for increment of haemoglobin.

Methods: This is a prospective study comparing intravenous iron to oral iron in chronic kidney disease patients who underwent maintenance hemodialysis at different centers and visited Kathmandu Medical College Teaching Hospital from April 2010 to April 2011. Patients having a haemoglobin level of ≤ 11 g/dl, transferrin saturation (TSAT) ≤ 25%, ferritin ≤ 300ng/ml and who were on erythropoietin therapy were allocated alternately into two groups to receive oral iron (iron fumarate) or IV iron (iv sucrose). Haemoglobin was measured after 30 days of therapy.

Results: A significant increase in haemoglobin levels was observed in both groups. But the mean haemoglobin increment was more in the IV iron group than in the oral iron group. Sixty percent 60% of patients in the IV iron group had an increase in the haemoglobin level of more than 1gm/dl while only 20% of the oral iron group had this increase.

Conclusions: Intravenous iron therapy is more effective in raising the hemoglobin level in hemodialysis dependent chronic kidney disease patients.

Keywords: *anemia, chronic kidney disease, iron*

INTRODUCTION

Iron deficiency anemia can develop relatively early in the course of chronic renal failure (CRF) and also in hemodialysis patients, especially when erythropoietin is given.[1,2] The clinical practice guidelines for the treatment of anemia in chronic kidney disease (CKD) is established in the U.S. by the National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI), and in Canada, by the Canadian Society of Nephrology.[1] Iron supplementation has become an integral part of the management of patients receiving epoetin therapy, and clinicians have found it necessary to learn how and when to use it to the best advantage. Iron therapy in dialysis dependent chronic kidney disease (HD-CKD) patients serves as an adjuvant to erythropoiesis-stimulating

Correspondence:
Dr. Laxman Adhikary
Department of Medicine
Kathmandu Medical College
Kathmandu, Nepal.
Phone: 9851087470
E-mail: adhikarylaxu@gmail.com

agents (ESAs), including epoetin alfa, epoetin beta, or darbepoetin. By contrast, in patients with non-dialysis dependent CKD (ND-CKD), only a third of patients receive ESA therapy.[3] Three routes of administration for iron are available: oral, intramuscular, and intravenous.[4] Moreover, iron deficiency is the most common cause of resistance to erythropoietin therapy, contributing to ineffective erythropoiesis and hematocrit/haemoglobin values below the recommended target range of 11 g/dL-12 g/dL (33% - 36%). Iron supplementation improves iron indices and haemoglobin concentration, and reduces the required ESA dose.[5-12]

Most of the randomized controlled trials have compared intravenous (IV) iron to oral iron in non-dialysis dependent CKD patients.[13-16] Transferrin saturation (TSAT), serum ferritin and haemoglobin levels are useful markers of iron deficiency.[17] In our population, most of the people have nutritional anemia adding to the anemia of CKD. To replenish a good amount of iron, supplements are used by means of oral or IV therapy.

METHODS

A prospective study was conducted in Kathmandu Medical College Teaching Hospital (KMCTH) from April 2010 to April 2011. Ethical approval was taken from the ethical clearance committee and verbal consent was taken from all the patients. CKD patients who had undergone maintenance hemodialysis at different centers and who had visited KMCTH were included in the study. A total of 90 patients who fulfilled the criteria of the study were enrolled in this study. All the patients were on oral iron and erythropoietin therapy. Patients with known allergy to ferrous compound, concurrent infection, co-morbidity other than hypertension and diabetes, who had received blood transfusion or IV iron eight weeks before the beginning of the study, whose stool occult blood was positive, recent surgery eight weeks before the beginning of the study, any known malignancy, and those who had not come for follow-up and hadn't given informed consent were excluded from study. Beside regular tests, their transferrin saturation, serum ferritin and haemoglobin (Hb) levels were measured and recorded at presentation. The patients who had a haemoglobin level of $\leq$ 11 g/dl, TSAT $\leq$ 25%, ferritin $\leq$ 300 ng/ml and who were on erythropoietin therapy were allocated alternately into two groups, 45 patients in each group) to receive oral iron or IV sucrose. In the oral iron group, ferrous fumarate (152 mg = 50 mg elemental iron) was given thrice a day and in the IV iron group, 200 mg of iron sucrose over five minutes in the first five dialysis sessions was given. Both the groups were on erythropoietin beta 4000IU once weekly, irrespective of their weight. The patient's haemoglobin in gm/dl, serum ferritin and transferrin saturation were noted before the division was done. The haemoglobin level was measured after 30 days, as patients who are under regular maintenance haemodialysis are not lost to follow-up in such a time interval. Previous studies have also demonstrated a significant increment of the haemoglobin level with IV irons in 28, 42 and 56 days. The haemoglobin level was measured before and after 30 days.

Comparable variables were analyzed by using the statistical package for software analysis (SPSS), version 16 for windows, with paired t test and chi square test. A P value of < 0.05 was taken to be significant.

Table 1. Baseline characteristics of patients

Variables	Oral iron group (N = 45) (mean $\pm$ SD/%)	IV iron group (N = 45) (mean $\pm$ SD/%)	p value
Age	40 $\pm$ 9.3	39.16 $\pm$ 8.07	0.575
Gender - Male	53.33 %	51.11%	0.833
Haemoglobin gm/dl	9.50 $\pm$ 0.93	8.81 $\pm$ 1.19	0.005
TSAT	15.8 $\pm$ 5.5	16.2 $\pm$ 5.8	0.59
Ferritin	92.2 $\pm$ 85	104 $\pm$ 80	0.50

RESULTS

Both the groups are comparable in the base line characteristics with a lower mean hemoglobin level in the IV iron group than in the oral group. (Table 1). Significant increase in haemoglobin levels was observed in both the groups. But the mean haemoglobin increment was more in the IV iron group than in the oral iron group (+1.06 vs. + 0.32) as shown in Table 2. Sixty percent of the patients in the IV iron group had an increase in the haemoglobin level of more than 1gm/dL while only 24.4% patients in oral iron group had the same level of increase which is statistically significant (p value < 0.05) (Table 3). Only 24.4% patients in IV iron group and 20% patients in oral iron group could achieve the target Hb level (11-12) gm/dl and the difference was not significant. No evidence of fatal hypotension or of allergic reaction was noted in group receiving IV iron.

Table 2. Hemoglobin increment after 30 days

Group	Before study	After 30 days	p value (CI of 95 %)
Oral iron group	9.50 ± 0.93	9.82 ± 1.02	0.014 (0.57 - 0.068)
IV iron group	8.81 ± 1.19	9.87 ± 1.09	0.000 (1.44 - 0.68)

Table 3. Result of increment of haemoglobin

Variables	Oral iron group	IV iron group]	p value
Increament of Hb >1 gm/dL	11 (24.4 %)	27 (60 %)	0.001*
Hb in range (11-12gm/dL)	9 (20 %)	11 (24.4 %)	0.612*

***Pearson Chi square test**

DISCUSSION

Iron deficiency is a known cause of anaemia and lack of response to ESAs in CKD patients. Treatment of iron deficiency with oral iron is associated with non compliance and adverse events.[18] The Current National Kidney Foundation Kidney Disease Outcome Quality Initiation Guideline recommended either oral or IV iron supplement in iron deficient anaemic CKD patients.[19] Some studies have already demonstrated that the efficacy of oral iron is as good as that of IV iron.[15,16] However, promising results were shown in terms of IV iron, not only increasing the Hb level but also replenishing the iron stores.[14,20] We have observed that IV iron is much more efficacious in raising the haemoglobin level by ≥ 1 gm/dl as the primary end point compared to oral iron in HD-CKD patients at the end of 30 days of treatment. Out of all patients, 60 % in the IV iron group had an increase in the Hb of ≥ 1 gm/dl after 30 days of therapy and this proportion was significantly higher compared to oral iron group. However, the rise in Hb as advised by the current NKF-DOQI Guideline (Hb 11 - 12 gm/dl) was observed in only 24.4 % of our patients. This discrepancy may be due to the short duration of study after commencement of iron therapy. Most of our patients were on erythropoietin beta 4000 IU s/c weekly irrespective of weight, and the results would likely meet the guideline criteria if the adequate dose of ESAs as recommended by NKF-DOQI guideline were used for therapeutic purpose. Patients on hemodialysis have lower intestinal iron absorption, greater iron losses, and require greater iron intake to maintain the ESA-driven red cell production than do healthy individuals. In these patients, intravenous iron reduces ESA dose requirements and increases the likelihood of maintaining levels of hemoglobin within the desired range. Oral iron is inferior to intravenous iron in patients on hemodialysis, in part because elevated serum levels of hepcidin prevent intestinal absorption of iron. Increased levels of hepcidin also impair the normal recycling of iron through the reticuloendothelial system.[21] Correction of anaemia in CKD patients has many benefits including the decrease in cardiovascular risk and increase in the quality of life. Studies have shown that 200 mg of IV iron sucrose administered over five min is well tolerated.[16] Among patients receiving oral iron a slight increment in Hb was noted but more increment in the mean Hb was observed with the IV iron group. This may be explained by the fact that in addition to the replenished iron store in CKD patients undergoing MHD, a substantial blood loss occurs during the process of hemodialysis alone, and this may in addition decrease the Hb levels. Administering IV iron will also replete the iron store in a shorter duration compared to oral iron thus raising the Hb levels in anaemic CKD patient undergoing hemodialysis on a fixed ESA regime. According to NKF-DOQI Clinical Practice Guidelines, hemodialysis patients with low serum ferritin or low transferrin saturation need supplementation with parenteral iron in excess of 1000 mg to achieve optimal response in hemoglobin/ hematocrit levels.[1] So we used the lowest possible dose to see the response. Again, for supplementation of the following dose, the IV sucrose at a dose of 200 mg (FDA approved) is well tolerated, with very few side effects, as seen in previous studies.[14] For oral iron, we used the maximum tolerated dose. In a study by Van Wyck DB et al a significant result was obtained when comparing IV iron with oral iron in 28, 42 and 56 days.[14] We analysed the results in a shorter period of 30 days, which would be beneficial in terms of patient compliance and follow-up. We sought to define a promising role of IV iron over oral iron in increment of Hb level as targeted in HD-CKD patients on ESAs therapy. IV iron is safe, compatible and more effective than oral iron treatment. However ESAs also have a role in replenishing some of the iron store in these patients,

which is dose-dependent. Future studies regarding ESA dosing is awaited to compare both oral iron and IV iron in HD-CKD patients.

CONCLUSIONS

IV iron therapy in hemodialysis-dependent CKD patients was more effective than oral iron in terms of raising Hb levels and was not associated with significant adverse effects. A practice to replenish the iron store by IV iron sucrose was a more convenient approach than oral iron therapy and had good compliance in our study population.

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