Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial

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Background and Objectives To evaluate the clinical efficacy of a single-dose intravenous infusion of iron isomaltoside compared with current treatment practice with oral iron measured by physical fatigue in women after postpartum haemorrhage.

Materials and Methods Single-centre, open-label, randomized controlled trial. Participants received intravenous iron (n = 97) or oral iron (n = 99), and completed the Multidimensional Fatigue Inventory and Edinburgh Postnatal Depression Scale, and haematological and iron parameters were measured. Primary outcome was the aggregated change in physical fatigue score from baseline to 12 weeks postpartum.

Results The difference in physical fatigue score was -0.97 (95% CI: -1.65; -0.28, P = 0.006) in favour of intravenous iron, but did not meet the predefined difference of 1.8. Across visits, we found statistically significant differences in fatigue and depression scores, as well as in haematological and iron parameters, all in favour of intravenous iron. There were no serious adverse reactions.

Conclusion A single dose of intravenous iron was associated with a statistically significant reduction in aggregated physical fatigue within 12 weeks after postpartum haemorrhage compared to standard medical care with oral iron below the prespecified criteria of clinical superiority. As patient-reported outcomes improved significantly and intravenous iron resulted in a fast hematopoietic response without serious adverse reactions, intravenous iron may be a useful alternative after postpartum haemorrhage if oral iron is not absorbed or tolerated.

Key words: anaemia, intravenous iron, iron deficiency, iron isomaltoside, postpartum fatigue, postpartum haemorrhage.

Introduction

Postpartum haemorrhage (PPH) may lead to iron deficiency and anaemia. Postpartum iron-deficiency anaemia is associated with clinical symptoms, most prominently maternal fatigue [1]. In women of reproductive age, iron deficiency without anaemia is associated with fatigue, impaired physical work performance, deficient cognitive
functions and mood disturbances, and it is plausible that sufficient iron supplementation is advantageous for these women [2,3].

In Denmark, the current treatment practice for women after PPH is oral iron supplementation. Red blood cell (RBC) transfusion is only indicated for severe symptoms of anaemia and haemoglobin (Hb) values below 7 g/dl, according to the Danish national guidelines for transfusion [4].

Ten randomized controlled studies compared intravenous (i.v.) iron to oral iron in women with postpartum iron-deficiency anaemia [5–14]. They found that i.v. iron was superior by Hb and iron parameters, but none of the trials primarily measured the effect of i.v. iron administration on clinical outcomes [15]. Fatigue and psychological well-being were reported as secondary outcomes by two studies. Westad et al. [6] reported a statistically significant improvement in the mean change from baseline to weeks 4, 8 and 12 for physical, mental and total fatigue in the group receiving i.v. iron treatment measured by the Fatigue Scale. Van Wyck et al. [8] used the Fatigue Linear Analog Scale Assessment for a mean total fatigue score measured at weeks 2, 4 and 6 and showed no difference in fatigue. Both studies used the SF-36 questionnaire to measure psychological well-being and found no difference between the treatment groups.

The objective of this study was to evaluate clinical efficacy of single-dose infusion of iron isomaltoside compared with current treatment practice with oral iron measured by physical fatigue in women with postpartum haemorrhage (PPH). This study tested the hypothesis that i.v. administration of iron isomaltoside is clinically superior to current treatment practice with oral iron supplementation, measured by self-reported physical fatigue as the primary outcome.

Materials and methods

This was a single-centre, open-label, randomized, parallel superiority study with a 1:1 allocation ratio conducted at the Department of Obstetrics, Rigshospitalet, University of Copenhagen, Denmark. The study was approved by the National Committee on Biomedical Research Ethics on 12 April 2013, approval number: H-4–2013-019, and by the Danish Medicines Agency (approval number: EudraCT 2012-005782-12).

From 3 May 2013 to 18 September 2014, we assessed the eligibility of all parturients, regardless of mode of delivery, with PPH ≥ 700 ml. Women were enrolled in the study if they fulfilled the inclusion criterion: PPH ≥ 700 and ≤1000 ml; or PPH > 1000 ml and Hb >6.5 g/dl (4.0 mmol/l) measured at least 12 h after delivery. The exclusion criteria included multiple births, peripartum RBC transfusion and history of multiple allergies. All exclusion criteria are listed in the published trial protocol [16].

Participants were randomly assigned to receive either iron isomaltoside (i.v.-iron group) or current treatment practice (oral iron group) using an interactive web response system (eClinical OS, Merge Healthcare, Morrisville, NC, United States). The randomization was 1:1 stratified by bleeding volume (700–1000 ml or >1000 ml).

The i.v.-iron group received a single dose of 1200 mg iron isomaltoside (Monofer, Pharmacosmos A/S, Holbaek, Denmark) diluted in 100 ml of 0.9% sodium chloride, and infused intravenously within 15 min.

The oral iron group received current treatment practice: a recommendation to continue oral iron supplementation, as during pregnancy (the Danish Health and Medicines Authority recommends 40–50 mg oral iron supplementation daily [17]), or to take 100 mg oral iron one or two times daily for a variable time period. The individual intake of elemental oral iron, including the type of preparation, dose and treatment duration, was monitored throughout the study period.

The randomized participants had six visits within 12 weeks: at inclusion in the hospital and five visits at home, 3 days, and one, three, eight and 12 weeks after inclusion.

The primary outcome was the aggregated change in physical fatigue score within 12 weeks postpartum, as measured by the physical fatigue subscale of the Multidimensional Fatigue Inventory (MFI) [18]. Secondary efficacy outcomes included changes in Hb, ferritin, iron, transferrin, transferrin saturation, reticulocyte count and reticulocyte mean haemoglobin content (Chr), other dimensions of fatigue by MFI and symptoms of depression measured by the Edinburgh Postnatal Depression Scale (EPDS) [19], time to lactogenesis, time to discontinuation of breastfeeding and transfusion of ‘rescue’ alloimmune RBCs. We monitored vital signs before, during and after infusion in the i.v.-iron group and recorded any adverse events and laboratory safety parameters listed in the published trial protocol [16].

The MFI evaluates five dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. The MFI has high feasibility, reliability and validity in chronically anaemic and postpartum women [20,21]. High scores indicate a high degree of fatigue. The EPDS detects symptoms of depression in puerperal women during the previous 7 days [22]. The maximum score is 30, and a score of 10 or higher indicates possible depression. The MFI was completed at all visits and the EPDS at the last five visits.
The sample size was determined according to the primary hypothesis that iron isomaltoside is superior to the current treatment practice with oral iron. The null hypothesis of no difference between groups was tested against the alternative by constructing a two-sided 95% confidence interval (CI) of the difference in aggregated change in physical fatigue score from baseline to 12 weeks postpartum. The use of the physical fatigue subscale of MFI allowed a maximum change of 16 points. We chose a difference greater than 10% in physical fatigue score for claiming clinically relevant superiority, corresponding to a difference of 1.8 (absolute value) with a SD of 4.2, based on a previous study [21]. Based on these presumptions, we needed 87 women per treatment group to demonstrate superiority with a power of 80%. With a margin for missing data and a dropout rate of approximately 10%, 200 women were included.

All statistical methods were prespecified in a statistical analysis plan and described in detail in the published trial protocol [16]. The statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided and performed on a 5% significance level. Demographic and efficacy analyses included all randomized participants who received the study drug and had at least one postbaseline physical fatigue score (full analysis set). Demographics and baseline characteristics were primarily summarized using descriptive statistics, and chi-square tests were applied if group differences were suspected. The aggregated change in physical fatigue score was calculated as the area under the curve (AUC) of the change from baseline to 12 weeks, using the trapezoidal method adjusted for the observation period. The primary end-point was analysed using an analysis of variance model (ANOVA), with treatment and bleeding volume (700–1000 ml, >1000 ml) as factors and baseline MFI physical fatigue score as the covariate. We also performed a per-protocol analysis that excluded participants who received less than 80% of the planned intravenous iron dose or received ‘rescue’ allogeneic RBC transfusion after inclusion.

Continuous secondary end-points were analysed by a mixed model for repeated measurements, and the estimation method was a restricted maximum likelihood-based approach. ‘Proportion’ end-points were analysed using logistic regression. Where relevant, the baseline value of the parameter in question was included as the covariate. Time to lactogenesis and time to discontinuation of breastfeeding were compared between treatments by a log-rank test. Safety analyses included all women who received study treatment. Adverse events were summarized using the Medical Dictionary for Regulatory Activities (version 16.0). Related and possibly related adverse events were defined as adverse drug reactions.

Results

A total number of 8860 women gave birth during the 18-month study period. Twelve per cent of the women \(n = 1001\) experienced a PPH \(\geq 700\) ml (Fig. 1). Some women were discharged before being informed of the trial \(n = 150\). The remaining 851 women were assessed for eligibility, and 389 met the eligibility criteria and were asked to participate in the study. Two hundred women gave their written consent within 48 hours after delivery and were randomized to the i.v.-iron group \(n = 100\) or the oral iron group \(n = 100\). The safety population included 198 women who received study treatment. The two women in the i.v.-iron group who did not receive study treatment withdrew their consent before intervention. The full analysis set consisted of 196 women who received the study drug and had at least one postbaseline physical fatigue score. Two women were excluded from the full analysis set. One woman in the i.v.-iron group withdrew her consent due to subcutaneous iron infusion, and one woman in the oral iron group did not have a measurement of baseline physical fatigue score. The per-protocol population consisted of 191 participants who received at least 80% of the planned intravenous iron dose and did not receive ‘rescue’ RBC transfusion after inclusion.

Baseline characteristics are presented in Table 1. There were 34 emergency caesarean deliveries in the oral iron group compared with 25 in the i.v.-iron group; 75% vs. 64% of the participants were primipara. These differences were not significant. The mean (±SD) total iron intake in the oral iron group was 4784 ± 4309 mg. Table 2 summarizes the elemental iron intake in the oral iron group throughout the study period.

Patient-reported outcomes

The difference between the two treatment groups in the change in aggregated physical fatigue from baseline to 12 weeks postpartum was –0.97 (CI 95% –1.65; –0.28) \((P = 0.006)\) in favour of i.v. iron (Table 3). Sensitivity analysis of the per-protocol population resulted in an unchanged statistically significant difference between the two treatment groups. The aggregated change in physical fatigue between the two treatment groups differed, when the data were stratified by PPH level. The difference was greater and statistically significant in the group of women with PPH > 1000 ml \(-1.13\) (CI 95% \(-2.10; –0.15)\) \((P = 0.02)\), and smaller and non-significant in the group of women with PPH 700–1000 ml \(-0.81\) (CI 95% \(-1.78;
Fig. 1 Study flow diagram. PPH, mpostpartum haemorrhage; Hb, haemoglobin; RBC, red blood cell; HELLP, haemolysis, elevated liver enzymes, low platelet count.
Table 1 Baseline characteristics of intravenous iron and oral iron group. Results are presented as mean (±SD), unless otherwise stated.

| Baseline characteristics           | Intravenous iron group (n = 97) | Oral iron group (n = 99) |
|------------------------------------|---------------------------------|--------------------------|
| Age (years)                        | 32.2 (±4.4)                     | 32.6 (±4.5)              |
| Prepregnancy weight (kg)           | 66.8 (±14.7)                    | 64.5 (±10.9)             |
| PPH (ml), median (min; max)        | 1000 (700; 3100)                | 1050 (700; 2800)         |
| 700–1000 ml                        | 49 (50.5)                       | 49 (49.5)                |
| >1000 ml                           | 48 (49.5)                       | 50 (50.5)                |
| Primiparas (n, %)                  | 62 (63.9)                       | 74 (74.7)                |
| Iron supplementation in pregnancy  |                                 |                          |
| Whole pregnancy                    | 63 (64.9)                       | 73 (73.7)                |
| Part of pregnancy                  | 27 (27.8)                      | 24 (24.2)                |
| No                                 | 6 (6.2)                         | 2 (2.0)                  |
| Gestational age (days)             | 281 (±10)                      | 280 (±10)                |
| Birth weight (g)                   | 3705 (±551)                    | 3599 (±499)              |
| Mode of labour (n, %)              |                                 |                          |
| Spontaneous                        | 49 (50.5)                       | 55 (56.6)                |
| Induced                            | 38 (39.2)                       | 31 (31.3)                |
| Mode of delivery (n, %)            |                                 |                          |
| Spontaneous vaginal delivery       | 57 (58.8)                       | 40 (40.4)                |
| Vacuum extraction                  | 6 (6.2)                         | 15 (15.2)                |
| Elective caesarean delivery        | 10 (10.3)                      | 10 (10.1)                |
| Emergency caesarean delivery       | 24 (24.7)                      | 34 (34.3)                |
| Perineal tear grade III–IV (n, %)  | 5 (5.2)                         | 5 (5.1)                  |
| Epidural pain relief (n, %)        | 36 (37.1)                       | 36 (36.4)                |
| Manual exploration of uterine cavity (n, %) | 32 (33.0) | 31 (31.3) |

The fatigue and depression scores decreased continuously in both treatment groups during the 12 weeks, with overall, statistically significant lower scores the i.v.-iron group.

Haematological and iron parameters

The mean baseline Hb was 9.71 g/dl in both treatment groups. The increase in mean Hb from baseline to all following time-points was significantly higher in the i.v.-iron group (Fig. 3). All participants in both treatment groups reached anaemia correction during the study period with no between-group difference in the median time to anaemia correction.

We found an increase in reticulocyte count within the first week in both treatment groups; however, the increase was significantly higher in the i.v.-iron group after 3 days and 1 week, compared with the oral iron group. The difference in mean CHr between the two treatment groups was significant at all visits after baseline, in favour of i.v. iron.

Serum ferritin increased promptly and significantly in the i.v.-iron group but remained unchanged at all time-points in the oral iron group (Fig. 4). At 12 weeks, the mean ferritin remained at a level indicating replenished iron stores in the i.v.-iron group, whereas iron stores remained in the lower end of normal range in the oral iron group (176 vs. 37 ng/ml). Significant difference in transferrin saturation in favour of iron isomaltoside was noted in the mean change from baseline to all study time-points.

Lactogenesis and breastfeeding

There was no significant difference in the median time (hours) to lactogenesis between the i.v.-iron group and the oral iron group (71.9 vs. 75.6; P = 0.78). Most participants were still breastfeeding at 12 weeks postpartum (84.5% in the i.v.-iron group and 87.8% in the oral iron group). Among the participants who discontinued breastfeeding, there were no between-group difference in the time of discontinuation (P = 0.52).

Table 2 Oral iron intake of oral elemental iron in the oral iron group. Data are presented as mean (±SD) daily intake of oral elemental iron between the planned visits at baseline, 3 days, 1, 3, 8 and 12 weeks

| Daily oral iron | BL–day 3 | Day 4–week 1 | Day 8–week 3 | Day 22–week 8 | Day 57–week 12 |
|----------------|---------|--------------|--------------|---------------|---------------|
| Dose (mg)      | 44.6 (57.0) | 81.0 (72.3)  | 78.9 (63.4)  | 59.1 (59.2)   | 36.4 (51.1)   |
| Number of women per dose group (n, %) |         |              |              |               |               |
| 0 mg           | 36 (36.4)  | 8 (8.1)      | 3 (3.0)      | 8 (8.1)       | 40 (40.4)     |
| 1–50 mg        | 33 (33.3)  | 45 (45.5)    | 47 (47.5)    | 53 (53.5)     | 36 (36.4)     |
| 51–100 mg      | 17 (17.2)  | 25 (25.3)    | 33 (33.3)    | 27 (27.3)     | 19 (19.2)     |
| 101–300 mg     | 13 (13.1)  | 21 (21.2)    | 16 (16.2)    | 11 (11.1)     | 4 (4.0)       |

n, number of participants, BL, baseline.

Data are presented as mean (±SD) unless otherwise stated.

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Table 3  Change in aggregated physical fatigue from baseline to 12 weeks postpartum. Results from an analysis of AUC of change in physical fatigue score measured by a subscale of the Multidimensional Fatigue Inventory in the full analysis set and per-protocol population

|                      | n     | LsMean | Contrast: i.v.-iron group – oral iron group | Estimate (95% CI) | P value |
|----------------------|-------|--------|---------------------------------------------|-------------------|---------|
| **Full analysis set**|       |        |                                             |                   |         |
| Intravenous iron group | 97    | −3.60  |                                             | −0.97 (−1.65; −0.28) | 0.006   |
| Oral iron group       | 99    | −2.63  |                                             |                   |         |
| **By PPH level**      |       |        |                                             |                   |         |
| PPH 700–1000 ml       |       |        |                                             |                   |         |
| Intravenous iron group | 49    | −3.46  |                                             | −0.81 (−1.78; 0.16) | 0.102   |
| Oral iron group       | 49    | −2.65  |                                             |                   |         |
| PPH >1000 ml          |       |        |                                             |                   |         |
| Intravenous iron group | 48    | −3.74  |                                             | −1.13 (−2.10; −0.15) | 0.024   |
| Oral iron group       | 50    | −2.61  |                                             |                   |         |

AUC, area under the curve; i.v., intravenous; n, number in analysis set; LsMean, least square mean; CI, confidence interval; PPH, postpartum haemorrhage.

The analysis is from an ANOVA model with treatment and PPH level as factors and baseline physical fatigue score as covariate. An absolute difference of 1.8 was the minimal clinical relevant difference for claiming superiority.

Fig. 2  Fatigue and depression. Results are shown as mean scores of the Multidimensional Fatigue Inventory, and Edinburgh Postnatal Depression Scale in the i.v.-iron and oral iron groups from baseline to 12 weeks postpartum. Whiskers indicate standard error. Between-group comparisons: *P < 0.05. Solid line, i.v.-iron group; dashed line, oral iron group.
RBC transfusion

‘Rescue’ RBC transfusions occurred in both groups. One woman with symptoms of severe anaemia in the i.v.-iron group received two units. In the oral iron group, two women with symptoms of severe anaemia received two units, and one woman with secondary PPH received four units.

Safety

The frequencies of adverse events of any cause were similar in the two treatment groups. Serious adverse events occurred in 9.2% of the women in the i.v.-iron group and 8.0% of the women in the oral iron group. None of the serious adverse events was considered drug-related. There were no deaths in either group. Adverse drug reactions occurred in 13.3% of the women in the i.v.-iron group and 22.0% in the oral iron group. The body systems with the highest incidence of adverse drug reactions were gastrointestinal disorders (1.0% and 22.0%, respectively) and general disorders and administration-site conditions (12.2% and 0.0%, respectively) (Table 4). Two women presented with back and chest pain during infusion that abated spontaneously over a few minutes without change in vital signs during infusion and without signs of allergic or anaphylactic reactions. The infusion was restarted in one participant without recurrence of symptoms. The second participant did not wish to restart the infusion. The mean values of safety laboratory parameters over time showed no between-group differences. We found transient increased values of alanine aminotransferase and aspartate aminotransferase without clinical symptoms in one participant in the i.v.-iron group measured one and 3 weeks after treatment, and in two participants in the i.v.-iron group and in three participants in the oral iron group at 12 weeks. These findings were classified as non-drug-related. There were five participants in
Table 4 Adverse drug reactions. Defined as related and possibly related adverse events in the safety population

| Adverse drug reactions                        | Intravenous iron group (n = 98) | Oral iron group (n = 100) |
|-----------------------------------------------|---------------------------------|--------------------------|
| Total adverse drug reactions (n, %)            | 13 (133)                        | 22 (220)                 |
| Gastrointestinal disorders                   | 22 (220)                        | 22 (220)                 |
| Constipation                                  | 1 (10)                          | 18 (180)                 |
| Haemorrhoids                                  | 7 (70)                          | 7 (70)                   |
| Paraesthesia oral                             | 1 (10)                          | 1 (10)                   |
| General disorders and administration-site conditions | 12 (122)    | 12 (122)                 |
| Infusion site discolouration                  | 3 (31)                          | 3 (31)                   |
| Infusion site irritation                      | 2 (20)                          | 2 (20)                   |
| Infusion site reaction                        | 2 (20)                          | 2 (20)                   |
| Pain*                                         | 2 (20)                          | 2 (20)                   |
| Puncture site swelling                        | 2 (20)                          | 2 (20)                   |
| Pyrexia                                       | 1 (10)                          | 1 (10)                   |
| Musculoskeletal and connective tissue disorders | 1 (10)                  | 1 (10)                   |
| Myalgia                                       | 1 (10)                          | 1 (10)                   |
| Vascular disorders                            | 1 (10)                          | 1 (10)                   |
| Phlebitis                                     | 1 (10)                          | 1 (10)                   |

L.v., intravenous, n, number of participants experiencing the event at least once.

*Acute back, neck, and chest pain during infusion that abated spontaneously over a few minutes (Fishbane reaction).

the i.v.-iron group and two in the oral iron group with phosphate levels <2 mg/dl at any time after baseline. All phosphate values <2 mg/dl were between 1.55 and 1.98 mg/dl, and the phosphate levels in all cases increased to above 2 mg/dl at the subsequent visit.

Discussion

We compared a single high-dose infusion of iron isomaltoside to current treatment practice with oral iron supplementation primarily measured by the aggregated change in physical fatigue within 12 weeks after PPH and found a between-group difference less than the predefined minimal clinically relevant difference. Thus, superiority of iron isomaltoside was not demonstrated in this study. However, the between-group differences in fatigue and depression symptoms, as well as haematological and iron-related biochemical parameters, were statistically significant in favour of i.v. iron, particularly in the first 3 weeks. The frequency of adverse events was similar between groups, and no subject had drug-related serious adverse reactions. Injection-site and general reactions occurred in 12% in the intravenous group, but iron infusion was otherwise well tolerated. The oral iron group had a high frequency of gastrointestinal adverse reactions of 22%, in spite of the individual dosing regimen.

This is to our knowledge the first randomized controlled trial to primarily focus on patient-reported outcomes in comparing treatment options for postpartum iron deficiency and anaemia, and a major strength is the almost complete follow up with minimal missing data.

Clinical relevance was ensured by the choice of amount of postpartum bleeding as inclusion criteria instead of biochemical parameters for iron deficiency and anaemia, which are unreliable shortly after delivery due to haemodilution and falsely raised acute phase reactants [16, 23]. As we know the amount of bleeding within hours after delivery, we could administer i.v. iron before an early discharge from the hospital.

The choice of an individualized oral iron treatment regimen, where the participants in the oral iron group adjusted their oral iron medication to suit their specific needs and tolerance as comparator to i.v. iron in this study, may be seen as a limitation due to the low mean iron intake in the study period. However, as gastrointestinal side-effects to oral iron supplementation are well known and result in poor compliance, especially in puerperal women [24], the individualized treatment regimen simulates normal clinical practice and ensures high external validity, as opposed to a fixed dosing regimen that results in poor compliance outside a clinical study setting.

An inherent weakness is the open-label design. The individualized regimen design implies that we were not able to blind the randomization. Also, i.v. iron is a black fluid and as iron tablets colour the stools, we thought that a double-blinded design would not be feasible. Accordingly, most previously published randomized controlled trials with iron treatment of women after childbirth have not been double-blinded [6–14]. The clinical outcomes from the self-reported questionnaires may have been influenced by participants’ knowledge of which treatment they received, and thus, we cannot exclude a placebo effect in the intravenous iron group. The study outcome might have been stronger, if physical tests had been included, such as exercise capacity or muscle strength measurements.

A recent systematic review regarding treatment of postpartum iron-deficiency anaemia suggests a need for trials with focus on clinical outcomes [15]. We chose the primary outcome physical fatigue measured by a subscale of the MFI, as Jansen (2007) found this measure to be associated with low Hb [21]. As it is difficult to predetermine a single time-point for measuring treatment effect on clinical symptoms postpartum, we defined the primary end-point as the aggregated physical fatigue score calculated by the AUC.

Based on clinical judgement, we chose a difference greater than 10% in the participant’s perception of physical fatigue for claiming clinically relevant superiority in...
hypophosphatemia was reported in 8% slightly below 2 mg/dL in the i.v.-iron group is in complement activation-related pseudo-allergy (CARPA) according to Rampton (2014), it is believed to be a reaction. The pathogenesis is unknown, but and chest pain) to i.v. iron described as the Fishbane reaction immediately after acute bleeding such as PPH [16]. Hence, the iron isomaltoside fixed dose of 1200 mg in this study is based on the expected iron deficiency in women after PPH. Body iron stores are approximately 500–750 mg and the average iron loss through PPH is approximately 500 mg, as 500 ml blood loss equals 250 mg iron loss [25]. This dose ensures replenishment of iron stores throughout the 12 weeks and reduces the risk of recurrence of iron-deficiency anaemia once menses resumes and during subsequent pregnancies.

In two women, we observed the acute reaction (back and chest pain) to i.v. iron described as the Fishbane reaction [26, 27]. The pathogenesis is unknown, but according to Rampton (2014), it is believed to be a complement activation-related pseudo-allergy (CARPA) triggered by iron nano-particles [28, 29].

The finding of a few cases of transient phosphate levels slightly below 2 mg/dL in the i.v.-iron group is in contrast to findings in another i.v.-iron study, in which hypophosphatemia was reported in 8–70% of women in postpartum and heavy uterine bleeding studies with another i.v.-iron preparation [30, 31].

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Conclusion

A single dose of intravenous iron was associated with a statistically significant reduction in aggregated physical fatigue within 12 weeks after PPH compared to standard medical care with oral iron, below the prespecified criteria of clinical superiority.

However, iron isomaltoside was also associated with a statistically significant improvement in depression scores and a significantly faster haematopoietic response and replenishment of iron stores. There was no difference in the frequency of adverse events between the two treatment groups, and there were no serious adverse reactions. Gastrointestinal disorders were predominant in the oral group, whereas general and administration-site conditions were predominant in the intravenous iron group.

Based on these findings, we conclude that intravenous iron is a useful treatment alternative for the treatment of postpartum physical fatigue or depression, if oral iron is not optimal, for example in case of intolerance to or mal-absorption of oral iron. Intravenous iron may also be useful for fast correction of iron deficiency and/or anaemia, and after major postpartum haemorrhage, to avoid blood transfusion.
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