Efficacy and safety of intravenous ferric carboxymaltose compared with oral iron for the treatment of iron deficiency anaemia in women after childbirth in Tanzania: a parallel-group, open-label, randomised controlled phase 3 trial

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Summary

Background Iron deficiency anaemia is of major concern in low-income settings, especially for women of childbearing age. Oral iron substitution efficacy is limited by poor compliance and iron depletion severity. We aimed to assess the efficacy and safety of intravenous ferric carboxymaltose versus oral iron substitution following childbirth in women with iron deficiency anaemia in Tanzania.

Methods This parallel-group, open-label, randomised controlled phase 3 trial was done at Bagamoyo District Hospital and Mwananyamala Hospital, Tanzania. Eligible participants were close to delivery and had iron deficiency anaemia defined as a haemoglobin concentration of less than 110 g/L and a ferritin concentration of less than 50 µg/L measured within 14 days before childbirth. Participants were randomly assigned 1:1 to receive intravenous ferric carboxymaltose or oral iron, stratified by haemoglobin concentration and site. Intravenous ferric carboxymaltose was administered at a dose determined by the haemoglobin concentration and bodyweight (bodyweight 35 kg to <70 kg and haemoglobin ≥100 g/L: 1000 mg in one dose; bodyweight 35 kg to <70 kg and haemoglobin <100 g/L, or bodyweight ≥70 kg and haemoglobin ≥100 g/L: 1500 mg in two doses at least 7 days apart; bodyweight ≥70 kg and haemoglobin <100 g/L: 2000 mg in two doses at least 7 days apart). Oral iron treatment consisted of three dried ferrous sulphate tablets of 200 mg containing 60 mg of elementary iron and 5 mg of folic acid every morning. Oral treatment was to be taken for 3 months after haemoglobin normalisation. The primary outcome was haemoglobin normalisation (>115 g/L) at 6 weeks. Follow-up visits were at 6 weeks, and 3, 6, and 12 months. Analyses were done in the modified intention-to-treat population of participants who had a 6-week haemoglobin concentration result, using logistic and linear regression models for binary and continuous outcomes, adjusted for baseline haemoglobin concentration and site. This trial is registered with ClinicalTrials.gov, NCT02541708.

Findings Between Oct 8, 2015, and March 14, 2017, 533 individuals were screened and 230 were enrolled and randomly assigned to a study group (114 to intravenous iron, 116 to oral iron). At 6 weeks, 94 (82%) participants in the intravenous iron group and 92 (79%) in the oral iron group were assessed for the primary outcome. 75 (80%) participants in the intravenous iron group and 47 (51%) in the oral iron group had normalised haemoglobin (odds ratio 4·65, 95% CI 2·33–9·27). There were two mild to moderate infusion-related adverse events; and five serious adverse events (three in the intravenous iron group, two in the oral iron group), unrelated to the study medication.

Interpretation Intravenous iron substitution with ferric carboxymaltose was safe and yielded a better haemoglobin response than oral iron. To our knowledge, this is the first study to provide evidence of the benefits and safety of intravenous iron substitution in a low-income setting.

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Introduction

Approximately 1·24 billion people globally are affected by iron deficiency anaemia and the Global Burden of Disease report highlights the substantial public health impact of this condition, with approximately 34·7 million disability-adjusted life-years attributable.[1] In Africa, anaemia is a major public health concern: approximately 60% of the population have anaemia[2] due to malnutrition, pregnancies, haemoglobinopathies, iron deficiency, or functional iron deficiency in chronic infectious diseases, negatively affecting quality of life and national socio-economic status.[3,4] It is generally assumed that 50% of the cases of anaemia are due to iron deficiency.[2] Menstruating individuals are at high risk of iron

Research in context

Evidence before this study

We searched PubMed in 2012, and in September, 2019, for studies comparing the use of intravenous ferric carboxymaltose versus oral iron in the treatment of iron deficiency anaemia in Africa or low-income countries using the terms "anaemia", "iron deficiency", "treatment", "low-income", AND "Africa". We did not find any studies reporting the use of intravenous ferric carboxymaltose in resource-limited settings. Iron deficiency prevention and treatment in resource-limited settings is done by oral nutritional iron fortification or iron tablets. A meta-analysis from 2017 included data from 14 studies in high-income settings and found a benefit of ferric carboxymaltose over oral iron in correcting anaemia and iron deficiency. Ferric carboxymaltose is known to be safer than the older intravenous iron preparations such as iron dextran or iron sucrose.

Added value of this study

To our knowledge, this is the first randomised trial to assess the efficacy and safety of intravenous ferric carboxymaltose compared with oral iron in the treatment of iron deficiency anaemia following childbirth in a resource-limited setting. We found that intravenous ferric carboxymaltose was more effective than oral iron therapy in correcting anaemia and iron deficiency, in line with results from high-income settings. We have shown that ferric carboxymaltose can be safely infused in district and local hospitals in a resource-limited setting.

Implications of all the available evidence

Use of intravenous iron in the peripartum period is safe, feasible, and provides better correction of iron deficiency and anaemia than oral iron in resource-limited settings where incidence is particularly high.

deficiency anaemia, and this risk is further increased during pregnancy and unsafe delivery.[2] Post-partum anaemia adversely affects maternal recovery, cognition, and maternal–infant interactions.[5]

The recommended therapy for iron deficiency anaemia in resource-limited settings is daily oral iron substitution for around 6 months.[6] Oral iron substitution is cheap, but requires fasting intake for maximal effect and good compliance over a long period, which might be challenging given the common side effects of obstipation, diarrhoea, and abdominal pain. Compliance in resource-limited settings is dependent not only on tolerance to the medication and its clinical effectiveness, but also on socioeconomic and educational factors.[7] Compliance with oral iron substitution might therefore be worse in resource-limited than in high-income settings, thus jeopardising its effectiveness.[8]

By contrast, intravenous iron substitution with ferric carboxymaltose is more expensive than oral iron but allows saturation of the body iron stores after just one or two infusions. Infusions can be delivered at times coinciding with routine medical visits. The efficacy and safety of intravenous ferric carboxymaltose has been shown in high-income countries[9–11] where this treatment is increasingly replacing oral iron substitution and intravenous iron substitution with iron dextran (which carries a risk of anaphylactic reactions) or iron sucrose (which has a different safety profile).[12–18] However, the different socioeconomic, cultural, and medical conditions in low-resource settings—including medication access, perception of medication needs, compliance, and the burden of concomitant diseases—might influence the effectiveness and safety of iron substitution modality compared with high-income countries. Therefore, the most effective treatment approaches for iron deficiency anaemia in different low-resource settings are not known. Our aim was to compare the safety and efficacy of intravenous iron substitution by ferric carboxymaltose versus oral iron substitution in post-partum women in a rural setting in Tanzania.

See Online for appendix

Methods

Study design

This was a parallel-group, open-label, randomised controlled phase 3 trial, and was a collaborative project between the Swiss Tropical and Public Health Institute, Basel, Switzerland and Ifakara Health Institute, Bagamoyo, Tanzania. Participants were initially recruited and followed up through the antenatal care services at Bagamoyo District Hospital, Bagamoyo, Tanzania. To achieve recruitment goals, we opened a second site at Mwananyamala District Hospital, Dar es Salaam region, Tanzania in November, 2016. Recruitment finished once the target sample size had been reached. The study was done in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice, and local regulations. The study was approved by the Ethics Committee of Northwestern and Central Switzerland (reference 245/13), the institutional review board of the Ifakara Health Institute (reference 05-2014), and the Medical Research Coordination Committee of the National Institute for Medical Research of Tanzania (reference NIMR/HQ/R.8c/Vol.I/427), and following regulatory clearance of the investigational product ferric carboxymaltose by the Tanzanian Food and Drug Authority (IFCIDA 001-2015). Written informed consent was obtained from each participant. The informed consent form was written in English and translated into Swahili. For a few illiterate participants, the form was read to them by a witness, who was not part of the study team, before the participant made a thumbprint on the signature page to confirm their willingness to participate. The protocol is shown in the appendix (p 19).

Participants

Women presenting to the hospital antenatal care services were screened by nurses of the ward under supervision of physicians or clinical officers of the Ifakara Health Institute. Eligible participants were close to delivery; had iron deficiency anaemia, defined as a haemoglobin concentration of less than 110 g/L and a ferritin concentration of less than 50 µg/L measured within 14 days before childbirth; lived close to the hospital; and agreed to attend scheduled follow-up visits. Participants were excluded if they were HIV positive; had a known haemoglobinopathy; had a C-reactive protein concentration of more than 20 mg/L; had chronic fever; had a psychiatric disorder precluding understanding of information on trial-related topics; were prescribed concurrent treatment with other experimental drugs or treatment in another clinical trial within 30 days before trial entry; had any serious underlying medical condition that could impair their ability to participate in the trial; or if they had a known allergy or hypersensitivity to any of the study drugs. Participants were tested for malaria by a rapid diagnostic test and microscopy, and for helminthic infections by stool ova and parasite examination; those testing positive were treated according to national guidelines and were eligible for enrolment.

Randomisation and masking

Participants were enrolled and randomly assigned by study personnel. Participants were randomly assigned in a 1:1 ratio to receive either intravenous ferric carboxymaltose or oral iron, stratified by haemoglobin concentration (<70 g/L, 70–100 g/L, or >100 g/L) and site. The trial statistician generated the treatment allocation scheme in advance by computer. Opaque envelopes were prepared on site according to this scheme by people who were independent from the trial, and were sealed and marked on the outside with a sequential number and the stratification information. The randomisation processes were subject to monitoring and verification by the trial statistician; it was found that the haemoglobin stratification was not properly applied during the first 68 random assignments, resulting in simple randomisation being applied for those enrolments. The process was corrected and continued as planned. Importantly, allocation concealment was maintained throughout the trial.

Procedures

Treatment was started within 14 days of screening and 7 days of childbirth. Eligible participants who did not deliver within 14 days of screening could be rescreened on a predefined subset of parameters including haemoglobin and ferritin concentrations.

Ferric carboxymaltose (Vifor Pharma, Villars-sur-Glâne, Switzerland) was administered intravenously according to the manufacturer at a dose determined by the haemoglobin concentration and bodyweight. Participants with a bodyweight of 35 kg to less than 70 kg and a haemoglobin concentration of 100 g/L or more received 1000 mg ferric carboxymaltose in one dose; participants with a bodyweight of 35 kg to less than 70 kg and a haemoglobin concentration of less than 100 g/L, or a bodyweight of 70 kg or more and a haemoglobin concentration of 100 g/L or more, received 1500 mg in two doses at least 7 days apart; participants with a bodyweight of 70 kg or more and a haemoglobin concentration of less than 100 g/L received 2000 mg in two doses at least 7 days apart.

Oral iron treatment consisted of three dried ferrous sulphate tablets of 200 mg containing 60 mg of elementary iron and 5 mg of folic acid every morning. Participants were advised by a trained nurse about intake modalities (30 min before food, tea, or coffee; or in case of side-effects, with a meal or in two separate doses per day [two tablets in the morning and one in the evening]). Oral treatment was to be taken for 3 months after correction of anaemia, defined as a haemoglobin concentration of more than 115 g/L. Drug accountability logs were used to record the number of tablets issued at each visit and pill counting was done to monitor adherence.

Follow-up visits in both groups were scheduled for 5–10 days, 6 weeks, 12 weeks, 6 months, and 12 months after treatment start. Clinical information from each visit was documented in standardised paper case report forms and double-entered in Open Data Kit software. Any discrepancies were solved by queries issued to the study team. Quality of life was assessed using the standardised 36-item Short Form Health Survey (SF-36) questionnaire version 2 (with 4 week recall) at enrolment and follow-up visits from week 6 onwards.[19,20]

For **information about Open Data Kit** see https://getodk.org/

At enrolment and all follow-up visits, whole blood cell counts were analysed on a Sysmex XE-2100 five populations analyser (Sysmex Europe, Norderstedt, Germany). Ferritin, hepatic function parameters, serum creatinine, and C-reactive protein were measured on a COBAS INTEGRA 400 plus analyser (Roche Diagnostics, Mannheim, Germany). Data from laboratory analyses were extracted from the analysers and linked to the respective clinical data by a common unique identifier.

Outcomes

The primary outcome was the proportion of participants with a normalised haemoglobin concentration (>115 g/L) at 6 weeks after treatment initiation. Secondary outcomes were the proportion of participants with corrected iron deficiency (defined as a normalised serum ferritin concentration of >100 µg/L) at 6 weeks after treatment initiation, haemoglobin and ferritin best responses (highest values), time to haemoglobin and ferritin best responses, adherence to study medication, adverse events, and wellbeing, as measured by the SF-36.

Sensitivity, specificity, and the negative and positive predictive values of erythrocyte indices for the diagnosis of iron deficient anaemia in Tanzania will be reported later.

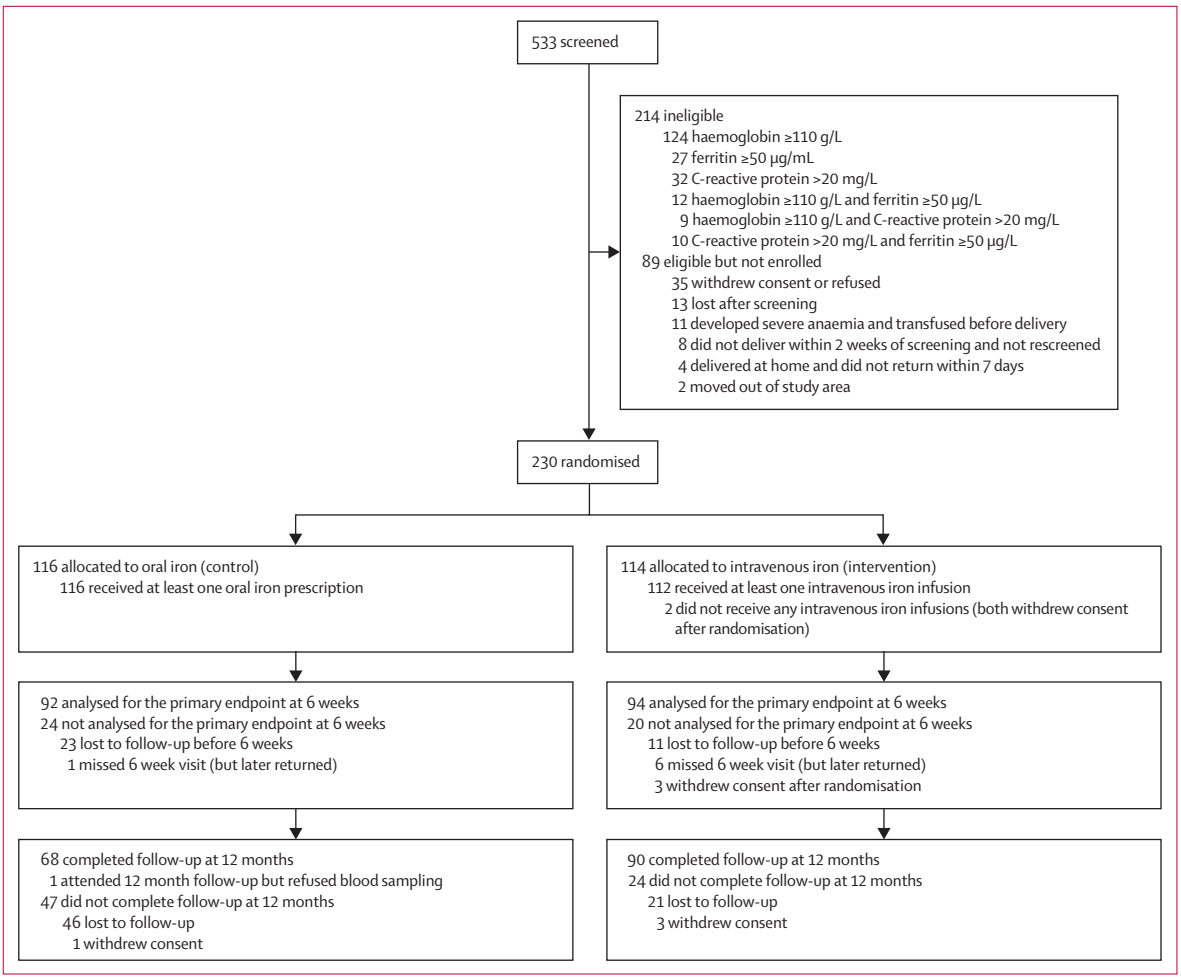

Figure 1: **Trial profile**

Statistical analysis

We assumed that 85% of participants in the intravenous iron group and 70% in the oral iron group would have a normalised haemoglobin concentration at 6 weeks. To detect a difference in response rates of 15%, with a one-sided type I error probability of 0·05 and 80% power, 95 participants per group were required (assuming a two-sided type I error of 0·05, this sample size yields 70% power). An additional 20% was added to the sample size to allow for loss to follow-up, yielding 230 participants overall.

Outcomes were analysed in the modified intention-to-treat population of participants who had a 6-week haemoglobin concentration result. We used logistic models for categorical outcomes and linear regression models for continuous outcomes, adjusted for baseline haemoglobin concentration and site. For the primary outcome, we estimated the prevalence difference using the marginal standardisation technique, with 95% CIs estimated using the delta method.[21] In preplanned sensitivity analyses, we adjusted for covariates that appeared unbalanced between groups at baseline by visual inspection or were associated with differential follow-up. We did the following post-hoc analyses: sensitivity analyses in which participants with missing primary outcome data were classified as not having haemoglobin normalisation at 6 weeks; sensitivity analyses excluding the first 68 participants for whom the randomisation stratification was not applied; unadjusted analyses; and analyses considering thresholds of more than 120 g/L for haemoglobin[22] and more than 30 µg/L for ferritin. We assessed a-priori effect modification by baseline haemoglobin concentration. Haemoglobin and ferritin best responses and times to best response were analysed descriptively.

For the intravenous iron group, adherence was assessed by the number and proportion of participants receiving infusions according to the protocol. There were some instances of incorrect dose calculation, for example screening values of haemoglobin being used to determine dosage, or participants with bodyweight, haemoglobin value, or both on the border of the thresholds for dosing

	Oral iron (N=116)	Intravenous iron (N=114)
Demographics		
Site		
Bagamoyo	98 (84%)	96 (84%)
Mwananyamala	18 (16%)	18 (16%)
Age, years	26 (22–30)	26 (22–31)
Education		
None	13 (11%)	13 (11%)
Primary	61 (53%)	66 (58%)
Secondary	39 (34%)	28 (25%)
Tertiary	3 (3%)	7 (6%)
Marital status		
Single	10 (9%)	5 (4%)
Married	87 (75%)	94 (82%)
Cohabiting	19 (16%)	14 (12%)
Widow	0	1 (1%)
Number of people living in the same household	4 (3–6)	4 (3–6)
Laboratory parameters		
Haemoglobin, g/L*	98 (86–105)	92 (85–103)
<70	3 (3%)	7 (6%)
70–100	70 (60%)	72 (63%)
>100	43 (37%)	35 (31%)
Ferritin, µg/L†	23 (13–42)	18 (11–39)
Creatinine, µmol/L‡	50·8 (44·1–57·2)	50·0 (42·7–59·0)
Alkaline phosphatase, IU/L§	157 (123–206)	157 (121–188)
Aspartate aminotransferase, IU/L¶	20·7 (16·4–27·7)	23·0 (16·9–28·3)
Alanine aminotransferase, IU/L¶	10·5 (8·2–14·5)	9·3 (7·5–12·9)
Total bilirubin, µmol/L¶	6·4 (3·9–10·3)	6·7 (4·8–9·3)
C-reactive protein, µg/L‡	26880 (11880–65820)	28860 (12160–86370)
(Table 1 continues in next column)		
(Continued from previous column)		
Anaemia prevention strategies		
Ferrous sulphate and folic acid, daily or intermittent use	106 (91%)	103 (90%)
Pregnancy characteristics		
Gravida	2 (1–3)	2 (1–4)
Attended medical visits during pregnancy	114 (98%)	113 (99%)
Any symptoms during past 2 weeks	29 (25%)	39 (34%)
Delivery characteristics		
Gestation week‖	40 (39–41)	40 (39–42)
Birth complications		
Perineal rupture	6 (5%)	7 (6%)
Tear of uterus	1 (1%)	0
Bleeding	2 (2%)	2 (2%)
Neonate characteristics		
Apgar score 10 min after birth		
Stillborn**	2 (2%)	1 (1%)
7–8	9 (8%)	6 (5%)
9–10	105 (91%)	107 (94%)

Data are n (%) or median (IQR). *Individuals could meet the inclusion criteria of haemoglobin <110 g/L at screening but have higher values by the time of randomisation. One participant had haemoglobin >110 g/L at screening and was enrolled; this was documented as a protocol deviation. †Individuals could meet the inclusion criteria of ferritin <50 µg/L at screening but have higher values by the time of randomisation. Three participants had ferritin >50 µg/L at screening, and one had missing screening ferritin, and were enrolled; these were protocol deviations. Result missing for one woman in the intravenous iron group. ‡Missing for five participants in the oral iron group and seven participants in the intravenous iron group. §Missing for six participants in the oral iron group and eight participants in the intravenous iron group. ¶Missing for five participants in the oral iron group and eight participants in the intravenous iron group. ‖Missing for one participant in the intravenous iron group (could not remember date of last menstrual period). **All occurred before randomisation and treatment start.

Table 1: **Baseline characteristics**

calculations (that is, bodyweight equal to 70 kg or haemoglobin concentration of 100 g/L) mistakenly allocated to the wrong dosage. We therefore also defined adequate dosage, permitting such participants to be allocated to doses defined by the adjacent bodyweight or haemoglobin values, and considering those who received at least their protocol-defined dose as adherent. For the oral iron group, adherence was assessed by pill count at every visit.

SF-36 results were reported as 0–100 scores for the eight health domains.[19,20] Analyses were done using Stata (version 15). A data safety monitoring board reviewed the trial progress and data at a meeting in September, 2016, and with a further short report in November, 2016. The trial is registered at ClinicalTrials.gov, NCT02541708.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 8, 2015, and March 14, 2017, 533 women were screened, of whom 214 (40%) were ineligible and 89 (17%) were eligible but not enrolled, therefore leaving 230 participants enrolled into the trial (114 randomly assigned to the intravenous iron group, 116 to the oral iron group; figure 1). The median age was 26 years (IQR 22–30; table 1). The median baseline haemoglobin concentration was 94 g/L (IQR 85–104); 10 (4%) participants had a haemoglobin concentration of less than 70 g/L, 142 (62%) had a haemoglobin concentration of 70–100 g/L, and 78 (34%) had a haemoglobin

	Oral iron (N=116)	Intravenous iron (N=114)
Time from screening to treatment start, days*†	6 (2–11)	5 (2–14)
Time from randomisation to treatment start, days*	0 (0–0)	0 (0–0)
Time from childbirth to treatment start, days*‡	1 (0–2)	1 (0–2)
Oral iron		
Prescribed oral iron at baseline	116/116 (100%)	..
At least one follow-up visit with pill count	101/116 (87%)	..
Adherence by pill count (proportion of scheduled doses taken), up to primary outcome measurement at 6 weeks§		
<20%	5/101 (5%)	..
20% to <50%	5/101 (5%)	..
50% to <70%	1/101 (1%)	..
70% to <90%	10/101 (10%)	..
≥90%	80/101 (79%)	..
Adherence by pill count (proportion of scheduled doses taken), over all follow-up§¶		
<20%	4/101 (4%)	..
20% to <50%	22/101 (22%)	..
50% to <70%	11/101 (11%)	..
70% to <90%	17/101 (17%)	..
≥90%	47/101 (47%)	..
Intravenous iron		
Received at least one infusion	..	112/114 (98%)
Received infusions as per protocol	..	84/114 (74%)
Did not receive infusions as per protocol	..	30/114 (26%)
Did not receive any infusions	..	2/30 (7%)
Did not receive second dose of 500 mg	..	16/30 (53%)
Did not receive second dose of 1000 mg	..	2/30 (7%)
Received second infusion of 500 mg instead of 1000 mg	..	3/30 (10%)
Received second infusion of 1000 mg instead of 500 mg	..	1/30 (3%)
Received second infusion of 500 mg (incorrectly)	..	6/30 (20%)
Reasons for not receiving infusions as per protocol		
Screening haemoglobin value used to determine dosage	..	12/30 (40%)
Consent withdrawal	..	7/30 (23%)
Lost to follow-up	..	4/30 (13%)
Borderline bodyweight of 70 kg assigned to wrong dose	..	2/30 (7%)
Borderline haemoglobin of 100 g/L assigned to wrong dose	..	2/30 (7%)
Protocol deviation	..	2/30 (7%)
Reaction	..	1/30 (3%)
Received adequate dosage, accepting borderline cases and those who received at least protocol-defined dose	..	93/114 (82%)

Data are median (IQR) or n/N (%). *Missing for two participants in the intravenous iron group who did not receive any infusions. †20 in the oral iron group and 27 in the intravenous iron group had more than 14 days between screening and treatment start; these were protocol deviations. ‡One in the intravenous iron group was randomly assigned 10 days after childbirth; this was reported as a protocol deviation. §Proportions are of those with at least one follow-up visit with pill count. ¶To 3 months after normalised haemoglobin or to last measured haemoglobin concentration if never normalised.

Table 2: **Adherence to intravenous and oral iron**

concentration of more than 100 g/L. The median baseline ferritin concentration was 21 µg/L (IQR 12–40). Baseline characteristics were broadly similar in both groups, with some differences in marital status, haemoglobin, ferritin, alanine aminotransferase, aspartate aminotransferase, C-reactive protein, and symptoms.

158 (69%) women completed follow-up at 12 months, with differences by group (90 [79%] of 114 in the intravenous iron group *vs* 68 [57%] of 116 in the oral iron group; figure 1). The timings of visits were broadly similar in each group (appendix p 16). Attendance at the 6 week visit was similar in the two groups, with 186 participants (81%) included in the primary outcome analysis (94 [82%] in the intravenous iron group and 92 [79%] in the oral iron group). Baseline characteristics were similar between participants for whom primary outcome data were available versus those for whom they were not available, except that a smaller proportion of women with primary outcome data were living with a partner, compared to those without primary outcome data (appendix p 2). Among the participants with primary outcome data, the distributions of baseline characteristics by group were broadly similar to those of all randomly assigned participants (appendix p 3). The median time from screening to treatment start, from randomisation to treatment start, and from childbirth to treatment start are shown in table 2.

At 6 weeks, 75 (80%) of 94 participants in the intravenous iron group and 47 (51%) of 92 in the oral iron group had normalised haemoglobin concentrations, yielding an adjusted odds ratio of 4·65 (95% CI 2·33–9·27; p<0·0001) and an adjusted prevalence difference of 31% (95% CI 19–44). Results were robust to sensitivity analyses (appendix pp 4–5). Haemoglobin concentrations increased more rapidly and remained higher throughout the duration of the trial in the intravenous iron group versus the oral iron group (figure 2A). The mean highest haemoglobin concentration was 125 g/L (SE 1) in the intravenous iron group and 118 g/L (1) in the oral iron group, with similar mean times to highest value (19 weeks [SE 2]) in both groups. These results were reflected in a higher proportion of participants with normalised haemoglobin in the intravenous versus oral iron groups throughout the trial (figure 3A; appendix p 4). There was a numerically greater benefit of intravenous versus oral iron among participants with lower baseline haemoglobin concentrations (≤100 g/L *vs* >100 g/L) but the p value was large (p=0·21; appendix pp 6, 17).

Ferritin concentrations increased substantially among participants in the intravenous iron group to a mean of 358 µg/L (SE 13) at 6 weeks, compared with a mean of 48 µg/L (4) in the oral iron group, and there remained large differences in ferritin concentrations between the groups at 52 weeks (figure 2B). The mean highest ferritin concentration was 322 µg/L (SE 15) in the intravenous iron group and 66 µg/L (7) in the oral iron group, with slightly faster mean time to highest value in the intravenous iron group (8 weeks [SE 1] *vs* 10 weeks [1] in the oral iron group). At 6 weeks, 85 (94%) of 90 participants in the intravenous iron group and ten (11%) of 89 in the oral iron group had a normalised ferritin concentration of more than 100 µg/L (p<0·0001; figure 3B) and interpretations were robust to a threshold of 30 µg/L (appendix p 4).

Almost all participants in the intravenous iron group received at least one dose, and the majority received it as per protocol, with the most common deviation being the screening haemoglobin value being incorrectly used to define the dose (table 2). Using the more lenient definition of adherence (accepting as adherent participants with borderline bodyweight of 70 kg, haemoglobin concentration of 100 g/L, or both who were mistakenly allocated to the wrong dose, and those who received at least their protocol-defined dose), 93 (82%) participants received an adequate dose. Among the 68 participants who received a second dose, the median time between doses was 7 days (IQR 7–7, range 6–21). Among the 101 (87%) participants in the oral iron group who had at least one pill count, 80 (79%) had at least 90% adherence as determined by pill count up to 6 weeks. Over all follow-up (to 3 months after normalisation of haemoglobin or to last measured haemoglobin concentration if never normalised), adherence was poorer, with 47 (47%) women having at least 90% adherence to oral iron.

There were 188 adverse events reported in 55 (48%) participants in the intravenous iron group, and 146 adverse events reported in 43 (37%) participants in the oral iron group. All adverse events were grade 1 or grade 2, except for two grade 3 events (mediastinal infection and urinary fistula) in the oral iron group (appendix p 7). The urinary fistula required admission to hospital and consequently was a serious adverse event. All adverse events were considered to be unrelated to the study medication, except for two in the intravenous iron group, which were an infusion-related reaction (grade 1) and itching (grade 2). Neither of these adverse events required intervention but for the itching the second planned infusion of 500 mg was not given. No infusions were paused or stopped because of intolerance or allergy. A further three grade 3 adverse events in two participants were detected through laboratory safety parameters (one participant had raised aspartate aminotransferase and alanine aminotransferase at 26 weeks, and one participant had raised alanine aminotransferase at 52 weeks; both were in the intravenous iron group; appendix pp 10–14). No participants were reported to receive further treatment for anaemia other than those indicated by the randomisation, and no participants were reported to become pregnant during follow-up.

Two (2%) participants in each group had at least one serious adverse event (three serious adverse events in the intravenous iron group and two in the oral iron group): all were hospital admissions considered to be not related to the study drug, and were due to gastrointestinal disorders, pain in extremities, urinary fistula, and uterine haemorrhage (appendix p 15). Three stillbirths occurred before random assignment to a study group, which is within the expected rate for this setting.[23] Quality of health scores on the SF-36 improved following childbirth in both groups, and remained close to 100% for most of the health domains (appendix p 18).

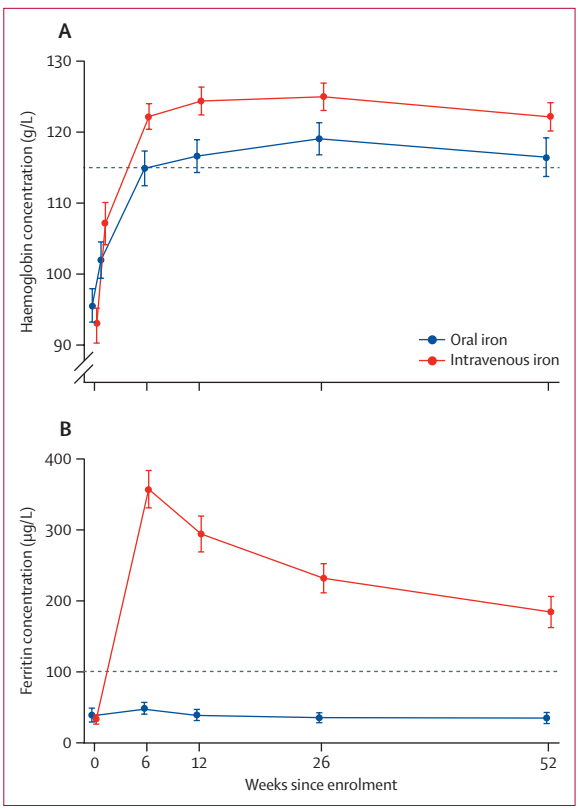

Figure 2: **Average haemoglobin concentration and ferritin concentration over time**
(A) Mean haemoglobin concentration. (B) Mean ferritin concentration. Error bars are the 95% CIs. Horizontal grey lines indicate normalisation values of 115 g/L for haemoglobin and 100 µg/L for ferritin.

Discussion

In this trial, intravenous iron substitution with ferric carboxymaltose was associated with significantly faster and more durable normalisation of haemoglobin and ferritin concentrations, compared with oral iron substitution. Overall, 80% of participants in the intravenous iron group with primary outcome data had normalised haemoglobin concentrations after 6 weeks, compared with only 51% of participants in the oral iron group. On average, ferritin concentrations remained below normal among those in the oral iron group, whereas 80% of participants in the intravenous iron group had a normalised ferritin concentration after 1 year, suggesting a restoration of iron stores. This might be an important gain in health for mother and child, particularly in subsequent pregnancies because many women might not receive medical care between births. In prespecified analyses, there was a numerically greater benefit of intravenous iron in terms of haemoglobin normalisation among participants with a lower baseline haemoglobin concentration at treatment initiation (<100 g/L *vs* ≥100 g/L), suggesting this population might be an important target group with greater benefit, but the p value was large.

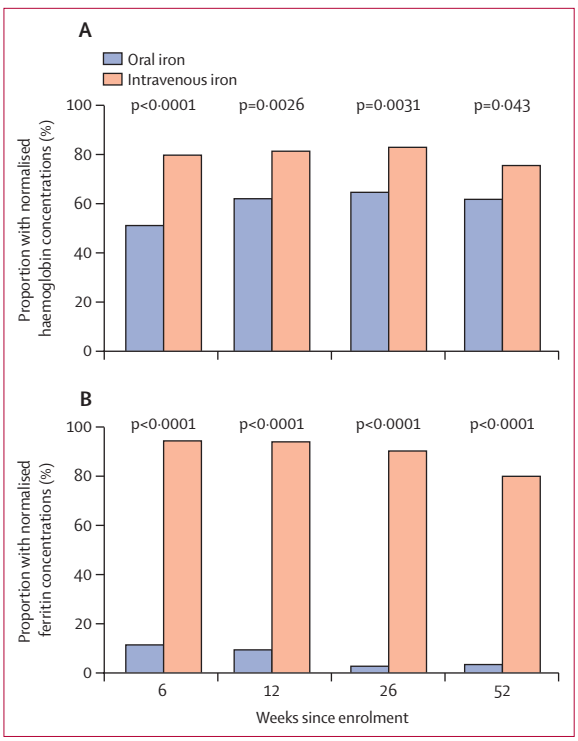

Figure 3: **Proportion of participants with a normalised haemoglobin concentration and proportion with a normalised ferritin concentration over time**

(A) Proportion of participants with a normalised haemoglobin concentration of more than 115 g/L. (B) Proportion of participants with a normalised ferritin concentration of more than 100 µg/L. Proportions are of those with a result available. For haemoglobin in the oral iron group, results were available for 92 (79% of randomly assigned participants) at week 6, 79 (68%) at week 12, 82 (71%) at week 26, and 68 (59%) at week 52; for haemoglobin in the intravenous iron group results were available for 94 (82%) at week 6, 86 (75%) at week 12, 94 (82%) at week 26, and 90 (79%) at week 52; for ferritin in the oral iron group results were available for 89 (77%) at week 6, 76 (66%) at week 12, 79 (68%) at week 26, and 62 (53%) at week 52; and for ferritin in the intravenous iron group results were available for 90 (79%) at week 6, 84 (74%) at week 12, 93 (82%) at week 26, and 85 (75%) at week 52. p values are for randomised group, from logistic regression for each outcome for the given week on randomised group, site, and baseline haemoglobin concentration.

Intravenous iron substitution with ferric carboxymaltose is routinely done in high-income settings. Our study shows that intravenous iron substitution with ferric carboxymaltose can be delivered safely in district hospitals in a resource-limited setting. Ferric carboxymaltose can be stored at room temperature (<30°C) and has a shelf life of 3 years from manufacture. With ferric carboxymaltose, the total required dose can be delivered in just one or two doses, and without a test dose as is needed for iron sucrose. Hospital attendance for delivery is used to provide medical prevention strategies such as vaccinations, and provides an ideal opportunity to also deliver a straightforward and effective iron supplementation strategy before discharge, after which individuals might become lost to medical care.

Increased infection rates, especially of malaria, after correction of iron deficiency might theoretically be of concern, particularly given previous studies of population-based iron supplementation for children in malaria-endemic settings.[24] However, we did not observe any grade 3 or grade 4 adverse events in the intravenous iron group. The safety concerns for anaphylactic reactions frequently observed with the application of iron dextran are not observed with iron carboxymaltose, neither in high-income settings,[12,14,15] nor in our study in a resource-limited setting. However, although iron dextran is registered for use in many low-income countries, including Tanzania, ferric carboxymaltose is not yet.

The high quality-of-health scores observed from 3 months following childbirth were somewhat higher than a previous study in an urban general population in Tanzania.[25] Despite the beneficial effects of intravenous iron on haemoglobin and ferritin normalisation, we did not observe any differences in quality-of-life between the intravenous and oral iron groups. This might be due to a ceiling effect, with many of the quality of life scores close to 100%, a limitation that has been noted by others.[25,26]

Our study has some limitations. First, completion of follow-up at 12 months was poorer among participants in the oral iron group compared with the intravenous iron group. However, the primary outcome was assessed at 6 weeks, at which time attendance was good in both groups, and in line with what was allowed for in the sample size calculation. Furthermore, results were robust to sensitivity analyses accounting for differential follow-up. Second, because ferric carboxymaltose is not registered for use in Tanzania and there are no prices available for low-income countries, a direct cost effectiveness analysis was not possible in our study. This analysis would be necessary to inform broader health-care programme strategies. However, extensive registration and therefore uptake across low-income countries will lead to lower prices, and a new situation might arise after the expiration of Vifor Pharma's patent for the drug in 2023 in Europe and 2026 in the USA. Third, for ethical reasons, we could not include participants with severe iron deficiency anaemia who received blood transfusions. Intravenous iron supplementation corrects or substantially improves even severe anaemia within a few days and can be used as an alternative to blood products if the anaemia is not life threatening. Therefore, women with severe iron deficiency anaemia that is not life threatening could be a good target for intravenous iron substitution to spare the limited supply of blood products for patients who have no other treatment options. This is of high importance for low-income and middle-income countries where the gap between need and supply of blood products is large,[27] and the risks associated with transfusions are high.[28] Fourth, we did not directly analyse acceptability in detail, but only a small proportion of eligible individuals explicitly refused consent. Furthermore, almost all participants in the intravenous iron group received at least one dose, and the vast majority received an adequate dose. Thus, our study

shows the feasibility and acceptability of intravenous iron in this population. By contrast, long-term adherence to oral iron was poor, reflected in the non-repletion of iron stores, thus limiting the potential of oral iron for correction of iron deficiency anaemia. Last, intravenous administration of iron preparations can cause hypophosphataemia, which is mainly transient and clinically irrelevant. According to published studies, there are only isolated cases of hypophosphataemia requiring treatment, mainly in patients with existing risk factors and after prolonged exposure to high-dose intravenous iron.[29] Measuring of serum phosphate was not included in the protocol of the study, which precluded collection of additional information on this topic.

In conclusion, individuals with iron deficiency anaemia at delivery had a better haemoglobin response and more complete repletion of iron stores over time with ferric carboxymaltose intravenous iron than with oral iron substitution. This study adds important data on the benefits of ferric carboxymaltose and provides evidence for its benefits in a low-income setting, thus paving the way for approval of this drug in such settings. Our data can now be discussed and shared with international funding organisations, ministries of health, and local health-care providers to inform how to best transfer this treatment to sub-Saharan countries and which financial mechanisms might be best suited to support it. Broad use in a peripartum setting might help reduce iron deficiency anaemia where there is the greatest burden. This study was done following childbirth in individuals with iron deficiency anaemia in Tanzania and our results are in line with those observed in similar populations in high-income settings. Therefore, one can anticipate similar benefits in other patient populations with iron deficient states in resource-limited settings as already observed in high-income countries, such as individuals with chronic kidney diseases, inflammation, or heart insufficiency. Studies in these patient populations in low-income countries are needed, especially because such populations are increasing. Further studies are needed to confirm the safety and cost-effectiveness of ferric carboxymaltose in other low-income settings with different socioeconomic and health-care contexts, and to assess the potentially long-term benefits of a highly effective iron substitution on mother and child health.

Contributors

MT and SM-M conceived and designed the study, and oversaw its implementation, analysis, and write-up. FV and TRG planned the statistical analyses. FV generated the random allocation and did the statistical analyses. OL led the field implementation of the study and was responsible for data entry. KDM, PA, and AI contributed to the field implementation of the study and did data entry. BS supervised storage and distribution of medication and supervised pill counting. SM and CD did the laboratory analyses. AK and SS implemented the quality assurance plan. FV, AK, and SS led the data management. SA, CD, MT, and SM-M provided trial oversight. FV, AK, and SM-M wrote the first draft of the manuscript. Data were accessible to FV, AK, and SM-M after data freezing on Aug 29, 2018; FV, AK, and SM-M checked the data. All authors read and approved the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

A subset of the key pseudo-anonymised individual participant data collected during the study, along with a data dictionary, is available upon request through the data repository Zenodo.

To **request access to the pseudo-anonymised individual patient data** see http://doi.org/10.5281/zenodo.3834141

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