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ORIGINAL ARTICLE - 1

Title : Ferric Carboxymaltose injection in the treatment of postpartum iron deficiency anemia

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Abstract:

Objective: The objective of the study was to evaluate the efficacy, safety, and tolerability of intravenous ferric carboxmaltose compared with oral ferrous sulfate in women with postpartum anemia. **Study Design:** In a Tertiary care hospital, randomized, controlled study, 100 women less than 10 days after delivery with hemoglobin 10 g/dL or less were randomized to receive ferric carboxymaltose (n = 50) 1000 mg or more intravenously over 25 minutes or less, repeated weekly to a calculated replacement dose (maximum 2500 mg) or ferrous sulfate (n = 50) 325 mg orally thrice daily for 6 weeks. **Results :** Ferric carboxymaltose-treated subjects were significantly more likely to: (1) Achieve a hemoglobin greater than 12 g/dL in a shorter time period with a sustained hemoglobin greater than 12 g/dL at day 42, (2) Achieve hemoglobin rise 3 g/dL or greater more quickly, and (3) Attain higher serum transferrin saturation and ferritin levels. Drug-related adverse events occurred less frequently with ferric carboxymaltose. **Conclusion :** Intravenous ferric carboxymaltose was safe and well tolerated with a superior efficacy to oral ferrous sulfate in the treatment of postpartum iron deficiency anemia.

Key words : Iron deficiency anemia, Ferric carboxy maltose,ferous sulfate, Postpartum anemia, Parenteral iron therapy.

Introduction :

Iron deficiency anemia, defined by the World Health Organization as a hemoglobin (Hb) less than 12 g/dL, is the most common cause of anemia in the postpartum period, with rates as high as 37% reported in the first postpartum week. [1,2]

One in 8 American women are iron deficient up to 12 months postpartum, and 1 in 12 women remain iron deficient 13 - 24 months after delivery.[1]Postpartum anemia is caused primarily by inadequate iron intake prior to and during pregnancy and by peripartum blood loss.[3,4]

Patients with postpartum anemia have a longer average length of hospital stay, are more likely to receive a blood transfusion, and incur higher hospitalization costs.[5] 18 % of women hospitalized with anemia and postpartum bleeding receive a blood transfusion. Postpartum anemia has been associated with postpartum depression, stress, anxiety, cognitive impairment,[2,6] poor mother-infant interactions, and delayed infant development.[7] Infants of mothers with iron deficiency anemia have lower developmental test scores at 10 weeks, and these developmental deficits in infants of iron deficient mothers have been shown to persist at 9 months of age, even after correction of maternal iron status.

Oral iron therapy is currently the treatment of choice for the majority of patients with iron deficiency anemia [8]; however, the utility of oral iron is limited by gastrointestinal complaints and patient nonadherence. Among pregnant women, non adherence rates to oral iron therapy are as high as 32% after 2 months of administration.[9] Current intravenous iron therapies also have limitations. Because iron dextran may provoke life-threatening hypersensitivity reactions, anaphylactoid reactions, arthralgia, myalgia, and/or fever, its use has been restricted by the necessity of a test dose, a black box warning in the package insert, and a maximum approved dose of 100 mg per day.[10,11,12,13,14,15]

Although the incidence of anaphylaxis and other adverse reactions with newer intravenous iron agents (eg, iron sucrose, ferric gluconate) is markedly lower, [14] multiple doses and prolonged infusion times are typically required.[15,16,17,18]

Blood transfusions remain a treatment of last resort for anemic postpartum patients because of concerns for the risk of transfusion reactions, immunological interactions and infections.[19,20]

Ferric carboxymaltose is an investigational intravenous iron replacement therapy. Because it does not contain dextran, the risk of anaphylaxis or serious hypersensitivity reactions is very low, and a test dose is

not required.[21]

Ferric carboxymaltose can be administered in single doses up to 1000mg over 15 minutes.[21,22] Our study was designed to test the hypothesis that ferric carboxymaltose is superior to oral iron in the correction of postpartum iron deficiency anemia.

Materials and Methods : This study was conducted at our tertiary care institute between June 2014, December 2014. All subjects given written informed consent before enrollment. Healthy women 10 days or less after delivery with postpartum anemia (mean point of care/local laboratory Hb10 g/dL or less on 2 or more laboratory tests conducted at least 12 hours apart) requiring iron supplementation were enrolled. Exclusion criteria included significant vaginal bleeding (estimated blood loss greater than 100 cc) in the 24 hours prior to randomization, a history of anemia other than iron deficiency anemia or blood loss due to delivery, current treatment with myelo-suppressive therapy or asthma therapy, recent blood transfusions, or erythropoietin within 3 months prior to screening. Study withdrawal was required if the subject required an intervention (i.e., erythropoietin, blood transfusion, intravenous or oral iron outside the study protocol). Subjects whose study medication was discontinued for safety reasons remained in the study. Subjects were stratified according to average baseline Hb levels (7.0-8.0,8.1-9.0, 9.1-10.0 g/dL) and were randomized in a 1:1 ratio to ferric carboxymaltose or ferrous sulfate by use of a centralized computer randomization system. The dosage of ferric carboxymaltose was based on the calculated iron deficit using a modified Ganzoni formula.[22] Ferric carboxymaltose was given weekly until the individual's calculated cumulative dose had been reached or a maximum of 2500 mg of ferric carboxymaltose had been administered. The maximum single weekly dose of ferric carboxymaltose was 15mg/kg, not to exceed 1000 mg/dose, administered intravenously over 15 minutes or less. Subjects randomized to ferrous sulfate were instructed to take 325 mg (65 mg elemental iron) orally 3 times daily for 6 weeks. All used and unused ferric carboxymaltose vials and oral iron blister packs were returned and counted to assess compliance. Central laboratory and safety assessments were performed on days 0, 7, 14, 28, and 42 (end of study) after randomization. Major secondary endpoints, in ranked order of testing, were: percentage of subjects with an increase in Hb 3 g/dL or greater; an Hb greater than 12 g/dL on or before days 14, 28, and 42; an increase in Hb 3g/dL or greater on or before days 14, 28,and 42; and time to achieve an Hb greater than 12 g/dL. Other predetermined secondary endpoints included changes from baseline in Hb, and time to achieve an increase in Hb 3 g/dL or greater. All laboratory data for efficacy analysis were collected and analyzed at a central laboratory. Safety measures included adverse events that were spontaneously reported, elicited, or observed by the investigator and determined by the investigator to be probably or possibly related to study drug. Adverse events for subjects who randomized to ferric carboxymaltose and withdrawn from the study early were reported for 28 days after the last treatment. Randomization of subjects was stratified by baseline hemoglobin. Power calculations were not conducted for the safety analyses because these were exploratory. However, the study does provide greater than 80% power to detect a difference in adverse event rates (oral iron and ferric carboxymaltose, respectively) of 1%and 7% for low frequency events, 5% and 15% for infrequent events, and 20% and 35% for more frequent events. All subjects who received at least 1 dose of study medication were included in the safety population. All subjects in the safety population who had at least 1 post baseline Hb were included in the study population; the protocol specified primary population for evaluating all efficacy endpoints, treatment administration/compliance, and subject characteristics. Five subjects (4 ferric carboxymaltose and 1 oral iron) were excluded from the study population. Subjects who discontinued or did not achieve success before study completion were right censored. The major secondary efficacy variables were tested in a hierarchical order (i. e, statistical significance was declared only if the tests of all preceding endpoints were statistically significant.)

Result : Hundred subjects were randomized to receive ferric carboxy-maltose (n50) or ferrous sulfate remaining 50 subjects were included in the safety population (graph-1). In both the study and safety

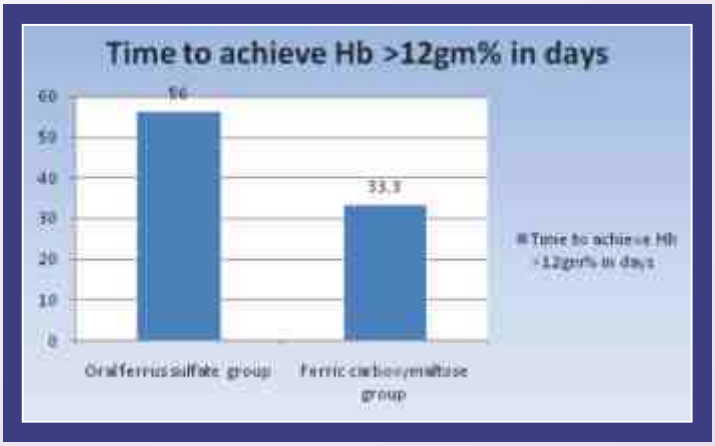
populations, mean study drug usage and the percentage of subjects who received 67% or greater of study drug were comparable between treatment groups, averaging 96% or greater. In the safety population, Mean iron exposure during the study was 1503.5 mg in the ferric carboxymaltose group and 7906.1mg in the oral iron group. There were 78 total injections of ferric carboxymaltose; approximately 88% of subjects received 1 or 2 doses (1 dose: 60%; 2 doses: 26; 3 doses:14 %).

The percentage of subjects in the study population who met the primary efficacy end point (Hb greater than 12 g/dL) was significantly greater in the ferric carboxymaltose group than in the oral iron group (91.4% vs 66.7%;). The percentage of subjects achieving this endpoint was examined in subgroups stratified by baseline Hb (graph 2). Among subjects who achieved an Hb greater than 12 g/dL at any time during the study, the largest difference between the ferric carboxymaltose and ferrous sulfate groups was observed in subjects whose baseline Hb was 8 g/dL or less (90% vs 47%).

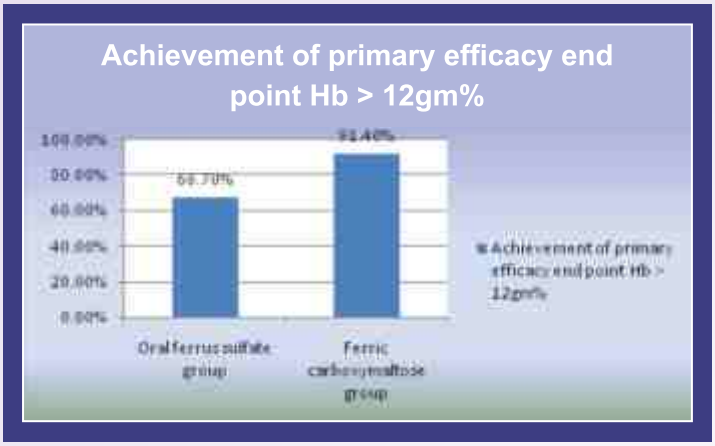
Achievement of all major secondary endpoints significantly favored ferric carboxymaltose over oral iron. Of the ferric carboxymaltose treated subjects, 80% had an increase in Hb 3 g/dL or greater from baseline at any time during the study, compared with 60% of subjects in the oral iron group.The between-group differences in the percentages of subjects achieving an Hb greater than 12 g/dL or an increase in Hb 3 g/dL or greater (graph 3) favored ferric carboxymaltose. The median time to achieve an Hb greater than12 g/dL (25 vs 45 days ;) and the median time to achieve an increase in Hb 3 g/dL or greater (33.3 vs 56 days;) were significantly shorter in subjects treated with ferric carboxymaltose. Finally, the percentage of subjects receiving ferric carboxymaltose who had a sustained Hb greater than 12 g/dL at day 42 was significantly greater than the percentage of subjects receiving ferrous sulfate (80% vs 50.0%;). (graph 4) The overall incidence of drug-related adverse events, defined as probably or possibly related to study medication, was lower in subjects treated with ferric carboxymaltose than with oral iron (Table 1). Adverse events were generally mild to moderate in severity, and no subjects in either treatment group experienced an adverse event that resulted in discontinuation from the study. Two subjects in the ferric carboxymaltose group (4%) were prematurely discontinued from study drug because of an adverse event (urticaria) considered probably related to study drug; Fifteen subjects who met hemoglobin entry criteria by local laboratory or point of care testing were enrolled and were subsequently determined after randomization to have a baseline Hb greater than 10 g/dL by central laboratory testing. These subjects were included in the efficacy and safety analyses. one withdraw from ferric carboxymaltose group and 12 from ferrous sulfate group the study prior to dosing; completed the study. No subjects in the oral iron group experienced an adverse event that led to premature discontinuation of study drug. No serious drug related adverse events (eg, hypersensitivity, anaphylaxis) were reported in either treatment group.

Conclusion : Ferric carboxymaltose produced significantly greater and sustained increases in Hb in a significantly shorter period of time than full therapeutic doses of oral iron. Additionally, the difference in efficacy between ferric carboxymaltose and oral iron was greatest in subjects with the most severe anemia. Our findings validate a recently published study of ferric carboxymaltose vs oral iron in postpartum women.[22]

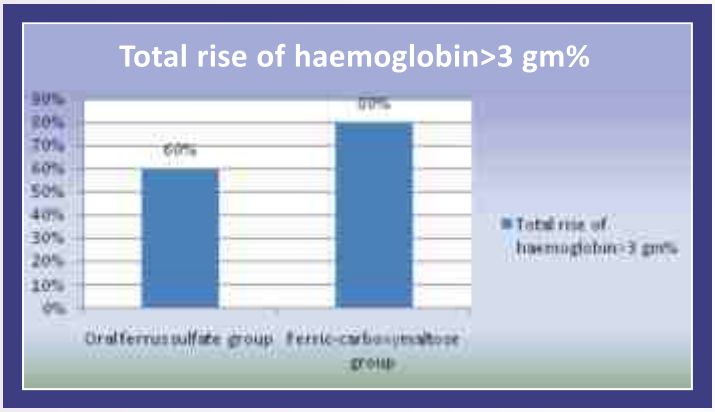
Collectively, these results demonstrate the clinical utility of ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. Ferric carboxymaltose was superior to oral iron.[23]



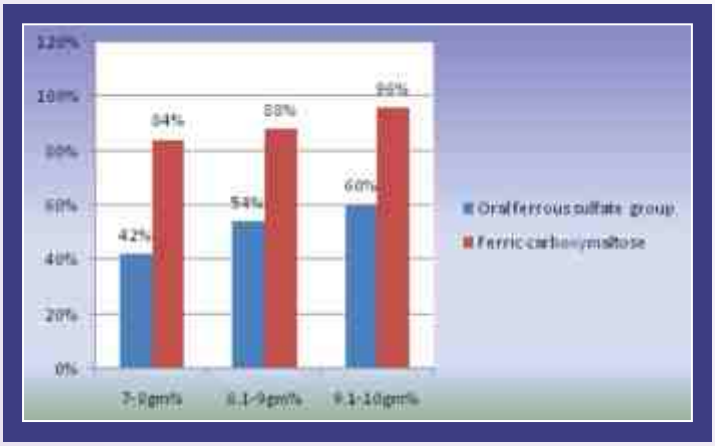
Graph 1:Time to achieve Hb >12gm% in days



Graph 2 : Achievement of primary efficacy end point Hb >12gm%



Graph 3:Total rise of haemoglobin>3 gm%



Graph 4: Subjects achieving target hemoglobin from baseline hemoglobin

Table1: Drug-related adverse events (defined as probably or possibly related to study medication) experienced by 1% or more of subjects in either treatment group: safety population

Preferred term	Ferric carboxymaltose (n 50)	Oral ferrous sulfate (n 50)
Patients reporting 1 or more drug-related	2(4%)	12(24%)
Urticaria	2(4%)	1 (2%)
Constipation	0	7 (14%)
Nausea	0	2 (4%)
Abdominal/ gastrointestinal pain	0	1 (2%)
Muscle cramp	0	1 (2%)

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