Abstract

Intravenous iron is used in combination with erythropoiesis-stimulating agents to treat the anemia of hemodialysis patients; however, there is variety in the dose and the frequency. So we compare bolus intravenous iron administration protocol vs an intermittent intravenous iron infusion protocol for 3 months in a single blinded design that was conducted on 30 patients randomized into 2 matching groups. Iron parameter, hemoglobin level, and CRP were monitored before and at the end of study. Patients with end stage renal disease on regular hemodialysis with iron deficiency anemia can be treated with intravenous iron administration either by the protocol of divided doses of IV iron through the sessions of hemodialysis or by giving the total dose of iron needed as a single large dose on only one session of hemodialysis, obtaining the same outcome in correction of iron parameters in treatment of iron deficiency anemia.

Introduction

Anemia is common among patients with ESRD and associated with increased morbidity, mortality, and risk of hospitalization [1]. The anemia of ESRD is managed primarily with erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron supplements [2]. Recent safety concerns about ESAs [3,4] as well as changes in reimbursement policies in Medicare’s ESRD program have led to increased reliance on IV iron for the management of anemia [5,6].

Iron supplementation is widely used in HD patients to treat iron deficiency, prevent its development in ESA-treated patients, reduce the ESAs dose and raise the Hb levels in the presence or absence of ESAs treatment, so its use has been increased last years [7,8]. The trend to greater use of iron is reinforced by evidence suggesting that more frequent iron use decreases ESA requirements in patients with treatment-refractory anemia [9,10]. Iron treatment strategies have been reported to vary substantially among clinicians [11-13]. Some nephrologists administer large repletion doses of iron over consecutive dialysis sessions on an intermittent, as-needed basis [11]. Others physicians instead provide low-dose administrations of iron (maintenance dosing) every 1-2 weeks to maintain iron stores. Currently, there is little evidence regarding the effectiveness of these different approaches to iron supplementation.

Aim of the work

This randomized controlled study has been initiated to investigate whether
intermittent intravenous iron intake differs from a protocol of total dose correction iron administration, in terms of achieved Hb level or iron parameters and EPO requirement.

**Method**

This was a randomized controlled study that was conducted on 30 adult chronic hemodialysis patients, on regular dialysis thrice weekly with acceptable urea reduction rate more than 65% who have iron deficiency anemia, with a stable hemoglobin and had no background of hematological disorder. They were divided into 2 groups: Group A & Group B matching number, age, gender of the patients, dialysis duration & type of vascular access used. Group A included 15 patients having a bolus intravenous iron administration protocol compared with Group B included 15 patients having an intermittent intravenous iron infusion protocol for 3 months. Patients with malignancy, recent history of bleeding, liver, thyroid, or infectious diseases, alterations in leucocyte count or formula, concurrent sepsis and/or treatment with steroids or immunosuppresses were excluded. In addition to recording demographic data, (Table 1) pre and post-study measurements of hemoglobin and Serum ferritin (ng/ml), Serum iron (mcg/ml), Total Iron Binding capacity TIBC (mcg/dl), TSAT (%) levels & CRP (mg/dl) were recorded.

Amount of iron required by (mg) throughout the study was measured by following equation (Target Hb-Patient Hb) g/l X body weight {kg} X 0.24+Iron stores{mg} 500 is recommended for iron stores in patients have body weight above 30kg (www.medicines.org.uk/emc/medicine/14139). These patients were closely observed for adverse reaction such as metallic taste, fever, hypotension, pruritis, phlebitis, dyspnea, nausea, vomiting and anaphylaxis. Any adverse events were recorded either during or immediately after the injection up to 30 minutes. The patient was also advised to contact the unit if they developed any subsequent symptoms.

**Statistical Methods**

Data were analyzed using PASW version 18 (IBM© Corp., Armonk, NY, USA). Normality of data was tested using D’Agostino-Pearson test, normally distributed numerical variables were presented as mean ± SD. Numerical data were compared using unpaired t test. Degree of change of different parameters was calculated as follows ((After-Before)/before), to calculate the ratio of change in reference to the baseline reading of each parameter (Table 2).

**Results**

Study was conducted on 30 patients randomized into 2 groups to receive either bolus iron infusion or intermittent iron therapy in a single blinded design, iron parameter, hemoglobin level, and CRP were monitored at the start and the end of study for change. In both groups there were a significant increase in hemoglobin level, TSAT (%) & ferritin level without significant change in CRP titer.

| Table 1: Demographic data. |
|---------------|----------------|----------------|
| **Age (Years)** | Bolus | Intermittent | P Value |
| 42±11 | 41.8±12 | 0.645 |
| **Gender** | | | |
| Male | 9 (60%) | 8 (53.3%) | 0.713 |
| Female | 6 (40%) | 7 (46.7%) | |
| **Duration on dialysis (Years)** | 4±2.8 | 4.3±1.5 | 0.54 |
| **HTN** | 7 (46.7%) | 8 (53.3%) | 0.87 |
| **DM** | 9 (60%) | 10 (66.7%) | 0.76 |
| **Vascular Access** | AVF | AVG | Access |
| 9 (60%) | 4 (26.7%) | 2 (13.3%) | 0.074 |
| 10 (66.7%) | 5 (33.3%) | |
| 0 | | | |
Discussion

The importance of intravenous (IV) iron as an adjunctive treatment had been increasingly recognized [14]. This is particularly true in hemodialysis patients, for whom iron losses are greater and IV iron supplementation often is necessary to optimize the erythropoietin activity. In some patients, IV iron may improve hemoglobin levels even before erythropoietin therapy is started, whereas concomitant use of IV iron along with EPO can enhance the erythropoietin response and reduce dose requirements of EPO. Data from studies have been pivotal in generating the recommendation in the revised European Best Practice Guidelines on renal anemia management that IV iron supplementation is likely to be required in all hemodialysis patients [15].

In our study 30 hemodialysis patients had iron deficiency anemia were divided into two matching groups for correction of iron deficiency, Group A included 15 patients took a bolus intravenous iron administration protocol (total dose correction of iron) & Group B included 15 patients having an intermittent intravenous iron infusion protocol for 3 months. We used iron dextran in both groups calculating the amount of iron by mg needed by the following equation: \( \text{Target Hb-Patient Hb) g/l X body weight (kg) X 0.24 + Iron stores (mg)} \) 500 is recommended for iron stores in patients have body weight above 30kg (www.medicines.org.uk/emc/medicine/14139) Comparing between the two groups in the outcome of correction of anemia with fixed dose of erythropoietin injection of 100mic/kg per week.

Patients Group A who received total dose correction of iron The median hemoglobin (Hb) level prior to infusion were 8.14 gm/dl and post-infusion significantly increased to 11.51 gm/dl (p<0.001). Ferritin levels increased significantly from a median of 249.73 ng/ml pre-infusion to 596.33 ng/ml post-infusion (p<0.001), also TSAT (%) significantly increased from 14.49 to 32.07 (p<0.001) & there was insignificant decrease in CRP 7.60 mg/dl to 6.13 mg/dl (p=0.036).

Patients Group B who received total dose correction of iron The median hemoglobin (Hb) level prior to infusion were 8.15 gm/dl and post-infusion significantly increased to 11.29 gm/dl (p<0.001). Ferritin levels increased significantly from a median of 249.87 ng/ml pre-infusion to 598.33 ng/ml post-infusion (p<0.001), also TSAT (%) significantly increased from 15.01 to 30.97 (p<0.001) & there was insignificant decrease in CRP 7.47 mg/dl to 6.73 mg/dl (p=0.452).

There were no significant difference between either methods of iron therapy as regard correction of hemoglobin level or iron parameters or risk of infection on the short term period (Table 3). Our results were compatible with Fenwick and Peebles [16], who concluded in their retrospective study the effectiveness of high total dose correction of iron in achieving good levels of iron stores in HD patients and offering a strong alternative to the wide practice of frequent (e.g. weekly/fortnightly) low-dose supplementation (intermittent doses) in management of anemia. The Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) I and II studies found that, in patients with high ferritin and low TSAT (a subgroup likely to be hypo responsive to
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In both DRIVE I and II, there were no increases in the risks of infection in the iron-treated groups. Feldman and colleagues examined the effect of IV iron administration and mortality in a cohort of over 32,000 dialysis patients and did not find an association of cumulative dose of IV iron with mortality [19]. Another study of over 58,000 patients by Kalantar-Zadeh and colleagues also did not find an association of iron dose with mortality, either all cause or cardiovascular mortality [20]. Rather, the administration of up to 400 mg was associated with improved survival overall, and among many relevant subgroups. At doses greater than 400 mg, there was a trend towards increased mortality. Abhijit et al. [21], results complement and extend these previous studies. Like them, they did not find a consistent or meaningful association of IV iron with cardiovascular morbidity or mortality.

Conclusion

Patients with end stage renal disease on regular hemodialysis with iron deficiency anemia can be treated with intravenous iron administration either by the protocol of divided doses of IV iron through the sessions of hemodialysis or by giving the total dose of iron needed as a single large dose on only one session of hemodialysis, obtaining the same outcome in correction of iron parameters in treatment of iron deficiency anemia. However, additional safety concerns of IV iron administration, including potential infectious complications and long-term cardiovascular safety warrant further scrutiny.

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Table 3: Paired testing of parameters before and after iron therapy in either group.

| Parameter     | Intermittent | Mean ± SD | P Value | Bolus | Mean ± SD | P Value |
|---------------|--------------|-----------|---------|-------|-----------|---------|
| Hb (gm/dl)    | Baseline     | 8.14 ± 0.43 | < 0.001 | After | 11.51 ± 0.52 | < 0.001 |
| Iron (mcg/dl) | Baseline     | 49.73 ± 20.89 | < 0.001 | After | 94.80 ± 15.94 | < 0.001 |
| TIBC (mcg/dl) | Baseline     | 333.20 ± 78.03 | 0.088 | After | 293.07 ± 43.36 | 0.047 |
| TSAT (%)      | Baseline     | 14.49 ± 3.77 | < 0.001 | After | 32.07 ± 3.24 | < 0.001 |
| Ferritin (ng/ml) | Baseline | 249.73 ± 42.35 | < 0.001 | After | 596.33 ± 26.52 | < 0.001 |
| CRP (mg/dl)   | Baseline     | 7.50 ± 2.72 | 0.036 | After | 6.13 ± 2.13 | 0.452 |
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