

Evaluation of the effect of oral versus intravenous iron treatments on anemia in patients with chronic kidney diseases.

Arif Sami Malik *FICMS*.

Abstract

Background: Correction of anemia as a result of renal failure improves cardiovascular function and also provides significant cognitive and emotional benefits. The most appropriate route for iron supplementation has not been determined for patients with chronic renal failure who are not yet on dialysis.

Objective: It is to compare the efficacy and tolerability of oral and intravenous iron as an adjuvant therapy for erythropoietin treated anemic patients with chronic kidney disease in predialysis state.

Methods: Forty five anemic patients with chronic kidney disease were prospectively randomized to receive an oral (ferrous sulfate 200 mg three times daily), or intravenous (300 mg iron dextran/ monthly) iron treatment, the duration of treatment was six months. Erythropoietin (rHuEpo) was simultaneously commenced and the dose adjusted according to pre-established protocol.

Results: There were no significant differences in baseline patients characteristics between the two groups. Four patients suffered possible

allergic reaction to iron dextran. Hemoglobin response in the end of study was similar in two groups, but serum ferritin was significantly higher in the intravenous group. The starting dose of rHuEpo temporarily discontinued in the patients on oral iron and the patients receiving iron dextran rHuEpo was increased after 3 months, final doses on EPO were (33.5) and (41.6) units /Kg/week respectively in the oral and intravenous group. Although gastrointestinal symptoms were more commonly reported in patients taking oral iron.

Conclusions: In pre-dialysis patients; the efficacy of monthly 300 mg iron dextran administered intravenously is not superior in regard to haemoglobin response and EPO dose as compared with daily oral dose of 300 mg of ferrous sulfate or equivalent.

Key words: Chronic renal failure, Erythropoietin, Dialysis, Ferritin, Iron dextran

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Introduction

Anemia increases cardiovascular risk in patients with chronic renal disease⁽¹⁻³⁾. Left ventricular hypertrophy (LVH) is present in approximately three quarters of patients commencing dialysis and predicts mortality⁽⁴⁻⁶⁾. Correction of anemia has been shown to improve cardiovascular function with partial reversal of LVH^(7, 8). There are also cognitive and emotional benefits, which are reflected in improved quality of life scores^(9, 10).

Previous studies have demonstrated that recombinant EPO can improve anemia in patients with renal insufficiency that are waiting for dialysis treatment^(11, 12). The importance of adjuvant iron therapy has not been demonstrated as clearly as for dialysis population^(13, 15), and there have been calls for more detailed studies, particularly comparative trials to ascertain the relative efficacy of different methods of administration⁽¹⁶⁾.

Patients and Methods

This prospective study (interventional study) was carried out in the Al-Kadhimiya Teaching Hospital, department of Internal Medicine. Records of data for all patients whether outpatients or inpatients who were examined to identify individual need to identify individual with Chronic kidney disease (defined

Dept. Medicine, College of Medicine, Al-Nahrain University.

Address Correspondence to: Dr. Arif Sami,
E-mail: dr_arif31@yahoo.com

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as progressive deterioration in renal function with serum creatinine more than 250µmol/L) and worsening of anemia (defined as progressive reduction in hemoglobin concentration to a value of less than 11 gm/dl) , irrespective of gender⁽⁵⁶⁾. Patients who had been treated with IV iron during the previous 6 months were excluded from the study, other exclusion criteria were recurrent gastrointestinal bleeding , previous intolerance of oral iron, poor compliance with medication and allergic reaction to intravenous iron (2, 6,2 and 4 respectively). After obtaining informed consent patients, they were assigned to one of either treatment schedule. One group received an oral ferrous sulfate at dose of 200 mg t.d.s, and the other group received infusion of iron dextran (300 mg over two hours repeated monthly according to serum ferritin level). All patients received subcutaneous EPO. The intended duration of follow up was 6 months. Age, gender, and baseline biochemical, and hematological and serological studies to exclude collagen vascular disease and hepatitis screen were recorded. Measurement of Hb, serum ferritin, creatinine, and CRP, were repeated on monthly basis, three stool specimen were checked for faecal occult blood after three months and whenever there was clinical suspicion of gastro-

intestinal hemorrhage, rHu EPO treatment at adose of 2000 units was discontinued if Hb concentration of 14 gm/dl was exceeded and then re-introduced if values below 12 gm/dl were obtained with subsequent measurements, in cases where the Hb response to treatment was delayed (failure to achieve Hb above 12gm/dl within three months of starting treatment (resistant anemia), EPO was increased to 4000 units twice weekly after the third month, further increase of EPO to maximum dose of 4000 units three times weekly was made if monthly Hb concentration remained below 12 gm/dl, iron therapy was not interrupted unless serum ferritin estimation exceeded 500mg/l.

Results

Fifty nine patients were identified from a systemic review of record and case notes. , 10 patients were excluded because of (recurrent gastrointestinal bleeding 2, previous intolerance of oral iron therapy 6 and four were unable to give their informed consent (Figure 1). Baselines characteristics of the remaining 45 patients are summarized in table one. Twenty-three patients were assigned to a group for which the randomized treatment was oral iron therapy, and the remainder was assigned to a group for which the treatment was a monthly intravenous infusion of iron dextran.

Table 1: Baseline characteristics of treatment group.

	Group receiving oral iron (n=23)	Group receiving IV iron (n=22)
Age	59.9 ± 13.4 *	57.3 ± 14
Gender (M:F Ratio)	15:8	10:12
Haemoglobin (g/dl)	9.7 ± 1.3	9.9 ± 1.6
Ferritin (µg/l)	74 ± 25	100 ± 31

* Mean ± SD

Table 2: The main possible causes of chronic kidney disease

	Group receiving oral iron (n=23)	Group receiving IV iron (n=22)
Pyelonephritis	9	7
Polycystic kidney disease	2	4
Diabetic renal disease	5	0
Glomerular disease (biopsy wise)	1	2
Uncertain	6	9

Two of the included patients had previously commenced low dose of rHuEpo (weekly doses of 2000 and 3000 unit started approximately 4 months prior to enrolment). Both patients were randomized to receive oral iron treatment.

Patients were followed up for an average of 5.2 months. The reasons for an early withdrawal from the study were intolerance to oral iron or gastrointestinal bleeding.

During the study period, a mean of 0.91(0.84-0.98) infusions of iron dextran per patient per month were administered.

The overall response to iron therapy in the both study groups is in table 3. There was no statistical difference in Hb response 12.2(10.6-12.8) versus 12.5(11.6-13.3) g/dl at 6months of treatment in patients who took the oral and I.V groups respectively).

Hb of 12 g/dl was achieved within the first 3 months of treatment in 70% of patients taking an oral iron compared with 59% of patients receiving iron dextran.

Serum ferritin estimation was significantly higher in those receiving intravenous iron from the second

month of treatment 95 (63-149) versus 330 (186-423) µg/l at 6 months.

The initial Epo prescription of 4000U/week could be temporarily discontinued in 43% of the oral iron group vs 33% of the intravenous group after mean intervals of 2.4 and 2.7 months, respectively (NS). The rHuEpo was increased after 3 months in 9% of patients taking oral iron and 19% of patients receiving IV iron. Of those who completed 6 months of treatments, median finishing doses Epo were 33.5 (0-66) U/Kg/week and 41.6(0-124) U/Kg/wk, respectively, in the oral and IV groups, with higher mean and median values in the iron dextran groups for preceding months (figure 4). For patients who discontinued EPO temporarily, the median fall in Hb concentration in the first month after discontinuation for the study population as a whole was 1.1 (0.7-1.2) g/dl, with no significant difference between both treatment groups.

Faecal occult blood testing after 3 months gave uniformly negative results for the 31 patients who provided stool sample.

Table 3: Mean Hb concentration in oral and IV iron treatments.

Months	Mean of Hb concentration(g/dl) in oral iron	Mean of Hb concentration(g/dl) in IV iron
0	9.5	9.7
1	11	11
2	11.4	11.8
3	13	12
4	13.2	11.5
5	12.4	12.8
6	12.2	12.5
Calculated t = 0.3197		
P value = 0.7547		
Degree of freedom =12		
Statistical analysis: p value > 0.05, there is no significant difference between the two groups in mean of Hb concentration		

Table 4: Serum ferritin level in oral and IV iron treated patients.

Months	Serum Ferritin in oral iron	Serum Ferritin in IV iron
0	80	102
1	50	105
2	45	150
3	45	190
4	72	280
5	100	286
6	96	327
Calculated t =3.7839		
p value = 0.0026		
Degree of freedom =12		
Statistical analysis: p value < 0.05, there is significant differences between the two groups.		

Discussion

Early correction of renal anemia is desirable, although the evidence-based for recommending a target Hb, a means of achieving it, has not been firmly established. It has previously been reported that IV iron has greater additive effect with EPO than has oral iron, perhaps as a result of reduced iron absorption from the gut⁽¹⁸⁾, and poor patient compliance with oral medications. Silverberg et al.⁽¹⁹⁾, reported a mean rise Hct of 1.9 vol %

(0.6 g/dl), for dialysis patients not receiving EPO in whom iron dextran (200mg monthly for 5 months) was substituted for oral iron. Later study showed that approximately one third of patients with chronic renal failure achieved Hct of 35% using iron dextran without EPO⁽²⁰⁾.

Individual response to iron could not be predicted from laboratory measurements such as serum creatinine, ferritin, or iron saturation,

The same group has administered more than 20000 mg infusion of iron dextran without complication. Other groups have reported infrequent symptoms with doses of 100⁽²¹⁾ and 200 mg⁽²²⁾ of iron dextran including chest pain, loin pain, and bronchospasm.

The aim of this prospective study was to directly compare the efficacy & tolerability of oral and IV iron as adjuvant therapy for EPO treated anemic patient with chronic renal failure.

The Hb response to EPO and iron was similar with oral and IV iron, a finding that runs contrary to the aforementioned reports but is consistent with observation of Anstasiades et al.⁽²³⁾

There were few limitations affect the results of the current study, the small sample, the adequacy of dialysis and the findings of high prevalence of anemia and malnutrition among our patients

In pre-dialysis patients; the efficacy of monthly 300 mg iron dextran given intravenously is not superior in regard to haemoglobin response and EPO dose as compared with daily dose of oral 600 mg of ferrous sulfate or equivalent.

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