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Transfusion policy after severe postpartum haemorrhage: a randomised non-inferiority trial

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Objective To assess the effect of red blood cell (RBC) transfusion on quality of life in acutely anaemic women after postpartum haemorrhage.

Design Randomised non-inferiority trial.

Setting Thirty-seven Dutch university and general hospitals.

Population Women with acute anaemia (haemoglobin 4.8–7.9 g/dl [3.0–4.9 mmol/l] 12–24 hours postpartum) without severe anaemic symptoms or severe comorbidities.

Methods Women were allocated to RBC transfusion or non-intervention.

Main outcome measures Primary outcome was physical fatigue 3 days postpartum (Multidimensional Fatigue Inventory, scale 4–20; 20 represents maximal fatigue). Non-inferiority was demonstrated if the physical fatigue difference between study arms was maximal 1.3. Secondary outcomes were health-related quality of life and physical complications. Health-related quality of life questionnaires were completed at five time-points until 6 weeks postpartum.

Results In all, 521 women were randomised to non-intervention (n = 262) or RBC transfusion (n = 259). Mean physical fatigue score at day 3 postpartum, adjusted for baseline and mode of delivery, was 0.8 lower in the RBC transfusion arm (95% confidence interval: 0.1–1.5, P = 0.02) and at 1 week postpartum was 1.06 lower (95% confidence interval: 0.3–1.8, P = 0.01). A median of two RBC units was transfused in the RBC transfusion arm. In the non-intervention arm, 33 women received RBC transfusion, mainly because of anaemic symptoms. Physical complications were comparable.

Conclusions Statistically, non-inferiority could not be demonstrated as the confidence interval crossed the non-inferiority boundary. Nevertheless, with only a small difference in physical fatigue and no differences in secondary outcomes, implementation of restrictive management seems clinically justified.

Keywords Anaemia, blood transfusion, postpartum haemorrhage, quality of life.

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Introduction

Postpartum haemorrhage is an important cause of maternal mortality. It causes acute anaemia with physical sequelae varying from fatigue to severe haemodynamic disturbance. A recent systematic review showed a worldwide incidence of severe postpartum haemorrhage (blood loss of at least 1000 ml during delivery)[1] of 1.9% in the period 1997–2006.[2]

The most important treatment of severe postpartum haemorrhage is red blood cell (RBC) transfusion, with the aim to reduce morbidity. In the past few years increasing concerns have arisen about the supply and safety of this treatment, encouraging more conservative management.[3] Despite the introduction of several new guidelines,[4,5] transfusion criteria still vary widely between clinicians. The decision whether to prescribe RBC transfusion is mainly based on postpartum haemoglobin (Hb) concentrations, where guidelines recommend RBC transfusion when Hb concentration is <6 g/dl and no transfusion in women with an Hb concentration >10 g/dl.[5–7] A survey among Dutch gynaecologists revealed that RBC transfusion for anaemic postpartum women was considered when Hb concentration was <5.0 mmol/l (8.1 g/dl).[8] To provide insight into potential risks of anaemia and benefits of transfusion in women with severe postpartum haemorrhage we conducted the Wellbeing of Obstetric patients on Minimal Blood transfusions (WOMB) study, a multicentre randomised non-inferiority trial assessing the effect of RBC transfusion on health-related quality of life in women with acute anaemia due to severe postpartum haemorrhage. A non-inferiority design was chosen because the non-intervention treatment in this study has greater availability, reduced costs, less invasiveness and leads to fewer adverse effects. Physical fatigue was chosen as primary outcome because it was considered the earliest arising complaint in acute anaemia. Based on the results of a pilot study the largest difference was expected at day three.[9]

Methods

The study was approved by the University of Rotterdam's Institutional Review Board (MEC-2003-247), and had local approval from the boards of all participating hospitals. The study was registered at ClinicalTrials.gov NCT00335023 and at the Dutch Trial Register (NTR335).

The methods have already been reported in detail.[10]

Patients

We enrolled women in 37 Dutch hospitals from May 2004 to February 2011. Eligible women sustained postpartum haemorrhage (blood loss of ≥1000 ml and/or a decrease in Hb concentration of ≥1.9 g/dl [1.2 mmol/l]) and had an Hb concentration between 4.8 and 7.9 g/dl (3.0–4.9 mmol/l) 12–24 hours after delivery. The lower Hb threshold was formulated at the request of the Institutional Review Board because in the original protocol no lower threshold was defined. Participants either delivered in hospital or were admitted after a home birth. Exclusion criteria were severe symptoms of anaemia (defined as dyspnoea, syncope, tachycardia [>100 beats/minute], angina pectoris and/or transient ischaemic attacks), RBC transfusion administered during or within 12 hours after delivery, severe pre-eclampsia, severe infectious disease, congenital haemolytic disease, compromised immunological status, malignancy, severe co-morbidity (ASA II/III), and death or critical condition of the neonate. Finally, a good knowledge of the Dutch language was required. Participants were seen by research midwives and nurses who provided counselling, obtained informed consent, monitored the study protocol and collected data.

Randomisation

After informed consent, women were randomly allocated in a 1:1 ratio to receive RBC transfusion or no intervention, using a web-based application for block randomisation with a variable block size of two to eight. Randomisation was stratified for mode of delivery and participating hospital. Due to the intervention's nature, the study was not blinded. From 2005 onwards, women who declined informed consent were asked to complete questionnaires; follow up was identical.

Women allocated to RBC transfusion received at least one unit of red blood cells; we aimed to reach an Hb concentration of at least 8.9 g/dl (5.5 mmol/l). The Hb and haematocrit concentrations were recorded before and after RBC transfusion. In women allocated to non-intervention, RBC transfusion was allowed if severe symptoms of anaemia developed or at their physicians' discretion. Additional use of iron and/or folic acid supplementation according to local protocol was allowed.

Follow up and outcome measures

The follow up period was limited to 6 weeks postpartum. Health-related quality of life questionnaires were to be completed at five points in time: at inclusion, 3 days, 1 week, 3 weeks and 6 weeks postpartum. Physical complications during follow up were recorded and Hb concentration was determined at inclusion and 6 weeks postpartum.

The primary outcome was physical fatigue at day 3, measured with the Multidimensional Fatigue Inventory.[11] This time-point was chosen as the difference between arms was expected to be largest at day 3 because data of the pilot study showed that Hb 12–24 hours postpartum was related to health-related quality of life at the same time-point but not

to health-related quality of life 1 week after delivery.[12] Secondary outcomes were remaining health-related quality of life scores, number of RBC units transfused, transfusion reactions, length of hospital stay and physical complications during follow up (infections, thromboembolic events, secondary postpartum haemorrhage and other physical complications).

Ethnicity was assessed according to the definition of Statistics Netherlands.[13] In twin pregnancies, we used the data of the first child in the analyses. With more than one mode of delivery method, one mode was recorded using the following order: caesarean section, operative vaginal delivery, spontaneous vaginal delivery. With more than one method of analgesia, this was recorded using the following order: general anaesthesia, locoregional anaesthesia, opiates.

Health-related quality of life

We used internationally validated health-related quality of life measures: the Multidimensional Fatigue Inventory and the Medical Outcome Study 36-Item Short-Form Health Survey version one (ShortForm-36). The Multidimensional Fatigue Inventory is a domain-specific measure for physical and mental fatigue. The Multidimensional Fatigue Inventory consists of 20 items grouped into five dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue.[11] The Multidimensional Fatigue Inventory scores range from 4 to 20; higher scores indicate a higher degree of fatigue. The health-related quality of life questionnaire Multidimensional Fatigue Inventory scores fatigue on several domains and has a high feasibility, reliability and validity in chronically anaemic women.[14] The ShortForm-36 is a generic health-related quality of life measure with eight dimensions: physical functioning, role limitations due to physical health problems (role–physical), bodily pain, general health perception, vitality, social functioning, role limitations due to emotional health (role–emotional) and mental health.[15] The ShortForm-36 scores range from 0 to 100; higher scores indicate better functioning or wellbeing. The ShortForm-36 is a generic questionnaire widely used for measuring patient-reported outcomes.[16] Population-based norm scores are available for the Dutch adaptation of ShortForm-36.[17] Both health-related quality of life questionnaires were previously validated in postpartum women in a pilot study.[9] The Multidimensional Fatigue Inventory was to be completed at all five time-points, whereas the ShortForm-36 was to be completed at 1 week, 3 weeks and 6 weeks.

Sample size

For the subscale physical fatigue (Multidimensional Fatigue Inventory), a minimum clinically important difference had not been established before our study. Therefore data from a pilot study, assessing health-related quality of life in postpartum women,[9] was used. We calculated that, with a sample size of 400 women (200 per arm), a difference of 1.3 points or greater (in favour of the RBC transfusion arm regarding physical fatigue at day 3) could be excluded (power: 80%, one-sided α: 0.025). This difference was considered small and clinically irrelevant and therefore used as non-inferiority boundary. Because we observed that 20% of health-related quality of life data was missing, in 2008 we decided to include 500 women.

Statistics

Analyses were conducted on an intention-to-treat basis. Continuous variables were summarised as means with standard deviations (SD), or medians with interquartile ranges (IQR). Health-related quality of life scores were presented as differences in adjusted means with 95% confidence intervals (CI).

Non-inferiority is intended to show that the effect of one treatment is not worse than that of an active control by more than a prespecified boundary. When the difference between study arms does not exceed this boundary, non-inferiority is demonstrated. A difference can be statistically significant but too small to be clinically relevant: only when the difference exceeds the non-inferiority boundary is clinical relevance demonstrated. The significance of the difference between study arms is therefore of minor importance.

Besides evaluation of physical fatigue in both study arms, we tested non-inferiority of the primary outcome measure by assessing whether the upper 95% CI lay within the non-inferiority boundary. Adjusted means of primary outcome and remaining Multidimensional Fatigue Inventory scores were calculated using repeated measurement analysis of variance (ANOVA) with an unstructured covariance matrix, while including baseline value (at inclusion) and mode of delivery as covariates. The same statistical method was used for the ShortForm-36 scores, with only mode of delivery as a covariate, because the ShortForm-36 was not completed at inclusion. Additionally, the influence of mode of delivery was analysed using repeated measurement ANOVA, with an unstructured covariance matrix including baseline value as covariate.

Multidimensional Fatigue Inventory scores were analysed if data were available at inclusion and at least one additional time-point. ShortForm-36 scores were analysed if at least one questionnaire (1 week, 3 weeks or 6 weeks) was completed. Internal consistency within questionnaires was assessed for each Multidimensional Fatigue Inventory and ShortForm-36 subscale by calculating Cronbach's α; this showed high reliability, with $\alpha > 0.70$ for all health-related quality of life subscales except the ShortForm-36 dimension bodily pain ($\alpha > 0.5$).

Prespecified exploratory subgroup analyses of the primary outcome were performed for Hb concentration at inclusion with categories 4.8–6.5, 6.6–7.3 and 7.4–7.9 g/dl

(3.0–4.0, 4.1–4.5 and 4.6–4.9 mmol/l) and for physical fatigue score at inclusion using quartiles. The significance of differences in primary outcome between subgroups (effect modification) was calculated. A post-hoc per-protocol analysis was performed after excluding women allocated to non-intervention who received RBC transfusion, and women allocated to RBC transfusion who did not receive RBC units. Estimates of ANOVA of health-related quality of life means were calculated to create graphics. Superiority analyses were used to analyse secondary outcomes. For secondary analyses, we used the chi-square test for comparing proportions and the Mann–Whitney *U* test for comparing continuous variables. *P*-values given are two-sided and 0.05 was considered the limit of significance. Data were analysed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study, 1011 women were approached; 521 gave informed consent for randomisation: 259 were allocated to RBC transfusion and 262 to non-intervention. After randomisation, two participants were excluded because they did not meet the inclusion criteria (Figure 1). Table 1 shows the baseline characteristics of both randomised and nonrandomised women. Among randomised women, no significant differences were found between study arms. Two neonatal deaths in preterm neonates occurred during follow up due to sepsis and necrotising enterocolitis.

Baseline characteristics of responders versus nonresponders (at least one completed questionnaire versus no questionnaires) showed significant differences for ethnicity, age and blood loss (responders versus nonresponders; western ethnicity in 81% versus 54%, mean age 31 versus 28 years, median blood loss 1500 versus 1150 ml).

Concentration of Hb at inclusion was comparable between study arms (Table 1). Women randomised to RBC transfusion received a median of two RBC units. In these women, median Hb concentration after transfusion was 9.0 g/dl and median Hb concentration at discharge was significantly higher than in women allocated to non-intervention (Table 2). Among women allocated to RBC transfusion, seven received no RBC transfusion: four withdrew consent, one appeared to have no health insurance, one had fever and one had irregular erythrocyte alloantibodies. Of women allocated to non-intervention, 33/261 (13%) received RBC transfusion during follow up. Indications were anaemic symptoms ($n = 28$), blood loss following retained placenta ($n = 3$), discomfort with parenteral iron supplementation ($n = 1$) and readmission for endometritis ($n = 1$). Compared with women who did not receive another transfusion during follow up, these women had lower Hb concentrations and higher physical fatigue scores at inclusion (median Hb 7.4 versus 6.9 g/dl, $P = 0.02$ and median physical fatigue score 19 versus 17, $P = 0.08$). In those women who suffered symptoms of anaemia, RBC transfusion was given at a median of 2 days (IQR 1–3), and five were readmitted. Three transfusion reactions

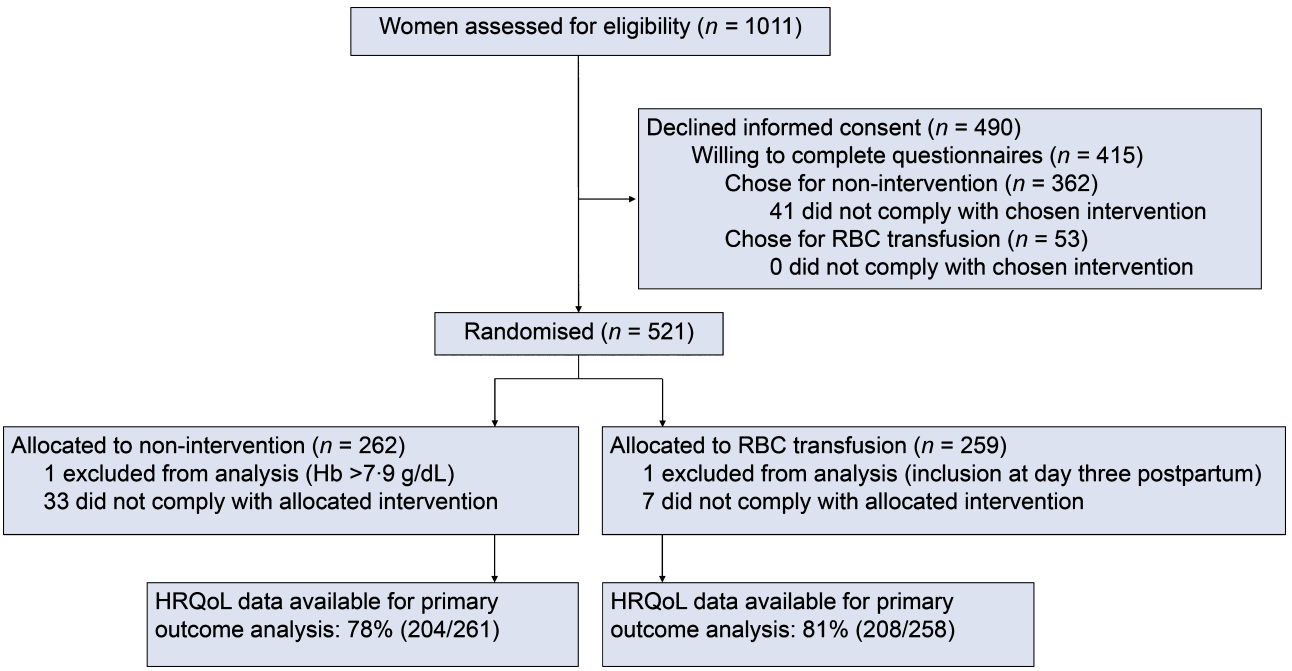

Figure 1. Randomisation flow chart.

Table 1. Baseline maternal characteristics of randomised and non-randomised women

	Randomised women		Non-randomised women	
	Transfusion (*n* = 258)	**Non-intervention (*n* = 261)**	**Transfusion (*n* = 53)**	**Non-intervention (*n* = 362)**
Age (years)	30.7 ± 5.0	30.9 ± 5.3	31.8 ± 4.8	31.2 ± 5.2
Preconception body mass index (kg/m^2)*	23.3 (21.1–26.6)	22.9 (20.8–26.5)	22.3 (20.9–25.1)	23.4 (21.1–26.0)
Western ethnic origin**	186 (78%)	177 (76%)	38 (91%)	255 (84%)
Highest education***				
None/Primary school	4 (3%)	5 (3%)	0	4 (2%)
Lower/Senior secondary vocational education	88 (56%)	77 (51%)	6 (24%)	91 (46%)
Higher professional education and university	64 (41%)	70 (46%)	19 (76%)	102 (52%)
Nulliparous	152 (59%)	143 (55%)	31 (59%)	207 (57%)
Delivery by community midwife****	41 (16%)	29 (11%)	8 (15%)	58 (16%)
Mode of delivery				
Vaginal	213 (83%)	206 (79%)	45 (85%)	292 (81%)
of which operative*******	62 (30%)	48 (24%)	6 (15%)	55 (20%)
Elective CS	8 (3%)	15 (6%)	2 (4%)	23 (6%)
Emergency CS	37 (14%)	40 (15%)	6 (11%)	47 (13%)
Twin pregnancies	13 (5%)	16 (6%)	5 (9%)	18 (5%)
Gestational age (weeks^{+days})	40^{+1} (38^{+5}–41^{+1})	40^{+0} (38^{+3}–41^{+0})	40^{+2} (38^{+6}–41^{+1})	40^{+0} (38^{+4}–41^{+0})
Birthweight neonate******				
<10th centile	8 (3%)	20 (8%)	3 (6%)	16 (5%)
10th to 90th centile	188 (75%)	189 (74%)	34 (69%)	258 (74%)
>90th centile	54 (22%)	47 (18%)	12 (25%)	75 (22%)
Estimated blood loss during delivery (ml)	1485 (1000–1950)	1500 (1000–1975)	1500 (925–2000)	1500 (1000–2000)
Hb concentration at inclusion (g/dl)	7.3 (6.8–7.7)	7.4 (6.8–7.7)	6.9 (6.4–7.4)	7.4 (6.9–7.7)

Data are *n* (%), Mean ± SD, or Median (Interquartile Range), as indicated. CS, caesarean section.
*Randomised: *n* = 232 and *n* = 234 respectively. Non-randomised: *n* = 49 and *n* = 322 respectively.
**Randomised: *n* = 239 and *n* = 232 respectively. Non-randomised: *n* = 42 and *n* = 304 respectively.
***Randomised: *n* = 156 and *n* = 152 respectively. Non-randomised: *n* = 25 and *n* = 197 respectively.
****Randomised: *n* = 253 and *n* = 255 respectively. Non-randomised: *n* = 52 and *n* = 352 respectively.
*****Randomised: *n* = 205 and *n* = 197 respectively. Non-randomised: *n* = 39 and *n* = 279 respectively.
******Randomised: *n* = 250 and *n* = 256 respectively. Non-randomised: *n* = 49 and *n* = 349.

(3/291) were recorded, all in the RBC transfusion arm: one developed a rash (WHO Category 1, mild transfusion reaction) and two a rise in temperature (WHO Category 2, moderate–severe transfusion reaction).[18]

Concentrations of Hb at 6 weeks were comparable between study arms, as demonstrated in Table 2.

Primary outcome (physical fatigue at day 3) was analysed in 208 women in the RBC transfusion arm and in 204 women in the non-intervention arm. Women randomised to non-intervention had a 0.78 higher mean physical fatigue score at day 3 than women randomised to RBC transfusion (95% CI 0.1–1.5, $P = 0.024$) (Figure 2, Table 3). The non-inferiority boundary was just exceeded by the 95% CI. At 1 week, the difference in physical fatigue scores between study arms was 1.06 (95% CI 0.3–1.8, $P = 0.007$) (Table 3). In Figure 3, mean differences in physical fatigue scores between study arms and confidence intervals are presented with the non-inferiority boundary. Primary outcome was not significantly affected by mode of delivery (interaction *P*-value: 0.40).

The remaining health-related quality of life scores are presented in the Supplementary material, Table S1. All Multidimensional Fatigue Inventory subscales, with the exception of mental fatigue at 3 days, showed slightly higher mean scores in the RBC non-intervention arm: the largest difference was 1.1 (physical fatigue at 1 week). Regarding the ShortForm-36, differences in subscale scores between arms ran up to 5.5 points (physical functioning at 1 week) with a tendency to lower health scores in the non-intervention arm. The difference was significant only in the subscale physical functioning at 1 and 3 weeks (scores respectively 5.5 and 4.3 points lower in the non-intervention arm). Again though, significance of the difference is of secondary interest to its magnitude, which seems relatively small on the scale of ShortForm-36.

Table 2. Blood loss, haemoglobin concentration, and RBC transfusion

Variable	Transfusion (*n* = 258)	Non-intervention (*n* = 261)	*P*
RBC transfusion			
Units per woman	2 (2–2)	0 (0–0)	<0.001
Total units*	517	88	<0.001
Hb concentration after transfusion, g/dl)**	9.0 (8.5–9.6)	8.9 (8.2–9.7)	0.56
Hb concentration at discharge (g/dl)***	9.0 (8.5–9.5)	7.4 (6.8–7.7)	<0.001
Cross-over	7 (3%)	33 (13%)	<0.001
Refused RBC transfusion	5		
Fever	1		
Erythrocyte alloantibodies	1		
Anaemic symptoms		28	
Retained products of conception		3	
Parenteral iron intolerance		1	
Infection (endometritis)		1	
Hb concentration at 6 weeks (g/dl)****	12.1 (11.3–12.6)	11.9 (10.9–12.6)	0.18

Data are *n* (%) or Median (Interquartile Range).
*Including units transfused during follow up.
**Non-intervention: *n* = 220. RBC transfusion: *n* = 25 (transfusion on second instance).
***Non-intervention: *n* = 231. RBC transfusion: *n* = 238.
****Non-intervention: *n* = 165. RBC transfusion *n* = 178. Blood samples for determining Hb at 6 weeks postpartum were collected at 45 (41–53) and 43 (40–48) days postpartum in the RBC transfusion and non-intervention arm respectively.

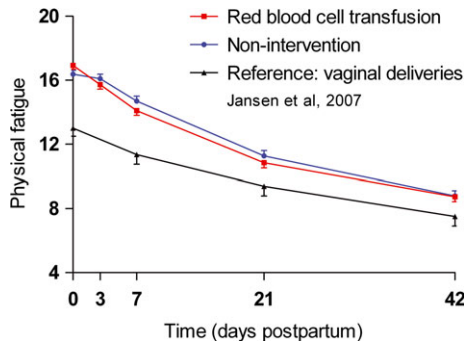

Figure 2. Physical fatigue score in randomised women (*n* = 447). Analysis of variance estimates of means, error bars represent standard errors. Reference curve obtained from the pilot study that included 141 consecutive women delivering in hospital. Seventy-one women delivered vaginally; in these women, median blood loss was 300 ml.[9]

Health-related quality of life results were similar after excluding questionnaires not completed within the prescribed time frames after follow up (0–2, 2–5, 6–10 days, 2–4 and 5–7 weeks postpartum) (138/1803 questionnaires excluded).

Length of hospital stay after delivery was equal in both study arms (median days: 2, $P = 0.37$) and physical complications were comparable (Table 4). Use of iron supplementation was more frequent in women allocated to non-intervention. The percentage of women who breastfed initially, as well as those who continued until 6 weeks postpartum, was not different between study arms (Table 4).

Results were consistent in a per-protocol analysis (mean physical fatigue score at day 3 was 0.80 higher in the non-intervention arm, $P = 0.03$, 95% CI 0.1–1.5).

The difference at day 3 in mean physical fatigue scores per category Hb at inclusion (Hb 4.8–6.5, 6.6–7.3 and 7.4–7.9 g/dl) was 1.19 (± SE 1.07), 0.91 (± SE 0.60), and 0.73 (± SE 0.44), respectively. These differences did not significantly differ from each other ($P = 0.91$). Per category physical fatigue score at inclusion (<14, 14–17, 18–19, 20) these differences were 1.58 (± SE 1.02), 1.22 (± SE 0.68), 0.61 (± SE 0.71) and 0.10 (± SE 0.49), respectively, and did not significantly differ from each other ($P = 0.42$).

Ten randomised women were retrospectively identified with an exclusion criterion: HIV (three), severe pre-eclampsia (four) and thalassaemia (three). Primary outcome analysis after excluding these women gave similar results (data not shown).

Non-randomised women

Of the 490 women who declined informed consent; 415 (85%) were willing to complete questionnaires: 53 chose RBC transfusion and 362 non-intervention. Characteristics of nonrandomised participants are described in Table 1. Compared with randomised women, nonrandomised women were less often of western ethnicity: 363/471 (77%) versus 293/346 (85%), $P = 0.01$; and had less often had an operative vaginal delivery: 110/402 (27%) versus 61/318 (19%), $P = 0.01$).

Among non-randomised women, Hb concentration was significantly lower in women who chose RBC transfusion (median Hb 7.4 versus 6.9 g/dl, $P < 0.001$). The women who chose RBC transfusion all received RBC units. Of women who chose non-intervention, 41/362 (11%) received RBC transfusion, 34 (9%) because of anaemic symptoms. These rates are comparable to the rates in randomised women.

Discussion

Main findings

In this study, the difference in physical fatigue at day 3 postpartum between both study arms was small. Although

Table 3. Difference in mean physical fatigue in randomised women, $n = 382$

Mean adjusted for baseline and mode of delivery							
Time point	**Non-inferiority boundary**	**Transfusion**	**Non-intervention**	**Difference**	***P***	**95% CI**	
						Lower limit	**Upper limit**
Three days	1.30	15.68	16.45	0.78	0.024	0.1	1.5
One week	1.30	14.02	15.08	1.06	0.007	0.3	1.8
Three weeks	1.30	10.88	11.54	0.66	0.14	−0.2	1.5
Six weeks	1.30	8.69	8.95	0.26	0.56	−0.6	1.1

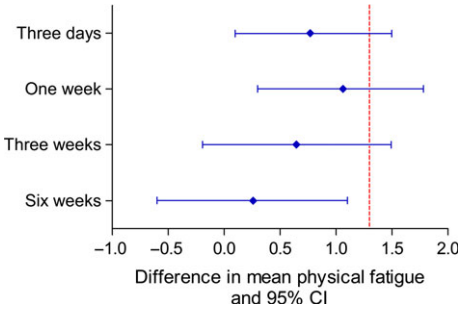

Figure 3. Mean differences and confidence intervals for physical fatigue in view of the non-inferiority boundary.

the difference was only 0.78, the 95% CI of this difference (0.1–1.5) just exceeded the non-inferiority boundary of 1.3. Although non-inferiority cannot be demonstrated, the clinical relevance of this difference seems negligible. No differences were found between study arms for secondary outcomes.

Regarding non-inferiority, its boundary is ideally based on the minimum clinically important difference, however, minimum clinically important differences for the Multidimensional Fatigue Inventory subscales had not been established in 2004. The prespecified level of 1.3 was the feasible detectable difference in physical fatigue calculated using data obtained in a pilot study[9]: this was not considered a valid estimate of the score's clinical relevance. Retrospectively, our prespecified level seems too strict considering the following arguments. First, the minimum clinically important difference for physical fatigue has recently been determined to be larger, namely 2.04, in radiotherapy

Table 4. Follow up in randomised women

Variable	**Transfusion**		**Non-intervention**		***P***
	n		***n***		
Iron supplementation	231		246		<0.001
Oral		93 (40%)		187 (76%)	
continued until 6 weeks*	66	37 (56%)	130	84 (65%)	0.31
Intravenous		0		30 (12%)	
None		138 (60%)		29 (12%)	
Breastfeeding at randomisation	252	194 (77%)	250	193 (77%)	1.00
continued until 6 weeks	154	99 (64%)	143	101 (71%)	0.30
Complications					
Transfusion reactions	227	3 (1%)	30	0	0.54
Thromboembolic event	227	2 (0.9%)	226	2 (0.9%)	1.00
Urinary tract infection	228	10 (4.4%)	225	14 (6.2%)	0.52
Infected surgery wound	41	0	46	1 (2.2%)	1.00
Infected episiotomy/rupture	145	6 (4.1%)	137	6 (4.4%)	1.00
Endometritis	228	5 (2.2%)	225	3 (1.3%)	0.74
Infectious complications, total	209	22 (10.5%)	211	24 (11.4%)	0.90

n are number of women in which variable is known. Data are *n* (%) unless otherwise specified.
*Oral supplementation users.

patients.[19] Second, the difference in physical fatigue score in this study is very small, given the large difference between scores after uncomplicated deliveries (derived from the pilot study) and scores after postpartum haemorrhage (this study). These scores, demonstrated in Figure 2, indicate that postpartum haemorrhage greatly increases physical fatigue irrespective of the treatment policy. Third, in social sciences, Cohen's effect size (d) is used to determine a relevant difference (relevant when $d \geq 0.50$).[20] In our data, values of d were <0.20 for all Multidimensional Fatigue Inventory subscales (calculated at all time-points), indicating no relevant differences. The disadvantage of Cohen's effect size, and the reason not to include it in this study design, is that the measure is distribution-based, whereas we think determining clinical relevance should be content-based. In addition, we analysed all randomised and nonrandomised patients together and found that the difference in physical fatigue between study arms was equal (0.8) to the difference in randomised patients alone, while its 95% CI was smaller (0.23–1.27) and so does not exceed the non-inferiority boundary.

Interpretation

Most trials investigating transfusion policy were conducted in intensive care, cardiovascular, and orthopaedic patients,[21–29] while recently a trial in patients with gastrointestinal bleeding has been published.[30] Six trials used as restrictive trigger an Hb threshold of ≥8 g/dl[22–26,30] and two used haematocrit thresholds of 24% and 30%.[27,28] To our knowledge, only Hébert conducted a randomised controlled trial with Hb thresholds below 8 g/dl (Hb <7 g/dl versus <9 g/dl).[21] This study in intensive care patients showed that a restrictive threshold was at least as effective regarding mortality, multi-organ failure, and length of hospital stay in patients without cardiac disease. A recent update on Cochrane evidence regarding Hb thresholds, including 19 randomised trials and more than 6000 women, demonstrated a relative risk for 30-day all-cause mortality of 0.85 (95% CI 0.70–1.03) in women allocated to a lower Hb threshold (threshold varying from 7 to 10 g/dl) compared with a more liberal transfusion policy. Also, a lower threshold was not associated with any significant differences in major complications.[31] In our study, physical complications between study arms were also comparable, as was duration of hospital stay.

Previously, few studies investigated postpartum health-related quality of life. The Multidimensional Fatigue Inventory was only used in our pilot study, to validate health-related quality of life measures in Dutch postpartum women.[9] This study found significant differences in Multidimensional Fatigue Inventory scores after different modes of delivery, though the present study has not confirmed this finding. After vaginal delivery, women in the pilot study had significantly more favourable scores than in the present study, whereas the scores after caesarean section in the pilot study were comparable to scores in the present study. Differences in physical fatigue between modes of delivery might be influenced by the large effect of postpartum haemorrhage on physical fatigue.

Minimum clinically important differences of Short-Form-36 subscales have not yet been determined in a postpartum population. Minimum clinically important differences determined in orthopaedic problems, chronic obstructive pulmonary disease, asthma and cardiac disease are at least 10 points so the differences found in Short-Form-36 subscales in this study (maximal difference 5.5) seem to not be clinically relevant.[32–34]

Strengths and limitations

Main strengths of this study are the comparison of randomised arms and the large study population. Questionnaires to score health-related quality of life outcomes were internationally validated. Primary outcome was available in 412/519 (80%) of randomised participants, a usual response rate in health-related quality of life studies. A large percentage of eligible women declined informed consent, mainly because they did not want an intervention. Baseline characteristics of randomised versus nonrandomised participants showed only differences in ethnicity and frequency of operative delivery.

The majority of participants in our study delivered vaginally. Women presumably receive RBC transfusions more reluctantly in operating theatres than after vaginal deliveries. As a result of the small numbers, comparisons between emergency and elective caesarean sections could not be made. Although iron supplementation is assumed to have no effect after RBC transfusion, still a remarkable percentage of women in the RBC transfusion arm used iron supplementation. Wide variations in type, dosage and duration of iron supplementation made it impossible to make comparisons. Though the assumption is that anaemia compromises breastfeeding,[35] our study showed that more women in the non-intervention arm were still breastfeeding 6 weeks postpartum although the intention to breastfeed had been similar in the study arms. These results should be interpreted with caution because reasons for discontinuation of breast feeding were not reported.

A minority of clinicians is unaware of or reluctant to accept lower transfusion thresholds.[36] Implementing a restrictive approach to RBC transfusion would lead to a striking decrease in demand for RBC units and adverse events. In our study, the use of RBC units in the non-intervention arm was 88/517 (17%) of that in the RBC transfusion arm (Table 2). A high percentage of women in the non-intervention arm (28/261, 11%) secondarily received RBC units for anaemic symptoms. Among

non-randomised women this percentage was similar, even though they were expected to be more motivated for non-intervention.

The randomised women allocated to non-intervention who received RBC transfusion during follow up had significantly lower Hb concentrations at inclusion. Also, a trend towards a larger difference in physical fatigue between study arms was seen in the women in the lowest category Hb concentrations and in highest category of physical fatigue scores at inclusion. Therefore, Hb concentration should be considered when counselling postpartum anaemic women: RBC transfusion seems to have the greatest effect in women with the lowest Hb and highest physical fatigue scores.

Conclusion

The difference in mean physical fatigue score between study arms was only small (0.78). The clinical relevance of this difference seems negligible even though non-inferiority of non-intervention policy could statistically not be demonstrated. The recently established minimum clinical difference of physical fatigue,[19] suggests that non-intervention policy is safe with regard to physical complications and only accompanied by slightly higher physical fatigue scores; we feel that our results justify the implementation of non-intervention in daily clinical practice. Future studies are needed to establish the optimal iron supplementation in these women and justify implementation of a non-inferiority policy.

Disclosure of interests

All authors confirm no conflicts of interest with regards to the data reported.

Contribution to authorship

AJGJ, DJR, WCJH, MLEB, CAUG and JJD designed the trial. AJGJ, BWP, JJD and BWJM coordinated the trial. BWP, EAPS, BMCA, MA, KWMB, KEB, HAB, AK, AJL, GCHM, DNMP, JAMP, MMP, RJPR, FJMER, HCJS, DHS, NWES, RHS, MDW, BWJ and JJD recruited participants and contributed to critical aspects of the conduct of the research. BWP and JJD wrote the grant applications and obtained funding; they also had full access to all data and take responsibility for the integrity of the data. BWP and WCJH analysed the data and take responsibility for the accuracy of the data analysis. BWP and JJD drafted and wrote the manuscript. All authors interpreted the data, revised the article, and approved the final version.

Details of ethics approval

The study was approved by the University of Rotterdam's Institutional Review Board (MEC-2003-247), and had local approval from the boards of all participating hospitals. The study was registered at ClinicalTrials.gov NCT00335023 and at the Dutch Trial Register (NTR335).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Health-related quality of life in randomised women during follow-up. ■

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