VoxSanguinis
The International Journal of Transfusion Medicine

ISBT International Society of Blood Transfusion

Vox Sanguinis (2017) **112**, 122–131

ORIGINAL PAPER

DOI: 10.1111/vox.12475

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

C. Holm,[1,2] L. L. Thomsen,[2] A. Norgaard[3] & J. Langhoff-Roos[1]

[1]*Department of Obstetrics, Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*
[2]*Pharmacosmos A/S, Holbaek, Denmark*
[3]*Section for Transfusion Medicine, Capital Region Blood Bank, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

Vox Sanguinis

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.

Received: 20 May 2016,
revised 6 October 2016,
accepted 12 October 2016,
published online 23 December 2016

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

Correspondence: Charlotte Holm, Department of Obstetrics, Juliane Marie Centre, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
E-mail: charlotteholm@dadlnet.dk

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 dosed according to 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.

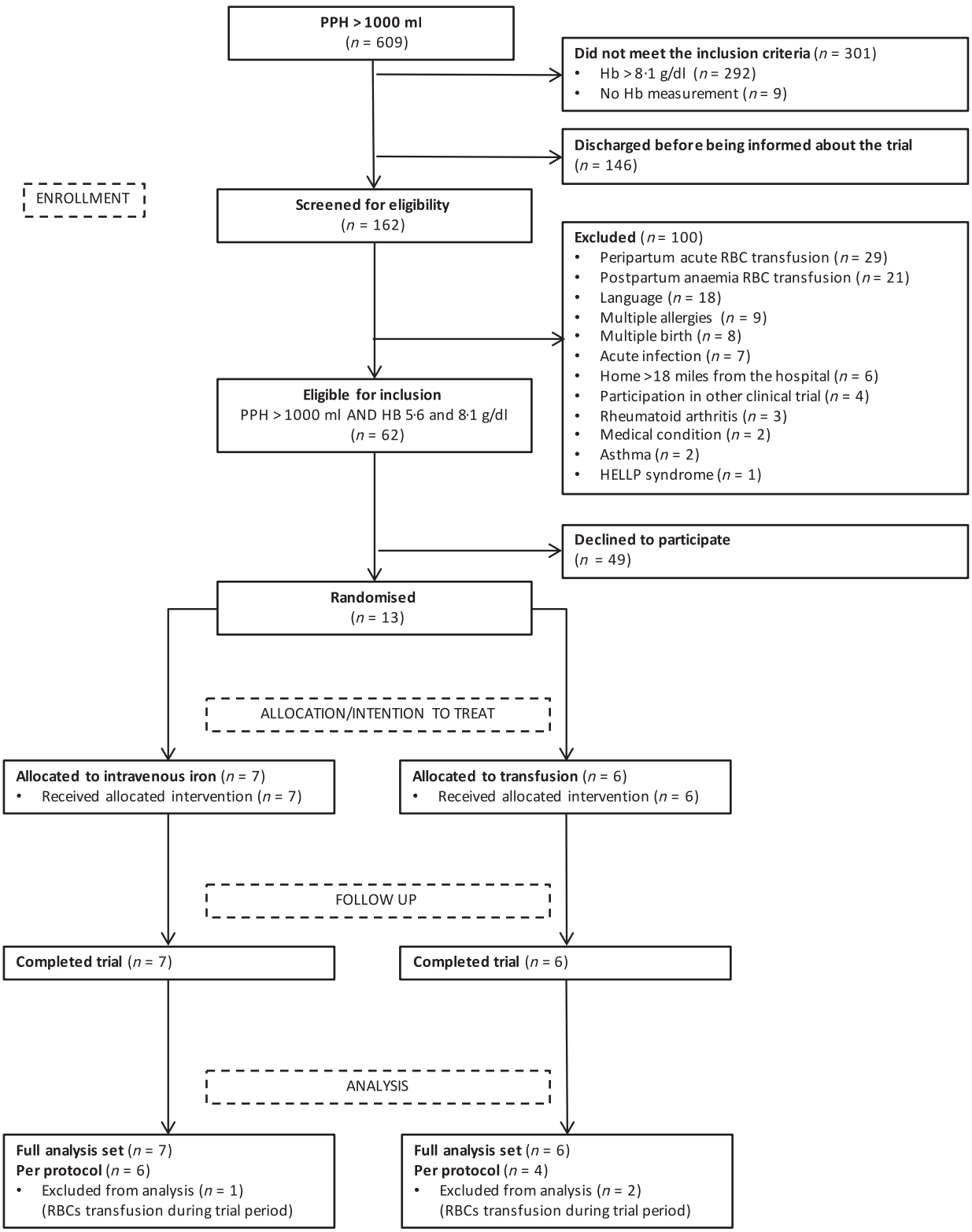

Fig. 1 Study flow diagram. PPH, postpartum haemorrhage; HB, haemoglobin; RBC, red blood cell; HELLP, haemolysis, elevated liver enzymes, low platelet count.

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 16·0) [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).

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, %)		
Vaginal	7 (100·0)	5 (83·3)
Caesarean section	0 (0·0)	1 (16·7)

IQR, Interquartile range.

Patient-reported outcomes

There was no statistically significant difference in aggregated change in physical fatigue 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 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.

Table 3 Adverse reactions. Defined as related and possibly related adverse events in the safety population

Adverse reactions	**I.v.-iron group (*n* = 7)**	**Transfusion group (*n* = 6)**
Total adverse reactions (*n*, %)	3 (42·9)	**2 (33·3)**
General disorders and administration site conditions	3 (42·9)	
Application site discolouration	1 (14·3)	
Infusion site irritation	1 (14·3)	
Pain[a]	1 (14·3)	
General disorders and administration site conditions		2 (33·3)
Pyrexia		2 (33·3)
Musculoskeletal and connective tissue disorders		1 (16·7)
Back pain[b]		1 (16·7)

I.v., Intravenous, *n*, Number of participants experiencing the event at least once.
[a]Acute back, neck and chest pain during infusion that abated spontaneously over a few minutes (Fishbane reaction).
[b]Lower back pain shortly after transfusion that abated spontaneously within 1 day.

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

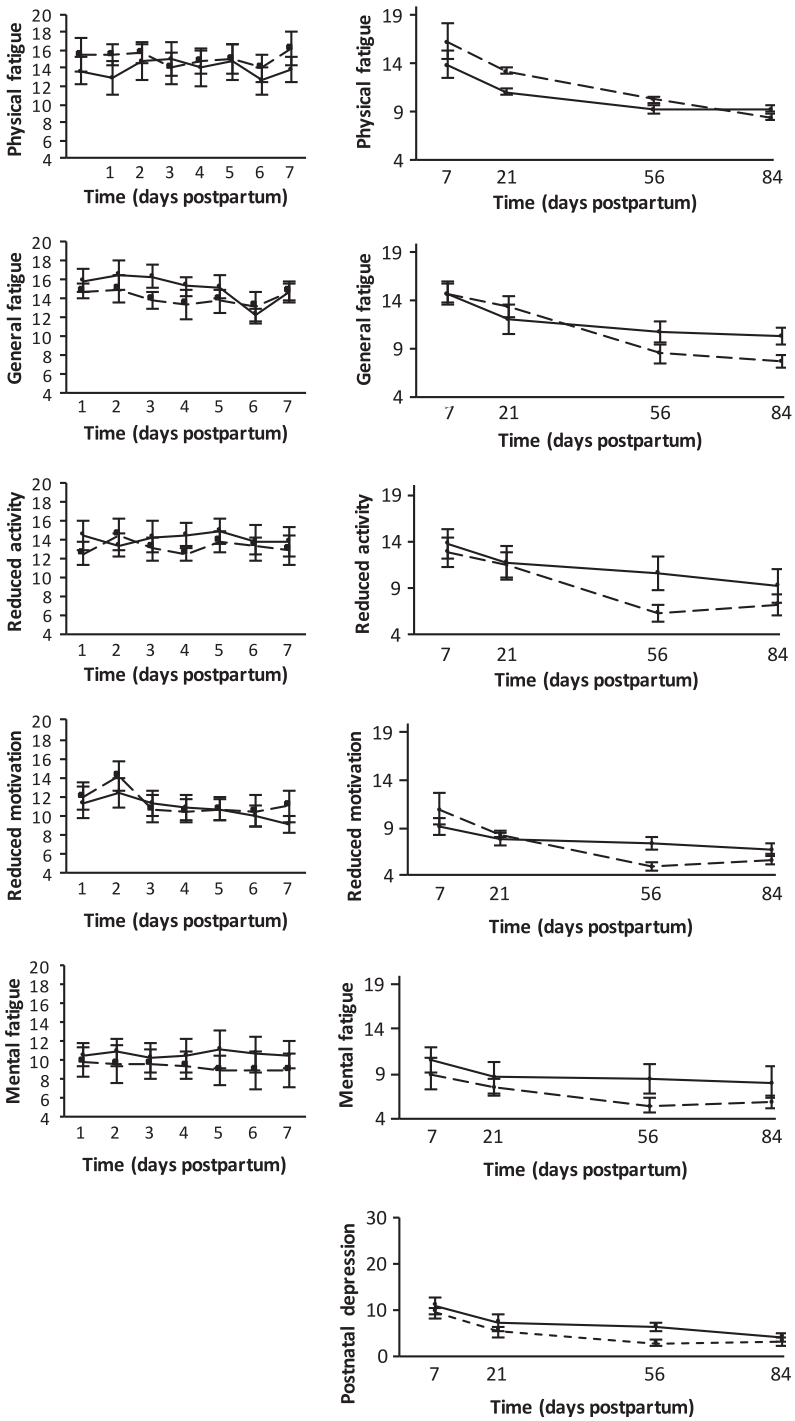

Fig. 2 Fatigue and depression. Results are shown as mean scores of the Multidimensional Fatigue Inventory, and Edinburgh Postnatal Depression Scale in the i.v.-iron and transfusion groups from baseline to 12 weeks postpartum. Whiskers indicate standard error. Solid line, I.v.-iron group; dashed line,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

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.

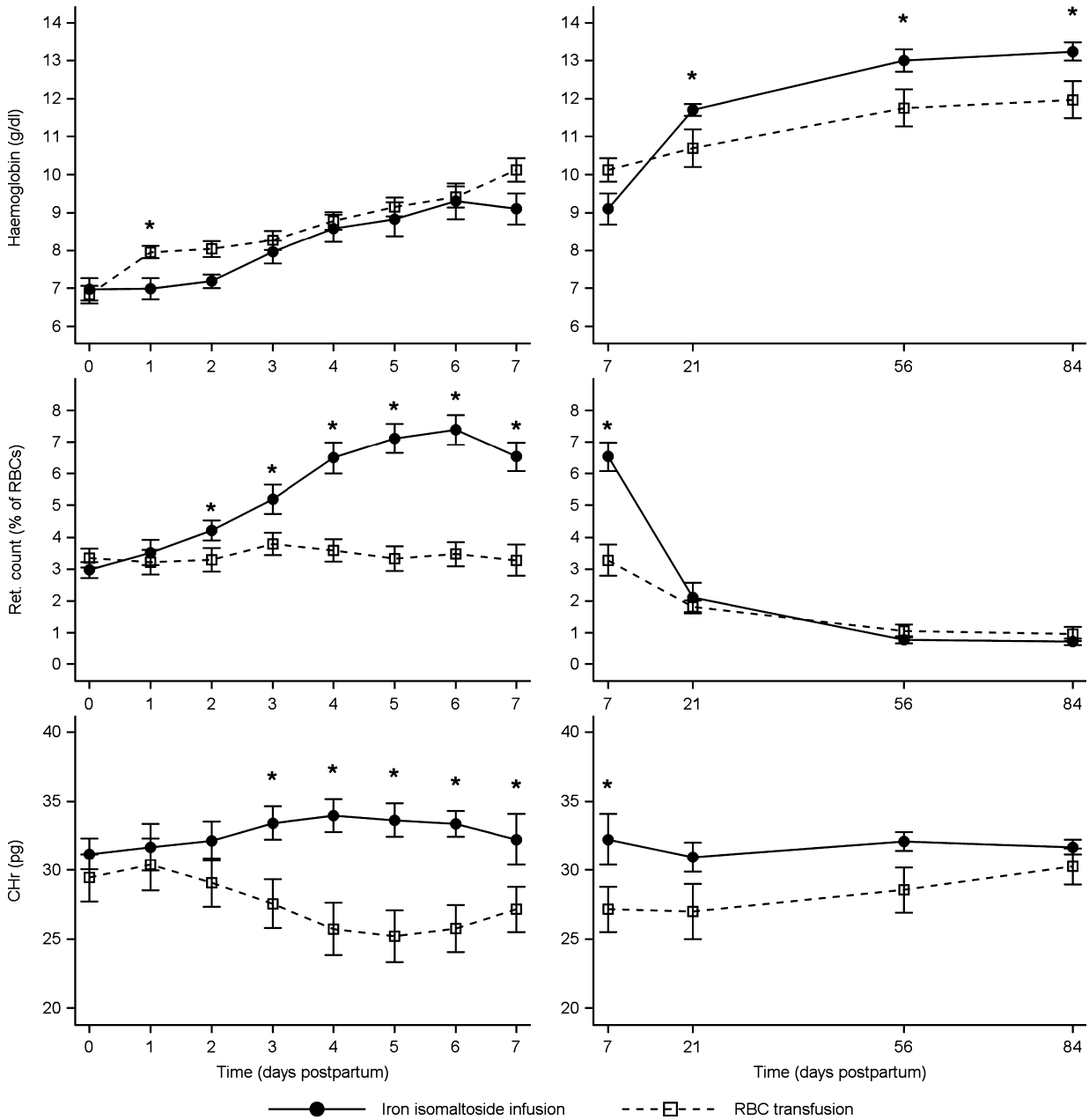

Fig. 3 a and b Mean iron and haematological biochemical parameters in the intravenous-iron and transfusion group from baseline to 12 weeks postpartum. Whiskers indicate standard error. Between-group comparisons: $*P < 0{\cdot}05$. Solid line, I.v.-iron group; dashed line, transfusion group. Ret, Reticulocytes, RBC, red blood cell, CHr, reticulocyte haemoglobin content.

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.

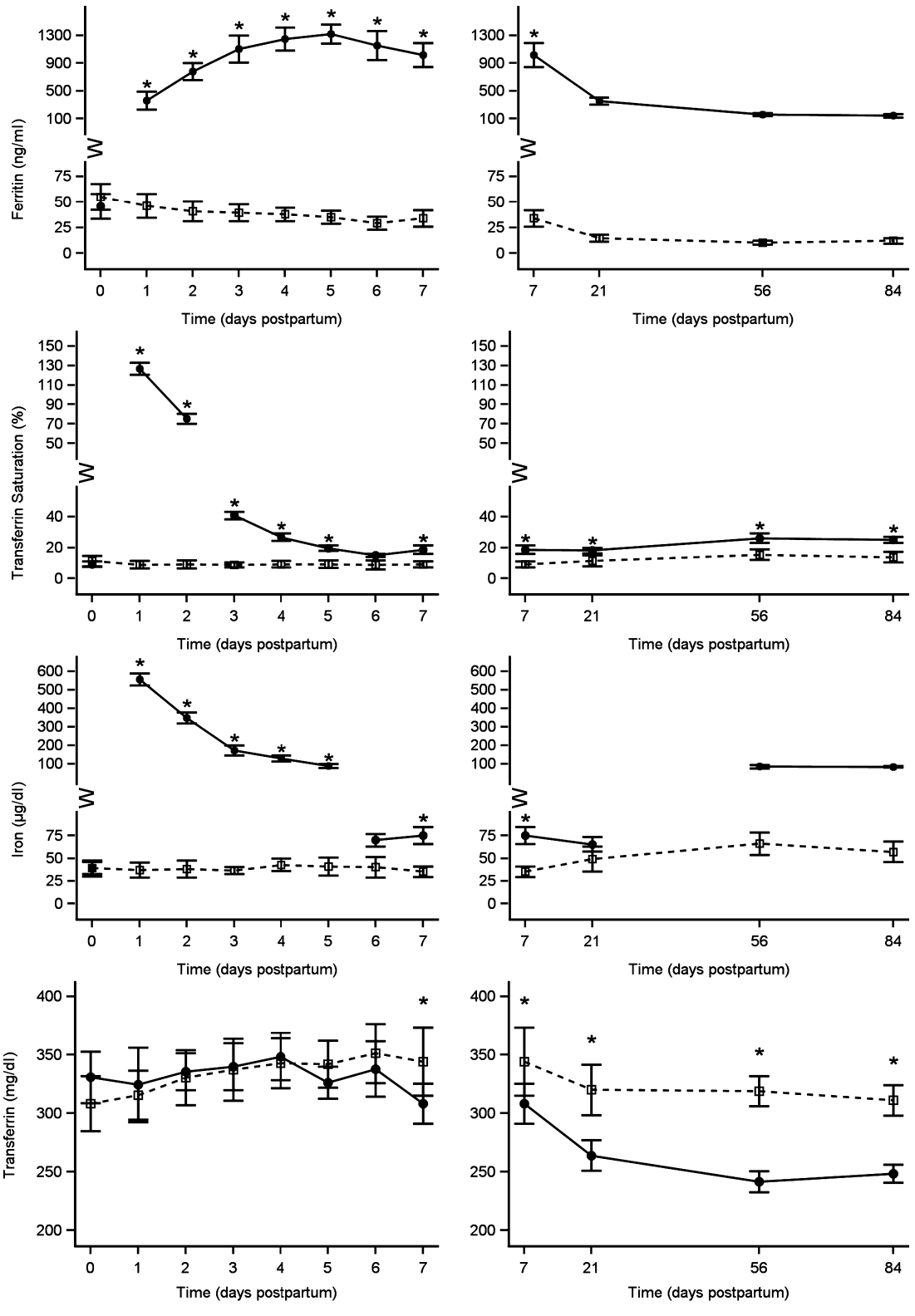

Fig. 3 (Continued)

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 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.

Acknowledgements

We would like to thank the project midwives (Trine Markussen Larsen, Katrine Høybye and Sara Winther) and Jens K Slott Jensen, MSc, who provided statistical support. Charlotte Holm and Jens Langhoff-Roos collected the trial data. Charlotte Holm, Jens Langhoff-Roos, Astrid Norgaard and Lars Lykke Thomsen designed the study, analysed and interpreted the data. Charlotte Holm drafted the manuscript and all authors approved the final version. Hence, the sponsor was involved in the design, analyses and interpretation of the data and approval of the final manuscript.

References

1 Holm C, Langhoff-Roos J, Petersen KB, *et al.*: Severe postpartum haemorrhage and mode of delivery: a retrospective cohort study. *Br J Obstet Gynaecol* 2012; **119**:596–604

2 Lee KA, Zaffke ME: Longitudinal changes in fatigue and energy during pregnancy and the postpartum period.

J Obstet Gynecol Neonatal Nurs 1999; **28**:183–191
3 Corwin EJ, Murray-Kolb LE, Beard JL: Low hemoglobin level is a risk factor for postpartum depression. *J Nutr* 2003; **133**:4139–4142
4 Jansen AJ, van Rhenen DJ, Steegers EA, *et al.*: Postpartum hemorrhage and transfusion of blood and blood components. *Obstet Gynecol Surv* 2005; **60**:663–671
5 Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2012; 4. Art. No.: CD002042. doi:10.1002/14651858.CD002042.pub3
6 Lee T-H, Paglieroni T, Utter GH, *et al.*: High-level long-term white blood cell microchimerism after transfusion of leukoreduced blood components to patients resuscitated after severe traumatic injury. *Transfusion* 2005; **45**:1280–1290
7 Salpeter SR, Buckley JS, Chatterjee S: Impact of more restrictive blood transfusion strategies on clinical outcomes: a meta-analysis and systematic review. *Am J Med* 2014; **127**:124–131.e3
8 Norgaard A, Gybel-Brask M, Rieneck K, *et al.*: Managing the bleeding emergency in a patient with red cell antibodies. *ISBT sci ser* 2016; **11**(Suppl. 1):44–53
9 Pavord S, Myers B, Robinson S, *et al.*: UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol* 2012; **156**:588–600
10 Prick BW, Jansen A, Steegers E, *et al.*: Transfusion policy after severe postpartum haemorrhage: a randomised non-inferiority trial. *Br J Obstet Gynaecol* 2014; **121**:1005–1014
11 Broche DE, Gay C, Armand-Branger S, *et al.*: Anémies sévères du post-partum immédiat. Pratique clinique et intérêt du fer par voie intraveineuse. *Gynecol Obstet Fertil* 2004; **32**:613–619
12 Smets EM, Garssen B, Bonke B, *et al.*: The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; **39**:315–325
13 Cox JL, Holden JM, Sagovsky R: Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987; **150**:782–786
14 Jansen AJ, Essink-Bot M-L, Duvekot JJ, *et al.*: Psychometric evaluation of health-related quality of life measures in women after different types of delivery. *J Psychosom Res* 2007; **63**:275–281
15 Wood KL, On Behalf of the Meddra Working Party. The medical dictionary for drug regulatory affairs (MEDDRA) project. *Pharmacoepidemiol Drug Saf* 1994; **3**:7–13
16 Sundhedsstyrelsen. National klinisk retningslinje om indikation for transfusion med blodkomponenter [Internet]. Copenhagen: Sundhedsstyrelsen; 2014. Available from Sundhedsstyrelsen: https://sundhedsstyrelsen.dk/da/udgivelser/2014/~/media/EEA1EA90C15E4A97B9E786D2850B3664.ashx [Last accessed 20 May 2016]
17 Silverman JA, Barrett J, Callum JL: The appropriateness of red blood cell transfusions in the peripartum patient. *Obstet Gynecol* 2004; **104**:1000–1004
18 So-Osman C, Cicilia J, Brand A, *et al.*: Triggers and appropriateness of red blood cell transfusions in the postpartum patient–a retrospective audit. *Vox Sang* 2010; **98**:65–69
19 Carson JL, Grossman BJ, Kleinman S, *et al.*: Red blood cell transfusion: a clinical practice guideline from the AABB*. *Ann Intern Med* 2012; **157**:49–58
20 Perry ES, Moore RH, Berger TA, *et al.*: In vitro and in vivo persistence of reticulocytes from donor red cells. *Transfusion* 1996; **36**:318–321
21 Larsen R, Berkowicz A, Lousen T, *et al.*: Massive fetomaternal hemorrhage: clearance of fetal red blood cells after intravenous anti-D prophylaxis monitored by flow cytometry. *Transfusion* 2008; **48**:1707–1712
22 Auerbach M, Ballard H, Glaspy J: Clinical update: intravenous iron for anaemia. *Lancet* 2007; **369**:1502–1504
23 Fishbane S, Ungureanu VD, Maesaka JK, *et al.*: The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996; **28**:529–534
24 Rampton D, Folkersen J, Fishbane S, *et al.*: Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica* 2014; **99**:1671–1676