Single-dose intravenous iron infusion versus red blood cell transfusion for the treatment of severe postpartum anaemia: a randomized controlled pilot study

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Background and Objectives There are no randomized trials comparing intravenous iron to RBC transfusion for the treatment of severe postpartum anaemia. The objectives of this study were to evaluate the feasibility of randomizing women with severe postpartum anaemia secondary to postpartum haemorrhage to RBC transfusion or intravenous iron, and to describe patient-reported outcomes, and haematological and iron parameters.

Materials and Methods Women with a postpartum haemorrhage exceeding 1000 ml and an Hb between 5.6 and 8.1 g/dl were randomized to 1500 mg of intravenous iron (n = 7) isomaltoside or RBC transfusion (n = 6). Participants completed the Multidimensional Fatigue Inventory and Edinburgh Postnatal Depression Scale, and blood samples were drawn at inclusion, daily during the first week and at weeks 3, 8 and 12.

Results We screened 162 women and included 13 (8%). There was no significant difference between groups in fatigue or depression scores. RBC transfusion was associated with a higher Hb on day 1, inhibition of reticulocytosis during the first week and low iron levels. Intravenous iron was associated with increased reticulocytosis during the first week, repleted iron stores and a higher Hb in weeks 3–12.

Conclusion This pilot study shows that intravenous iron could be an attractive alternative to RBC transfusion in severe postpartum anaemia, and that a larger trial is needed and feasible.

Key words: clinical trial, haemoglobin measurement, medicine, patient blood management, transfusion.

Introduction

Approximately 2% of mothers in Denmark receive red blood cell (RBC) transfusion as a result of postpartum haemorrhage (PPH) [1]. RBC transfusion may be a lifesaving treatment for acute haemorrhage, but it is also widely used after PPH to alleviate anaemia. Postpartum anaemia is associated with clinical consequences including fatigue and symptoms of depression [2, 3]. A low postpartum Hb is the most important reason to prescribe RBC transfusions [4]. The indication for RBC transfusion, however, is not to increase postpartum Hb level, but to reduce morbidity and improve the health-related quality of life, especially fatigue, which may influence the ability to care for a newborn.

There are increasing concerns about adverse effects and costs of current transfusion practice [5, 6]. Adverse effects of transfusion include increased health-care-associated infections, volume overload and a number of...
immunologic adverse effects including RBC alloantibodies which may complicate future transfusions and pregnancies [7–9]. An alternative treatment is therefore warranted to diminish RBC transfusion-related risks in otherwise healthy women with severe postpartum anaemia defined as Hb ≤8.1 g/dl (5.0 mmol/l).

The WOMB study (Well-being of Obstetric patients on Minimal Blood transfusion) compared RBC transfusion to non-intervention in the treatment of severe postpartum anaemia in a randomized controlled trial with 500 women. The study showed that RBC transfusion led to a small improvement in physical fatigue measured 3 days after transfusion compared to the non-transfused [10].

In a retrospective study by Broche (2004), administration of intravenous (i.v.) iron reduced the number of transfused puerperal women by 65% [11]. However, there are no published randomized controlled trials comparing i.v. iron with RBC transfusion in the treatment of severe postpartum anaemia. The drug profile of iron isomaltoside seems optimal for treating severe postpartum anaemia, as it is approved for high single dosing, which is preferable in the treatment of puerperal women, who may have their iron deficit corrected without extra visits to the obstetric unit.

The objective of this pilot study was to evaluate the feasibility and explorative outcomes of a high single-dose infusion of iron isomaltoside compared with RBC transfusion for the treatment of severe postpartum anaemia in haemodynamically stable women.

Materials and methods

The study was a single-centre, open-label randomized feasibility trial with a 1:1 allocation ratio at the Department of Obstetrics, Rigshospitalet, University of Copenhagen, Denmark. The study was approved by the Danish Medicines Agency (approval number: Eudra CT 2012-005783-10).

From June 16, 2013 to April 29, 2015, we assessed the eligibility of all parturients with a PPH >1000 ml, regardless of mode of delivery. Women were asked to participate in the study if they fulfilled the inclusion criterion: PPH >1 000 ml (the amount of blood loss was quantified by weighing the delivery items) and Hb between 5.6 and 8.1 g/dl (3.5–5.0 mmol/l) – In Denmark Hb is expressed in mmol/l) measured at least 12 h after delivery. The exclusion criteria included multiple births, peri-partum RBC transfusion and a history of multiple allergies (Fig. 1).

Participants were randomly assigned to receive either iron isomaltoside (i.v.-iron group) or RBC transfusion (transfusion group) using an interactive web response system (eClinical OS, Merge Healthcare, Morrisville, NC, United States). The i.v.-iron group received a single dose of 1500 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 1500 mg dose of iron isomaltoside was calculated based on the estimated size of body iron stores and expected iron deficiency in women with severe postpartum haemorrhage. The transfusion group received RBC transfusion based on the following trigger Hb levels: Women with Hb 5.6–6.3 g/dl (3.5–3.9 mmol/l) received 2 units of RBCs, and women with Hb 6.4–8.1 g/dl (4.0–5.0 mmol/l) received 1 unit of RBCs. Oral iron intake was prohibited in both treatment groups throughout the study period. The randomized participants had 11 visits within 12 weeks, one at inclusion (in the hospital) and daily visits during the first week after inclusion (hospital or home), and at 3, 8 and 12 weeks at home. Blood samples were drawn and questionnaires filled in concurrently.

The primary endpoint was the aggregated change in physical fatigue score within 12 weeks postpartum, as measured by a subscale of the Multidimensional Fatigue Inventory (MFI), similar to the fatigue measure used in the WOMB study [12]. Secondary endpoints included other dimensions of fatigue, symptoms of postpartum depression and changes in haematological and iron biochemical parameters (Hb, ferritin, iron, transferrin, transferrin saturation (TSAT), reticulocyte count and reticulocyte mean haemoglobin content (CHr)). We monitored vital signs before, during and after infusion, and recorded any adverse events and laboratory safety parameters in both groups.

Questionnaires

We used two self-reported questionnaires, the fatigue measure MFI and the depression measure Edinburgh Postnatal Depression Scale (EPDS) [13]. The MFI evaluates five dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. The MFI has previously been evaluated in a postpartum population, where the findings demonstrated a significant correlation between Hb and physical fatigue score [14]. The MFI consists of 20 statements for which the participant indicates, on a 5-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. The minimum clinically relevant difference for the MFI has not been established for women in the puerperium. The EPDS consists of 10 questions to detect symptoms of depression in puerperal women during the previous 7 days. The maximum score is 30 and a score of 10 or higher indicates possible depression. The MFI was completed at all 11 visits, whereas the EPDS was assessed at 1 week, 3 weeks, 8 weeks and 12 weeks.
Enrollment
Screened for eligibility
Eligible for inclusion
Randomised
Allocated to intravenous iron
Allocated to transfusion
Completed trial
Analysis

PPH > 1000 ml
(n = 609)

Did not meet the inclusion criteria
(n = 301)
- Hb > 8.1 g/dl (n = 292)
- No Hb measurement (n = 9)

Discharged before being informed about the trial
(n = 146)

Excluded
(n = 100)
- Peripartum acute RBC transfusion (n = 29)
- Postpartum anaemia RBC transfusion (n = 21)
- Language (n = 18)
- Multiple allergies (n = 9)
- Multiple birth (n = 8)
- Acute infection (n = 7)
- Home > 18 miles from the hospital (n = 6)
- Participation in other clinical trial (n = 4)
- Rheumatoid arthritis (n = 3)
- Medical condition (n = 2)
- Asthma (n = 2)
- HELLP syndrome (n = 1)

Declined to participate
(n = 49)

Allocated to intravenous iron
- Received allocated intervention
(n = 7)

Allocated to transfusion
- Received allocated intervention
(n = 6)

Completed trial
(n = 7)

Completed trial
(n = 6)

Full analysis set
- Per protocol (n = 7)
  - Excluded from analysis (n = 1)
    (RBCs transfusion during trial period)

Full analysis set
- Per protocol (n = 6)
  - Excluded from analysis (n = 2)
    (RBCs transfusion during trial period)

Fig. 1 Study flow diagram. PPH, postpartum haemorrhage; HB, haemoglobin; RBC, red blood cell; HELLP, haemolysis, elevated liver enzymes, low platelet count.
Statistical analysis

The nature of the trial was considered explorative and regarded as a pilot for future powering of confirmatory studies. Hence, no power calculation was performed. The statistical methods were pre-specified in a statistical analysis plan and the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The statistical tests were two sided and performed on a 5% significance level. Demographic and efficacy analyses included the randomized participants who received the study drug and had at least one post-baseline physical fatigue score (full analysis set). 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 and analysed using an analysis of variance model (ANOVA), with baseline MFI physical fatigue score as the covariate. Descriptive statistics were applied for the secondary endpoints. The latter endpoints were analysed by a mixed model for repeated measurements, and the estimation method was a restricted maximum likelihood-based approach. Safety analyses included all women who received study treatment. Adverse events were summarized using the Medical Dictionary for Regulatory Activities (version 16) [15]. Related and possibly related adverse events were defined as adverse reactions.

Results

A total of 162 women were screened for eligibility (Fig. 1). In all, 62 women met the eligibility criteria and were asked to participate in this study. Forty-nine women (79%) of the eligible women declined to participate. The main reasons given for declining participation were the intense follow-up visits, the risks associated with red blood cell transfusion and exhaustion prohibiting the women from giving an informed consent. Thirteen women gave their written consent within 48 h after delivery and were randomized to the i.v.-iron group (n = 7) or the transfusion group (n = 6). The per-protocol population included 10 women who did not receive ‘off-protocol’ RBC transfusion after the randomized treatment at baseline. Table 1 shows the baseline characteristics. None of the women in the i.v.-iron group and one woman (16-7%) in the transfusion group had a caesarean delivery, and women in the transfusion group were on average approximately 4 years older than women in the i.v.-iron group. All participants received the planned treatment according to the protocol and no participants were lost to follow up. All women in the i.v.-iron group received the full dose of 1500 mg iron isomaltoside. In the transfusion group, five women received 1 unit and one woman received 2 units according to protocol. ‘Off-protocol’ RBC transfusion was given to women at the clinician’s discretion in both treatment groups with symptoms of severe anaemia, after the randomized treatment at baseline. One woman in the i.v.-iron group received 2 units (indication noted in medical file: overwhelming fatigue), and two women in the transfusion group received 1 unit ‘off-protocol’ RBC transfusion (indication noted in medical file: continuous headache and low Hb, respectively).

Patient-reported outcomes

There was no statistically significant difference in aggregated change in physical fatigue score from baseline to 12 weeks [-0.63 [95% CI: -3.28; 2.02, P = 0.61]]. Sensitivity analysis with exclusion of the participants who received ‘off-protocol’ RBC transfusion after the randomized treatment at baseline (per protocol population) did not alter this (Table 2). In the first week, there was no change over time or between the treatment groups in any of the five dimensions of fatigue outcomes (Fig. 2). In the transfusion group, a decrease in fatigue was observed in all five dimensions from 1 week to 8 weeks postpartum. In the i.v.-iron group there was a slight decrease over time in all five dimensions of fatigue from 1 week and 12 weeks postpartum. The mean score of the EPDS at baseline decreased over time in both treatment groups.

Haematological and iron parameters

The transfusion group had a significantly higher Hb than the i.v.-iron group at day 1, but Hb was significantly lower from week 3, and even lower than normal range.

Table 1 Baseline characteristics of intravenous iron and transfusion group. Results are presented as mean (SD), unless otherwise stated.

| Baseline characteristics | Intravenous-iron group (n = 7) | Transfusion group (n = 6) |
|--------------------------|-----------------------------|--------------------------|
| Age (years)              | 30.4 (2.6)                  | 34.5 (3.5)               |
| Pre-pregnancy weight (kg)| 64.9 (9.5)                  | 63.5 (8.4)               |
| PPH (ml), median (min; max)| 2000 (1700; 2500)          | 2000 (1600; 2500)        |
| Haemoglobin (g/dl), median (IQR) | 6.80 (6.4–7.6) | 6.75 (6.4–6.9) |
| Primiparas (n, %)        | 4 (57.1)                    | 3 (50.0)                 |
| Gestational age (days)   | 281 (14)                    | 284 (7)                  |
| Birth weight (g)         | 3437 (416)                  | 3769 (274)               |
| Mode of delivery (n, %)  | 7 (100.0)                   | 5 (83.3)                 |
| Caesarean section        | 0 (0.0)                     | 1 (16.7)                 |

IQR, Interquartile range.
until week 12 (Fig. 3a). The reticulocyte count remained unchanged within the first week, and decreased from 1 week to 12 weeks. The mean CHr decreased from day 1 to day 5 followed by an increase throughout the remaining study period, slowly approaching the normal limit of 29 pg at week 8. The ferritin level remained low throughout the study period, and at 12 weeks the mean ferritin was below normal (Fig. 3b). The mean TSAT was below normal throughout the study period. This indicates a persisting iron deficiency throughout the study period.

In the i.v.-group the mean Hb was lower than in the transfusion group at day 1. Hb then increased, and by week 3 and onwards Hb was significantly higher in the i.v.-iron group, and normalization occurred between weeks 3 and 8. The reticulocyte count increased steeply from baseline to day 6 followed by a decrease throughout the remaining study period. The mean CHr increased from day 1 to day 4 followed by a decrease till 3 weeks and remained at a normal level till week 12. Ferritin increased promptly after baseline till day 5, followed by a decrease throughout the remaining study period. At week 12 the mean ferritin was 141 ng/ml. The TSAT increased promptly from baseline to day 1, normalized at day 3 and remained normal throughout the remaining study period.

Safety

Adverse reactions, all non-serious, were reported in both treatment groups. In the i.v.-iron group, three participants experienced events categorized as general disorders/administration site conditions and in the transfusion group two participants experienced pyrexia and one participant experienced back pain. The back pain was not associated with other symptoms or clinical signs of a transfusion reaction. The iron infusion was interrupted in one participant with acute back and chest pain (the event was categorized as general disorder). The symptom occurred within the first 2 minutes of infusion and abated spontaneously over a few minutes without change in vital signs or hypersensitivity reaction, and the infusion was restarted without recurrence of the symptoms. We found an increased value of alanine aminotransferase without clinical symptoms in one participant in the i.v.-iron group measured at 12 weeks. This finding was classified as non-drug related.

Discussion

This is the first study to test feasibility and exploratory outcomes of a high single-dose infusion of iron isomaltoside compared with RBC transfusion for the treatment of severe postpartum anaemia. A large part of the women did not meet the eligibility criteria of the study. Overall, fatigue and depression scores decreased over time from 1 to 12 weeks, but there was no change over time in the fatigue outcomes within the first week, and no between-group differences. RBC transfusion resulted in a short-lived effect on Hb at day 1, whereas iron stores and the haematopoietic response were significantly impaired. I.v. iron improved iron biochemical outcomes, allowed a normal, iron-replete haematopoietic response to severe

Table 2 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

|                  | Contrast: I.v.-iron group – transfusion group |
|------------------|---------------------------------------------|
|                  | n     | LsMean | Estimate (95% CI) | P value |
| Full analysis set|       |        |                  |        |
| I.v.-iron group  | 7     | -3.67  | -0.63 (-3.28; 2.02) | 0.61   |
| Transfusion group| 6     | -3.04  |                  |        |
| Per Protocol     |       |        |                  |        |
| I.v.-iron group  | 6     | -3.25  | 0.30 (-3.26; 3.86) | 0.85   |
| Transfusion group| 4     | -3.55  |                  |        |

I.v., Intravenous; AUC, Area under the curve, n, Number in analysis set, LsMean, Least square mean, CI, Confidence interval. The analysis is from an ANOVA model with treatment as factor and baseline physical fatigue score as covariate.
postpartum anaemia and provided a long-term normalization of Hb.

**Strengths and limitations**

The participants had no RBC transfusion prior to inclusion and no oral iron intake in the follow-up period. This ‘clean’ design is unique in randomized controlled trials with RBC transfusion, and allows a study of the effect of RBC transfusion on haematopoiesis in severe anaemia after bleeding. The daily clinical scores with simultaneous blood sampling during the first week after intervention represented a detailed exploration in time variation during the first week.

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_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 transfusion groups from baseline to 12 weeks postpartum. Whiskers indicate standard error. Solid line, i.v.-iron group; dashed line, transfusion group.
Even though this was a pilot study, the very low number of participants is a major weakness. Hence, the results should be interpreted with caution. A limitation was also the ‘off-protocol’ RBC transfusion given in both treatment groups, causing interference in the ‘clean’ group comparison.

An additional limitation might be that the upper Hb boundary may be too high. In Denmark, the recommendations for a transfusion trigger for puerperal women in the time shortly after delivery rely on the general recommendations, i.e. clinical signs of severe anaemia and a Hb below 7.0 g/dl (4.3 mmol/l) [16]. Data from the blood bank, Rigshospitalet, showed that in practice the Hb trigger for transfusion in the Department of Obstetrics is often up to 8.0 g/dl (5 mmol/l), and for this reason we chose this upper Hb boundary.
Fig. 3 (Continued)
Interpretation

It was possible, but difficult to include eligible women with severe postpartum anaemia and allocate them to i.v. iron or RBC transfusion. The RBC transfusions given before screening as well as the ‘off-protocol’ transfusions might be avoidable according to previous findings of significant proportion of transfusions are given inappropriately in the postpartum period [17, 18]. Applying rigorous clinical indications for RBC transfusion (e.g. chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation [19]) might improve recruitment and reduce ‘off-protocol’ transfusions. Acute peripartum RBC transfusion is occasionally indicated, and to increase inclusion in a future larger study, this exclusion criteria could be abandoned. However, this would complicate an unbiased safety assessment of RBC transfusion compared to i.v. iron.

We also found that a large part of the eligible women declined to participate. Due to the explorative pilot nature of this study we collected questionnaires and blood samples daily in the first week. However, many women argued that the intense follow-up visits were a reason to decline participation, and fewer follow-up visits should be considered in the design of a future larger trial. In our experience the home visits contributed to the trial compliance.

The WOMB study compared RBC transfusion to expectant management of severe postpartum anaemia and were not able to confirm the hypothesis of expectant management being non-inferior to RBC transfusion assessed by physical fatigue; however, the authors acknowledged that their non-inferiority threshold may have been set too stringently [10]. The results from the WOMB study indicate a need for treatment of fatigue, and our pilot study suggest that i.v. iron might be an alternative to RBC transfusion. However, larger trials are needed to confirm the exploratory results on patient-reported outcomes. Furthermore, there is a need to establish the minimal clinical relevant difference for the MFI for women in the puerperium.

The haematological and iron parameters demonstrated that a high single dose of iron isomaltoside allowed a fast haematological response to severe anaemia, compared with RBC transfusion. We believe that for the first time we demonstrated an impaired haematopoietic response to severe postpartum anaemia in the transfusion group. These women had not earlier received RBC transfusion, and it has previously been demonstrated that donor reticulocytes only persist in the circulation of the recipient for 24–48 h [20, 21]. Therefore, the low CHr demonstrated after day 2 must represent the women’s own haematopoiesis, and the CHr was not normalized for many weeks in the transfusion group. This indicates a slow, iron-deficient haematopoietic response. Even though the additional mature donor RBCs might dilute the percentage of reticulocytes with 10–20%, this cannot fully explain the difference seen in Fig. 3a.

In this study, a single high-dose i.v. infusion of iron isomaltoside was well tolerated and not associated with any allergic or serious adverse reactions. Acute back and chest pain was experienced by one participant shortly after the iron infusion was started. This corresponded to the previously described Fishbane reaction [22, 23]. The pathogenesis remains unknown, but it is believed to be an iron-triggered activation of the complement system [24].

Conclusion

The results of this pilot study of intravenous iron versus RBC transfusion have shown that enrolment and allocation of women with severe postpartum anaemia was possible, but difficult. The preliminary results of patient-reported outcomes were inconclusive, whereas the laboratory investigations suggested that a single-dose infusion of iron isomaltoside may be an attractive alternative to RBC transfusion in treatment of severe postpartum anaemia. A large well-powered trial is needed to clarify this, and we suggest a slightly adjusted design for a future multicentre trial.

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