Comparative Study of Efficacy of Intravenous Iron Sucrose versus Ferric Carboxymaltose in the Treatment of Iron Deficiency Anaemia

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ABSTRACT

Background: Iron deficiency anaemia (IDA) is a common haematological complication with potentially serious clinical consequences that may require intravenous iron therapy. Parenteral iron therapy results faster and higher replenishment of iron stores and correction of Haemoglobin (Hb) levels with better compliance. The study was to compare the efficacy of intravenous ferric carboxymaltose with intravenous iron sucrose to treat iron deficiency anaemia.

Methods: 188 patients were included in the study. 100 patients were given iron sucrose. After a 25 mg test dose on the first infusion only, this was given at a dose of 300 mg by intravenous infusion diluted in 100 ml of normal saline, every alternate day. 88 patients were treated with ferric carboxymaltose at a dose of 500 mg diluted in 100 ml of normal saline by intravenous infusion. Hb level and serum Ferritin of both groups were done before iron therapy and 3 weeks after iron therapy.

Results: The mean±SD rise of haemoglobin concentration 3 weeks after iron therapy in iron sucrose group was 11.0±0.61 g/dL, while in ferric carboxymaltose group was 11.2±0.64 g/dL. The mean±SD ferritin 3 weeks after iron therapy in iron sucrose group was 76.0±14.28 ng/mL, while in ferric carboxymaltose group was 80.0±15.16 ng/mL. No serious adverse events were reported in either the ferric carboxymaltose group or iron sucrose group.

Conclusions: Ferric carboxymaltose causes higher rise in Hb level as compared to parenteral iron therapy.

Keywords: Ferric carboxymaltose, Iron sucrose, Iron deficiency anaemia, Intravenous iron therapy.

Introduction

Iron is one of the most common elements in the Earth’s crust, yet iron deficiency is the most common cause of anaemia, affecting about 500 million people worldwide.¹ It is particularly frequent in low income populations, such as in sub-Saharan Africa or South-Asia, where the diet can be of poor quality and
parasites (e.g. hookworm or schistosomiasis), which cause iron loss due to haemorrhage, may be present. Moreover, the body has limited ability to absorb iron. Iron deficiency is the major cause of a microcytic, hypochromic anaemia, in which the two red cell indices, mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH), are reduced and the blood film shows small (microcytic) and pale (hypochromic) red cells. This appearance is caused by a defect in haemoglobin synthesis. Oral administration of iron is the conventional approach in the treatment of IDA. However, bioavailability of oral iron is low and intestinal absorption is compromised in many cases. Therapeutic effect of oral iron supplement is relatively slow so it took at least six months to replenish iron stores completely.2 Intravenous iron therapy is a useful treatment option for the rapid correction of iron deficiency anaemia and can be used to avoid or reduce the requirement for blood transfusion. Several intravenous iron preparations are available commercially which differ in cost, mode of administration and side effect profile. There are few data directly comparing the efficacy of these preparations. In this prospective single-centre study, one hundred and eight-eight patients were treated using two different iron preparations (iron sucrose and ferric carboxymaltose) and compared the effect on haemoglobin levels, serum iron, Total iron-binding capacity (TIBC) and serum ferritin three weeks after treatment.

Materials and Methods

This was a prospective, randomized study without blinding. One hundred and eighty-eight patients, 84 male and 104 females with iron deficiency anaemia were included in this study. The study was conducted in the Department of Haematology, CMH Dhaka from Jan 2015 to Dec 2017. Patients were directly reported to our haematology department or referred by medical or surgical teams for assessment and management of anaemia. After through clinical assessment by a haematologist, patients underwent intravenous iron treatment.

Inclusion criteria: a) Patients with proven iron deficiency anaemia. b) Patients with intolerant to or unresponsive to oral iron treatment. c) Patients who had elective surgery schedule and required a rapid correction of anaemia. d) When it was felt by a consultant haematologist that oral iron treatment alone would be insufficient treatment.

Exclusion criteria: (a) Patients with severe anaemia in decompensated state requiring blood transfusion. (b) Patients suffering from anaemia due to acute blood loss. (c) Any haematological disorder other than iron deficiency anaemia. (d) Patients suffering from chronic illness like renal cardiac or hepatic. (e) Known hypersensitivity to injectable iron compounds.

100 patients were given iron sucrose. After a 25 mg test dose on the first infusion only, this was given at a dose of 300 mg by intravenous infusion over two hours diluted in 100 ml of normal saline, every alternate day. The median number of infusions was 4, and the range was 3–6.

88 patients were treated with ferric carboxymaltose at a dose of 500 mg diluted in 100 ml of normal saline by intravenous infusion over 30 minutes.

3 weeks after completion of iron therapy, patients were reviewed and blood sample was taken for measurement of full blood count and serum ferritin.

The baseline changes and the values at week 3 for continuous variables were compared between ferric carboxymaltose and iron sucrose groups. Before iron therapy and 3-week after iron therapy value of Hb, MCV, serum iron, TIBC, serum Ferritin levels were compared using one-way ANOVA tests. Also, the statistical analyses of parameters were obtained from a comparison using the unpaired t-test. Repeated measure analysis was carried out to see the trend of parameters with time. The statistical analysis was done using SPSS version 20.

Results

Table 1 shows among 188 patients, males were 84 (44.68%) and females 104 (55.32%) with female to male ratio being 1.2:1. The maximum number of patients 77 (40.95%) was found in the age group of 15-30 years, followed by 57 (30.31%) and 33 (17.55%) in the age group of 31-45 and 46-60 respectively.

Table 1: Age distribution (n:188)

| Age group in year | Male; n (%) | Female; n (%) | Total; n (%) |
|-------------------|-------------|---------------|--------------|
| 15-30             | 30 (15.96)  | 47 (25.00)    | 77 (40.96)   |
| 31-45             | 25 (13.30)  | 32 (17.02)    | 57 (30.32)   |
| 46-60             | 19 (10.11)  | 14 (7.45)     | 33 (17.55)   |
| >60               | 10 (5.32)   | 11 (5.85)     | 21 (11.17)   |
| **Total**         | **84 (44.68)** | **104 (55.32)** | **188 (100.00)** |
The red blood cell parameters of patients with iron deficiency anaemia before iron therapy. The mean±SD haemoglobin concentration was 6.1±1.31 g/dL, while mean±SD value of total red blood count, HCV and MCH was 3.45±0.58 x10^{12}/L, 65.80±5.17 fL and 20.40±3.46pg respectively in iron sucrose group. The mean±SD value of RDW of iron sucrose group was 16.60±4.20%. The mean±SD value of haemoglobin concentration, MCV, MCH and RDW was 6.3±1.37 g/dL, 3.36±0.69x10^{12}/L, 64.90±5.20 fL, 19.40±3.50 pg and 15.20±5.01% respectively in ferric carboxymaltose group. (Table 2)

Table 2: Baseline red blood cell parameters before iron therapy (n:188)

| Variables | Iron sucrose (n:100) | Ferric carboxymaltose (n:88) | P-value |
|-----------|---------------------|-----------------------------|---------|
| Hb (g/dL) | Mean±SD             | Mean±SD                     |         |
|           | 6.1±1.31            | 6.3±1.37                    | 0.3     |
| RBCs (x10^{12}/L) | 3.45±0.58           | 3.36±0.69                   | 0.33    |
| MCV (fL) | 65.80±5.17          | 64.90±5.20                  | 0.23    |
| MCH (pg) | 20.40±3.46          | 19.40±3.50                  | 0.05    |
| RDW      | 16.60±4.20          | 15.20±5.01                  | 0.03    |

The concentration of serum iron profiles of the study population before iron therapy. The mean±SD concentration of serum iron, TIBC and serum ferritin was 32±15.18 µg/dL, 424±56.10 µg/dL and 8.7±8.7 ng/mL respectively in iron sucrose group, while the mean±SD concentration of serum iron, TIBC and serum ferritin was 30±14.21 µg/dL, 456±59.13 µg/dL and 10.9±8.8 ng/mL respectively in ferric carboxymaltose group. (Table 3)

Table 3: Baseline serum iron profile before iron therapy (n:188)

| Variables | Iron sucrose (n:100) | Ferric carboxymaltose (n:88) | P-value |
|-----------|---------------------|-----------------------------|---------|
| Iron (µg/dL) | Mean±SD             | Mean±SD                     |         |
|           | 32±15.18            | 30±14.21                    | 0.35    |
| TIBC (µg/dL) | 424±56.10           | 456±59.13                   | 0.0002  |
| Ferritin (ng/mL) | 8.7±5.51            | 10.9±8.8                    | 0.03    |

Three weeks after the last iron infusion the red cell parameters and iron parameters had raised from baseline significantly in both groups. Table 4 shows the mean±SD haemoglobin concentration 3 weeks after iron therapy in iron sucrose group was 11.0±0.61 g/dL, while in ferric carboxymaltose group was 11.2±0.64 g/dL. (Table 2)

Table 4: Red blood cell parameters after 3 weeks of iron therapy (n=188)

| Variables | Iron sucrose (n:100) | Ferric carboxymaltose (n:88) | P-value |
|-----------|---------------------|-----------------------------|---------|
| Hb (g/dL) | Mean±SD             | Mean±SD                     |         |
|           | 11.0±0.61           | 11.2±0.64                   | 0.36    |
| RBCs (x10^{12}/L) | 4.5±0.28             | 4.6±0.26                    | 0.01    |
| MCV (fL) | 84±5.52             | 85±6.05                     | 0.23    |
| MCH (pg) | 26±1.37             | 27±1.26                     | 0.0001  |
| RDW      | 12.5±1.48           | 13.4±1.53                   | 0.0001  |

The mean±SD ferritin 3 weeks after iron therapy in iron sucrose group was 76.0±14.28 ng/mL, while in ferric carboxymaltose group was 80.0±15.16 ng/mL.

Table 5: Serum iron parameters after pg. 3 weeks of iron therapy (n:188)

| Variables | Iron sucrose (n:100) | Ferric carboxymaltose (n:88) | P-value |
|-----------|---------------------|-----------------------------|---------|
| Iron (µg/dL) | Mean±SD             | Mean±SD                     |         |
|           | 62±16.20            | 64±15.14                    | 0.38    |
| TIBC (µg/dL) | 280±21.41           | 289±21.60                   | 0.004   |
| Ferritin (ng/mL) | 76±14.28            | 80±15.16                    | 0.06    |

The mean±SD haemoglobin concentration before iron therapy in iron sucrose group was 6.1±1.31 g/dL, while in ferric carboxymaltose group was 6.1±1.31 g/dL. Baseline serum iron profile before iron therapy in iron sucrose group was iron 32±15.18 µg/dL, TIBC 424±56.10 µg/dL, ferritin 8.7±5.51 ng/mL, whereas in ferric carboxymaltose group was iron 30±14.21 µg/dL, TIBC 456±59.13 µg/dL, ferritin 10.9±8.8 ng/mL. Three weeks after the last iron infusion the red cell parameters and iron parameters had raised from baseline significantly in both groups. The mean±SD haemoglobin concentration 3 weeks after iron therapy in iron sucrose group was 11.0±0.61 g/dL, while in ferric carboxymaltose group was 11.2±0.64 g/dL. The mean±SD ferritin 3 weeks after iron therapy in iron sucrose group was 76.0±14.28 ng/mL, while in ferric carboxymaltose group was 80.0±15.16 ng/mL.

In our study, no serious side effects were observed in either group. Three patients experienced an adverse event attributable to intravenous iron therapy. Two patients in the iron sucrose group experienced hypotension during infusion and one patient in the ferric carboxymaltose group noticed an urticarial rash shortly after the infusion.

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Discussion

Anaemia is present when the haemoglobin level in the blood is below the lower extreme of the normal range for the age and sex of the individual. The lower limit of normality is reduced during pregnancy.3

According to the World Health Organization (WHO), anaemia is defined as a haemoglobin level <13 g/dl in men, <12 g/dl nonpregnant women and <11 g/dl in pregnancy.4

Iron is a trace element that is required for numerous cellular metabolic functions. As iron is toxic when present in abundance, tight regulation is required to avoid iron deficiency or iron overload.5 The amount of iron in the adult human body is normally about 50 mg/kg in males and 40 mg/kg in females.6 Iron deficiency anaemia is a worldwide health problem and is the most common form of nutritional deficiency. It has been estimated that 20 percent of the world’s population is iron deficient and iron deficiency anaemia is the most common type of anaemia met with in clinical practice.3 The current first line of therapy for patients with iron deficiency anaemia is oral iron supplementation. Oral supplementation is cheap, safe, and effective at correcting iron deficiency anaemia. However, it is not tolerated by some patients and in a subset of patients it is insufficient. In these types of patients, intravenous iron therapy should be considered. Indications when intravenous iron therapy should be considered:7

- Intolerance, nonresponse, poor adherence to oral iron
- Rapid or significant correction of anaemia and/or iron deficiency needed
- Medical and surgical conditions with decreased absorption (cause cannot be treated)
- Iron-refractory iron deficiency anaemia (IRIDA)
- Chronic heart disease (systolic, NYHA class II–IV)
- Chronic kidney disease (dialysis, or with ESA treatment)
- Inflammatory bowel disease (active disease or haemoglobin <10 g/dl)
- Preoperatively (surgery scheduled in < 6 weeks)
- Pregnancy (second trimester if haemoglobin <10.5 g/dl and third trimester).

ESA, erythropoiesis-stimulating agents; NYHA, New York Heart Association.

There are various iron preparations available for administration but differs in their efficacy and safety profile. In our study we have compared two parenteral preparations iron sucrose and ferric carboxymaltose for the treatment of iron deficiency anaemia. Both compounds are equally safe and effective to improve Hb levels and iron stores rapidly.

Formula to calculate iron requirements to replete iron stores: Total deficit in mg = weight (Kg) X (Ideal haemoglobin-Actual haemoglobin) X 0.24 + Depot iron.8

Depot iron is calculated as 15 mg/kg up to 34 kg, maximum is up to 500 mg after 34 kg body weight.

188 patients were included in the study. 100 patients were given iron sucrose. After a 25 mg test dose on the first infusion only, this was given at a dose of 300 mg by intravenous infusion diluted in 100 ml of normal saline, every alternate day. 88 patients were treated with ferric carboxymaltose at a dose of 500 mg diluted in 100 ml of normal saline by intravenous infusion. Hb level and serum Ferritin of both groups were done before iron therapy and 3 weeks after iron therapy.

The mean±SD rise of haemoglobin concentration 3 weeks after iron therapy in iron sucrose group was 11.0±0.61 g/dL, while in ferric carboxymaltose group was 11.2±0.64 g/dL. The mean±SD ferritin 3 weeks after iron therapy was 76.0±14.28 ng/mL, while in ferric carboxymaltose group was 80.0±15.16 ng/mL. No serious adverse events were reported in either the ferric carboxymaltose group or iron sucrose group.

In the present study the mean haemoglobin level achieved in intravenous ferric carboxymaltose group was significantly higher than in intravenous iron sucrose group. In ferric carboxymaltose group, the target haemoglobin was achieved faster in a number of cases than iron sucrose group. Notably, serum ferritin which is a marker of iron stores increased significantly in ferric carboxymaltose group in comparison to iron sucrose group which prevents the recurrence of iron deficiency anaemia.

In Lee S et al study ferric carboxymaltose was as effective as iron sucrose in achieving Hb ≥10 g/dL within 2 weeks after the first administration (78.8% vs 72.3%). The time to reach Hb ≥10 g/dL was significantly shorter in the ferric carboxymaltose group than in the iron sucrose group (7.7 days vs 10.5 days). Mean Hb levels were higher in the ferric carboxymaltose-treated patients than in the iron sucrose-treated patients with borderline significance.9
In Joshi SD et al study there was statistically significant rise of Hb in ferric carboxymaltose group 4.68 g/dl compare to iron sucrose group 3.92 g/dl. Mean rise of serum ferritin was 71.07±27.23 and 95.39±45.84 in iron sucrose and ferric carboxymaltose group.

In Seid M et al study ferric carboxymaltose-treated subjects were significantly more likely to achieve a haemoglobin greater than 12 g/dl in a shorter time period with a sustained haemoglobin greater than 12 g/dl at day 42, achieve haemoglobin rise 3 g/dl or greater more quickly and attain higher serum transferrin saturation and ferritin levels.

Intravenous iron therapy with iron sucrose and ferric carboxymaltose both are effective in treating iron deficiency anaemia. But treatment with ferric carboxymaltose seems to be more cost-effective when compared to iron sucrose because of fewer administrations are required and more convenient for patients.

Conclusion
Intravenous iron therapy in the form of ferric carboxymaltose is more convenient, effective, faster acting and safe than intravenous iron sucrose therapy for the treatment of severe iron deficiency anaemia. Iron deficiency anaemia is a significant public health concern that can cause debilitating clinical consequences across age groups, genders and clinical conditions. Early diagnosis and effective management are thus needed to avoid harmful clinical complications.

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