Official Title of the Study:

Randomized Trial Comparing Intravenous Iron Carboxymaltose, Intravenous Iron Isomaltoside and Oral Iron Sulphate for Postpartum Anemia

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RATIONALE

Anemia affects between 20 and 50 % of women in the postpartum period (1). It is associated with several adverse health consequences, such as impaired physical work capacity, deficits in cognitive function and mood, reduced immune function and reduced duration of breastfeeding (1-5). Postpartum anemia has also been shown to be a major risk factor for postpartum depression and to significantly disrupt maternal–infant interactions (1-3).

Iron deficiency is the principal cause of anemia after delivery (1). Oral iron supplementation with ferrous sulfate has been considered the standard of care with blood transfusion reserved for more severe or symptomatic cases (6,7). However, efficacy of oral iron is limited by gastrointestinal side effects, patient non-adherence as well as prolonged time required to treat anemia and replenish body iron stores (7-9). Blood transfusion, on the other hand, is associated with several hazards, including transfusion of the wrong blood type, infection, anaphylaxis and lung injury (7,8,10).

In last decades, modern formulations of intravenous iron have emerged as safe and effective alternatives to oral iron supplementation for iron deficiency anemia management outside pregnancy (11). Several studies have also evaluated efficacy of intravenous iron preparations for treatment of postpartum anemia. Westad et al. reported no significant difference in hemoglobin levels at 4, 8 and 12 weeks postpartum in women receiving intravenous iron sucrose (Venofer®) compared to those receiving oral ferrous sulphate, whereas the total fatigue score was significantly improved in the intravenous iron supplementation group at weeks 4, 8 and 12 (6). In addition, mean serum ferritin value after 4 weeks was significantly higher in the iron sucrose group. Several other authors came to similar conclusion, intravenous iron sucrose and oral ferrous sulphate were both effective in correcting peripartum anemia, although intravenous iron restored stores faster than oral iron (7,12-14).

In the last decade, two new intravenous iron compounds have been registered for clinical use: ferric carboxymaltose (Iroprem®) and iron isomaltoside (Monofer®) (15-18). These treatments were designed to be administered in large doses by rapid intravenous injection. They have been demonstrated to be more efficacious than intravenous iron sucrose in patients with inflammatory bowel disease and in patients with chronic kidney disease (19-21). In the postpartum period, ferric carboxymaltose has been compared to oral iron supplements in four randomized trials. All reported a faster rise in hemoglobin levels compared to oral ferrous

sulphate (15,16,22,23). Pfenninger et al. compared efficacy of intravenous ferric carboxymaltose with iron sucrose for the treatment of postpartum anemia in a retrospective cohort study. Both drugs offered rapid normalization of hemoglobin levels after delivery with no difference in mean daily hemoglobin increase between the groups up to 8 days after treatment (24). Only one randomized study to date compared intravenous ferric carboxylase to intravenous iron sucrose and oral ferrous sulphate for treatment of postpartum anemia. Radhod et al. found a significantly faster rise in hemoglobin and ferritin levels with ferric carboxylase compared to iron sucrose and ferrous sulphate in Indian women presenting with anemia after delivery (25). This study, like most randomized trials on efficacy of various iron treatments, focused solely on hematological biomarkers. However, iron deficiency, even without anemia, contributes significantly to fatigue experienced by women in the puerperium, and these women may benefit from iron supplementation as well (1,16,26). Data on patient reported outcomes associated with different iron treatments are, therefore, very much needed. Holm et al. compared the effects of single-dose intravenous iron isomaltoside to oral iron supplementation on physical fatigue in women after postpartum haemorrhage (17,18). They found significant reduction in fatigue within 12 weeks postpartum in women who received iron isomaltoside (16). Iron isomaltoside treatment was also associated with improved haematological and iron parameters compared to oral ferrous sulfate (17,18).

No study to date, however, compared efficacy of iron carboxymaltose to iron isomaltoside for treatment of postpartum anemia. The only head-to-head comparison between these two compounds merely examined economic aspects of each treatment, showing potential reduction of costs associated with the use of iron isomaltoside vs. iron carboxymaltose (27).

OBJECTIVE

The objective of the study is to compare efficacy of intravenous iron carboxymaltose to intravenous iron isomaltoside and oral iron sulphate for treatment of postpartum anemia.

METHODS

Single-center, randomized, open-label trial.

Inclusion criteria

Postpartum patients with a hemoglobin level between 70 g/L and 100 g/L within 48 hours after delivery.

Exclusion criteria

- Contraindications for any of the study drugs.
- Anemia due to causes other than iron deficiency.
- Signs of systemic infection.
- Renal or hepatic dysfunction.
- Depression during pregnancy or pre-existing depressive disorders.

After signed informed consent patients will be allocated randomly in a 1:1:1 fashion into one of three groups:

1. Iron carboxymaltose group. Total dose of intravenous ferric carboxymaltose (Iroprem®) needed to correct anemia and replenish iron stores will be calculated using the Ganzoni formula (28) modified to include adjustment for baseline iron status: prepregnancy weight in kilograms X (15–baseline Hb) X 2.4 + 500. Fifteen is the target Hb in g/dL, 2.4 is a unit less conversion constant and 500 is the target iron stores in mg. The maximal dose administered in a single day will not exceed 15 mg/kg (current weight) or 1000 mg (for participants with body weight > 67 kg). If total calculated dose will exceed 15 mg/kg or 1000 mg, subsequent doses will be administered weekly until the total calculated dose will be reached.
2. Iron isomaltoside group. Total dose of intravenous iron isomaltoside (Monofer®) needed to correct anemia and replenish iron stores will be calculated as described above. The maximal dose administered in a single day will not exceed 20 mg/kg (current weight) or 1500 mg (for participants with body weight > 75 kg). If total calculated dose will exceed 20 mg/kg or 1500 mg, subsequent doses will be administered weekly until the total calculated dose will be reached.
3. Iron sulphate group. Participants will receive oral ferrous sulphate (Tardyfer®) 160 mg daily for 6 weeks with instruction to take two tablets by mouth once daily 1 hour before meal. They will receive no additional iron supplementation.

We will monitor blood pressure and record adverse events in all patients before and after administration of IV iron and ask all patients to report any untoward medical event at its onset.

Outcomes

Primary outcome

- Multidimensional Fatigue Inventory (MFI) score at 6 weeks postpartum. The MFI evaluates five dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue, and consists of 20 statements for which the participant indicates, on a five-point scale, the extent to which the particular statement applies with regard to aspects of fatigue experienced during the previous days. Higher scores indicate a higher degree of fatigue.

Secondary outcomes

- Edinburgh Postnatal Depression Scale (EPDS) score at 6 weeks postpartum. EPDA is a 10-item questionnaire which evaluates different depression symptoms, such as guilt feeling, sleep disturbance, low energy, anhedonia, and suicidal ideation. Overall assessment is done by total score, which is determined by adding together the scores for each of the 10 items. Higher scores indicate more depressive symptoms.
- Mean hemoglobin level at 6 weeks postpartum.
- Proportion of participants with hemoglobin level > 120 g/L at 6 weeks postpartum.
- Proportion of participants with ferritin level > 50 mcg/L at 6 weeks postpartum.
- Mean reticulocyte count at 6 weeks postpartum.
- Mean ferritin level at 6 weeks postpartum.
- Mean transferrin level at 6 weeks postpartum.
- Costs of treatments
- Compliance with oral ferrous sulphate treatment
- Side effects of all three study treatments in mothers (e.g. constipation, headache, infusion site burning) and infants (e.g. constipation, erythema, diarrhea, abdominal pain, upper respiratory tract infection)

Statistical analysis

The planned sample size of 100 patients per group was based on a 80% power to detect non-inferiority using a margin of 5 (half the estimated clinically relevant difference in MFI), an α of 0.01, and expected standard deviation (SD) of 10, with a 20 % dropout rate.

All data will be analyzed according to a pre-established statistical plan. Statistical analyses will be performed with SPSS software (version 24.0; IBM Corporation, Armonk, New York). Data will be entered as numerical or categorical, as appropriate. Shapiro-Wilk test will be used to assess normality of distribution. Parametric statistics will be carried out for normally distributed variables; for non-normal distribution, we will use nonparametric statistics. Data with normal distribution will be described using minimum, maximum, and mean with standard deviation. Data with non-normal distribution will be described using minimum, maximum, median, and interquartile range (IQR). Comparisons will be carried out between the study groups using independent Student's t test or Mann-Whitney U test for continuous and with Chi-square test for categorical variables.

REFERENCES

1. Bodnar LM, Cogswell ME, McDonald T. Have we forgotten the significance of postpartum iron deficiency? Am J Obstet Gynecol. 2005;193:3644.
2. Beard JL, Hendricks MK, Perez EM, Murray-Kolb LE, Berg A, Vernon-Feagans L, et al. Maternal iron deficiency anaemia affects postpartum emotions and cognitions. J Nutr. 2005; 135:26772.
3. Corwin EJ, Murray-Kolb LE, Beard JL. Low hemoglobin level is a risk factor for post partum depression. J Nutr. 2003; 133:413942.
4. Lee KA, Zaffke ME. Longitudinal changes in fatigue and energy during pregnancy and the postpartum period. J Obstet Gynecol Neonatal Nurs. 1999;28(2):183–91. 30.
5. Rioux FM, Savoie N, Allard J. Is there a link between postpartum anemia and discontinuation of breastfeeding? Can J Diet Pract Res. 2006;67(2):72–6.
6. Westad S, Backe B, Salvesen KÅ, Nakling J, Økland I, Borthen I, et al. A 12-week randomised study comparing intravenous iron sucrose versus oral ferrous sulphate for treatment of postpartum anemia. Acta Obstet Gynecol Scand. 2008;87(9):916–23. 53.
7. Bhandal N, Russell R. Intravenous versus oral iron therapy for postpartum anaemia. BJOG. 2006;113(11):1248–52.

8. Cook JD. Diagnosis and management of iron-deficiency anaemia. Best Pract Res Clin Haematol. 2005;18(2): 319-32
9. Cançado RD, Muñoz M. Intravenous iron therapy: how far have we come? Rev Bras Hematol Hemoter. 2011;33(6):461-9.
10. Holm C, Thomsen LL, Norgaard N, Langhoff-Roos J. Single-dose intravenous iron infusion versus red blood cell transfusion for the treatment of severe postpartum anaemia: a randomized controlled pilot study. Vox Sanguinis 2017: 112; 122–31.
11. Nash CM, Allen VM. The Use of Parenteral Iron Therapy for the Treatment of Postpartum Anemia. J Obstet Gynaecol Can. 2015;37(5):439-442.
12. Froessler B, Cocchiaro C, Saadat-Gilani K, Hodyl N, Dekker G. Intravenous iron sucrose versus oral iron ferrous sulfate for antenatal and postpartum iron deficiency anemia: a randomized trial. J Matern Fetal Neonatal Med 2013;26:654–9.
13. Jain G, Palaria U, Jha SK. Intravenous iron in postpartum anemia. J Obstet Gynecol India. 2013;63(1):45–8.
14. El Khouly NI. Comparison of intravenous ferrous sucrose and oral ferrous sulphate in treatment of postpartum iron deficiency anemia. J Matern Fetal Neonatal Med. 2017 Apr;30(8):967-71.
15. Van Wyck DB, Martens MG, Seid MH, Baker JB, Mangione A. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. Obstet Gynecol. 2007;110(2 Pt 1):267–78.
16. Breymann C, Gliga F, Bejenariu C, Strizhova N. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. Int J Gynaecol Obstet. 2008;101(1):67–73.
17. Holm C, Thomsen LL, Langhoff-Roos J. Intravenous iron isomaltoside treatment of women suffering from severe fatigue after postpartumhemorrhage. J Matern Fetal Neonatal Med. 2018;20:1-8.
18. Holm C, Thomsen LL, Nørgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial. Vox Sang. 2017 Apr;112(3):219- 28.
19. Evstatiev R, Marteau P, Iqbal T, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. Gastroenterology.2011;141:846–853.

20. Macdougall I, Bock AH, Carrera F, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chornic kidney disease and iron deficiency anaemia. Nephrol Dial Transplant, 2014;29:2075-84.
21. Derman R, Roman E, Modiano MR, Achebe MM, Thomsen LL, Auerbach M. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. *Am J Hematol*. 2017;92(3):286-91.
22. Seid MH, Butcher AD, Chatwani A. Ferric Carboxymaltose as Treatment in Women with Iron-Deficiency Anemia. Anemia. 2017;2017:9642027.
23. Seid MH, Derman RJ, Baker JB, Banach W, Goldberg C, Rogers R. Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. Am J Obstet Gynecol. 2008;199(4):435.e1-7.
24. Pfenniger A, Schuller C, Christoph P, Surbek D. Safety and efficacy of high-dose intravenous iron carboxymaltose vs. iron sucrose for treatment of postpartum anemia. J Perinat Med. 2012;40(4):397-402.
25. Rathod S, Samal SK, Mahapatra PC, Samal S. Ferric carboxymaltose: A revolution in the treatment of postpartum anemia in Indian women. Int J Appl Basic Med Res. 2015 Jan-Apr;5(1):25-30. doi: 10.4103/2229-516X.149230.
26. Scott SP, Murray-Kolb LE. Iron status is associated with performance on executive functioning tasks in nonanemic young women. J Nutr. 2016;146(1):30-7.
27. Pollock RF, Muduma G. A budget impact analysis of parenteral iron treatments for iron deficiency anemia in the UK: reduced resource utilization with iron isomaltoside 1000. Clinicoecon Outcomes Res 2017. 10;9:475-83.
28. Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities [in German]. Schweiz Med Wochenschr 1970;100:301–3.