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CLINICAL ARTICLE

Randomized controlled trial comparing ferric carboxymaltose and iron sucrose for treatment of iron deficiency anemia due to abnormal uterine bleeding

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ABSTRACT

Objective: To evaluate the efficacy and safety of intravenous ferric carboxymaltose (FCM) in comparison with intravenous iron sucrose (ISC) in the treatment of anemia due to abnormal uterine bleeding (AUB). *Methods:* A randomized controlled trial was conducted between April 2013 and May 2014 in patients older than 18 years of age presenting at a hospital in New Delhi, India, with anemia due to AUB. Patients were randomized in a 1:1 ratio to receive treatment with intravenous FCM or ISC. The primary outcome, increase in hemoglobin above baseline, was monitored over a 12-week period. Patients completing the full treatment and follow-up protocol were included in the analyses. Participants and investigators were not masked to treatment allocations. *Results:* Overall, 30 patients were assigned to each group. Increases in mean hemoglobin levels from baseline were significantly higher in the FCM group at 6 weeks ($P = 0.005$). At 12 weeks, there was no significant difference in hemoglobin increase from baseline between the two groups ($P = 0.11$). Adverse events were similar between both treatment groups. *Conclusion:* Treatment with FCM resulted in a rapid increase in hemoglobin levels in patients with anemia due to AUB, with similar increases in hemoglobin over a 12-week period.

Clinical Trial Registration (www.ctri.nic.in): CTRI/2015/09/006224

1. Introduction

Abnormal uterine bleeding (AUB) is the most commonly observed symptom among women of reproductive age (15–49 years) presenting to gynecologic outpatient departments [1]. Although treating the specific pathology that is causing heavy bleeding is essential, many patients with AUB have anemia due to acute or chronic blood loss. India has one of the highest prevalences of anemia in the world across all age groups [2]. The 2005–2006 National Family Health Survey reported that the prevalence of anemia among women of reproductive age in India was 55% [3].

The causes of this high prevalence of anemia in India include a low intake of dietary iron and folic acid, poor bioavailability of iron in the phytate-rich Indian diet, and chronic blood loss due to infections such as malaria and hookworm [4]. Additionally, AUB and untreated gynecologic problems are major causes of anemia in adolescents and women of reproductive age [5].

Although oral iron therapy is the gold-standard treatment for iron deficiency anemia, gastrointestinal adverse effects, poor patient compliance, and the prolonged time taken to increase hemoglobin levels limit its clinical utility [6]. Additionally, in patients requiring rapid correction of anemia owing to surgery, oral iron therapy has limited utility.

Intravenous iron preparations have revolutionized the treatment of anemia. Iron dextran was among the first parenteral iron preparations to be marketed; however, owing to anaphylactic adverse effects, it is no longer in use [7]. Over the past 20–30 years, intravenous iron sucrose (ISC) has become the preferred iron preparation for parenteral use. The only significant disadvantage of ISC is that it necessitates multiple infusions and prolonged infusion times. Repeated visits to a clinic are required because patients cannot receive more than 600 mg in 1 week [8].

A recently developed parenteral iron preparation is ferric carboxymaltose (FCM). It is a type-I iron complex that can be administered in doses of up to 1000 mg per session [9]. FCM is dextran free and, consequently, does not cause similar anaphylactic reactions to iron dextran.

The aim of the present study was to compare the efficacy, safety, impact on patient fatigue levels, and cost-effectiveness of intravenous FCM and ISC in patients with anemia due to AUB.

2. Materials and methods

The present prospective randomized controlled trial was conducted at the Department of Obstetrics and Gynecology of the All India Institute

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of Medical Sciences, New Delhi, India between April 1, 2013 and May 31, 2014. Ethical clearance was received from the institute's Ethics Committee before beginning the study. All patients provided written informed consent before the start of the study.

Patients presenting to the study institute with AUB were screened for eligibility. Eligible patients were older than 18 years of age, had a serum hemoglobin concentration of 60.0–109.9 g/L, were experiencing heavy uterine bleeding with a pictorial bleeding assessment chart (PBAC) score higher than 100, and did not intend to conceive during the 3-month study period. Patients were excluded from the study if they were experiencing anemia with any cause other than iron deficiency anemia; if they had erythropoiesis, hemochromatosis, chronic infections like hepatitis and HIV, gynecological malignancies, or endometrial hyperplasia with atypia; if they were receiving myelosuppressive therapy; if they were consuming alcohol or using illicit drugs; or if they had a serum transaminase level greater than 1.5 times the upper limit of normal or had a serum creatinine level of higher than 20.0 mg/L.

Patients were randomized in a 1:1 ratio using a computerized randomization table to receive treatment with either FCM (group I) or ISC (group II). Investigators and participants were not masked to treatment allocations.

Following recruitment, full patient medical histories were recorded and each patient underwent a thorough general examination. Patient blood loss was assessed by PBAC scoring [10] and the cause of AUB was categorized according to the PALM-COEIN criteria [11].

Baseline hematological measurements were made, including serum hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, serum ferritin, and serum iron, using a commercially available system (Sysmex 1800i; Sysmex, Mississauga, Canada). Other baseline measurements included platelet count, total/differential leukocyte count, liver-function tests, kidney-function tests, ultrasonographic examination of the abdomen and pelvis, endometrial aspiration, and hysteroscopy. Patient fatigue was measured using a four-point numeric scale [8] and a linear analog scale assessment (LASA) that recorded scores between 0 (no fatigue) and 10 (worst possible fatigue) [12].

The total iron deficit was calculated for each patient using the Ganzoni formula [13]:

$$\textit{Total iron deficit}(mg) = \textit{Patient weight}(kg) \times (150 - \textit{Patient Hb}[g/L]) \times 2.4 + 500$$

After calculating the total iron deficit, patients in group I received FCM (Inj Orofer FCM, Emcure Pharmaceuticals Ltd, Pune, India) at up to a maximum dose of 1000 mg once per week (administered as 1000 mg diluted in 200 mL 0.9% normal saline over 15 minutes). Patients in group II received a 300-mg dose of ISC (Inj Orofer S; Emcure Pharmaceuticals Ltd, Pune, India) twice a week (in 200 mL 0.9% normal saline over 2 hours). After receiving sufficient doses to meet their iron deficit, patients attended follow-up appointments every 2 weeks after the initiation of treatment for a total of 6 weeks; after this, patients attended a final follow-up visit 12 weeks after treatment. Serum hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, serum ferritin, and patient fatigue were recorded at each follow-up visit. Patients reported minor or major adverse events at follow-up visits. Details of any patient withdrawals from the study were recorded.

The primary outcome was the rise in hemoglobin levels above baseline. Secondary outcomes included the proportion of patients in each group achieving normal hemoglobin levels (≥120.0 g/L), improvements in serum ferritin levels, improvements in patient-fatigue levels, and cost-effectiveness (measured as the total cost of treatment per patient). All adverse events occurring in the study population were recorded.

Sample size was calculated based on the findings of a study by Van Wyck et al. [14] where, after 6 weeks of follow-up, patient hemoglobin levels increased to 128 ± 13 g/L following treatment with FCM, and increased to 121 ± 16 g/L in patients who received treatment with ISC. With a study power of 80% and an alpha-error value of 5%, it was calculated that 26 participants were necessary in each treatment arm. The decision was made to enroll 30 patients in each group to account for a dropout rate of 10%.

Data were expressed as the mean ± SD, the number of patients (percentage), or the median (range), as appropriate. Statistical analyses were performed using Stata version 11.0 (StataCorp LP, College Station, TX, USA). Analyses of the primary and secondary outcomes excluded any patients who did not complete the full study protocol. Continuous variables were analyzed using a Student *t* test for independent samples and a Wilcoxon rank-sum test when the data were not normally distributed; categorical variables were analyzed using the Fisher exact test. For each of the follow-up visits, the primary and secondary outcomes were compared between the study groups using the generalized estimating equation. Serum ferritin was compared between the groups and within the groups using the Wilcoxon rank-sum test and the Wilcoxon signed-rank test, respectively. A Student *t* test for independent samples was used to compare the cost effectiveness between the study groups. The results of the analyses were reported as the difference in the means (95% confidence interval [CI]) between the groups for each variable. Results were considered to be statistically significant when $P < 0.05$.

3. Results

During the study period, 73 patients presented at the study department with AUB and were screened for enrollment. A total of 60 patients met the inclusion criteria and consented to participate in the present study, and 30 patients were randomized to each group. Adverse events resulted in one patient withdrawing from each treatment group; consequently, 29 patients were included in the analyses for each group (Fig. 1).

The mean age of participants was 35.7 ± 8.2 years. Table 1 details the baseline characteristics of the two study groups. Across the whole study cohort, moderate anemia (80–109.9 g/L) was recorded in 24 (40%) patients and severe anemia (<80 g/L) was observed in 36 (60%) patients. The mean baseline PBAC scores were 586.3 and 526.3 in the FCM and ISC groups, respectively ($P = 0.4$). Beta thalassemia was recorded in three patients and raised fetal hemoglobin was recorded in one patient. Classification of AUB according to the PALM-COEIN criteria was performed and the most common causative factor for AUB across the whole study population was fibroids, accounting for 25 (42%) patients.

After 6 weeks, the increase in hemoglobin from baseline was significantly higher in the FCM group than in the ISC group (48 ± 13 g/L vs 37 ± 15.3 g/L; $P = 0.005$); however, at 12 weeks there was no significant difference in the hemoglobin increase from baseline between the two groups ($P = 0.11$) (Table 2). Fig. 2 plots patient hemoglobin levels across the duration of the study.

The target hemoglobin following intravenous iron therapy was 120.0 g/L. By 12 weeks, this target was achieved by 22 (75%) patients in the FCM group and 19 (65%) patients in the ISC group; the number of patients meeting the target did not differ significantly between the two groups ($P = 0.38$). The median serum ferritin level in the FCM group was 10.0 (3.9–28.0) μg/L at baseline and 92 (30–600) μg/L after 12 weeks ($P < 0.001$). The baseline serum ferritin level in the ISC group was 8.8 (2.3–20.0) μg/L at baseline and 57 (10–150) μg/L after 12 weeks. The increase in serum ferritin levels were significantly higher in the FCM group ($P < 0.001$). Fig. 3 illustrates the changes in median serum ferritin levels at baseline, and 6 and 12 weeks in both groups. At baseline, all patients in the FCM group and 28 (93%) patients in the ISC group were experiencing fatigue, as assessed using the four-point numeric scale and LASA score. After 12 weeks, a significant reduction from baseline fatigue ($P < 0.001$) was recorded in both study groups, with only 3 (10%) and 4 (13%) patients experiencing fatigue in the FCM and ISC groups, respectively. There was no significant difference in the change in numeric-scale score between the FCM (−1.31 ± 0.6)