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ORIGINAL RESEARCH ARTICLE

IRON NOF trial: IV iron for anaemic patients with femoral fracture

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Abstract

Background: Preoperative anaemia is associated with increased use of blood transfusions, a greater risk of postoperative complications, and patient morbidity. The IRON NOF trial aimed to investigate whether the administration of i.v. iron in anaemic patients during hip fracture surgery reduced the need for blood transfusion and improved patient outcomes.
Methods: This phase III double-blind, randomised, placebo-controlled trial included patients >60 yr old with preoperative anaemia undergoing surgery for femoral neck or subtrochanteric fracture across seven Australian Hospitals. Patients were randomly allocated on a 1:1 basis to receive either i.v. iron carboxymaltose 1000 mg or placebo (saline) at operation. The primary endpoint was blood transfusion use, with secondary endpoints of haemoglobin concentration at 6 weeks, length of hospital stay, rehabilitation duration to discharge, and 6-month mortality. Subgroup analysis compared outcomes in patients <80 yr old and patients >80 yr old. All analyses were performed by intention-to-treat. This trial was terminated early because of jurisdictional changes of more restrictive transfusion practices and changes in consent requirements.
Results: Participants (n=143) were recruited between February 2013 and May 2017. There was no difference observed in the incidence of blood transfusion between the treatment group (18/70) (26%) compared with the placebo group (27/73) (37%) (odds ratio for transfusion if receiving placebo: 1.70; 95% confidence interval [CI] 0.83–3.47; P=0.15) and there was no overall difference in the median number of blood units transfused between groups (odds ratio 1.52; 95% CI 0.77–3.00; P=0.22). Patients receiving i.v. iron had a higher haemoglobin 6 weeks after intervention compared with the placebo group (Hb 116 g L^{-1} *vs* 108 g L^{-1}; P=0.01). No difference was observed in length of hospital stay, rehabilitation duration to discharge, or 6-month mortality. However, in younger patients without major bleeding, the use of placebo compared with i.v. iron was associated with an increased number of units of blood transfused (placebo transfusion incidence rate ratio 3.88; 95% CI 1.16–13.0; P=0.03).
Conclusions: In anaemic patients undergoing surgery for hip fracture, i.v. iron did not reduce the overall proportion of patients receiving blood transfusion. The use of i.v. iron may reduce the amount of blood transfused in younger patients. The use of i.v. iron is associated with increased haemoglobin concentrations 6 weeks after the operation.
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Hip fractures are the leading cause of injury-related mortality and disability in older individuals, affecting 1 in 500 Australians over the age of 45[1] and >1.5 million people worldwide per year.[2] The risk of hip fracture increases with age and is associated with osteoarthritis, disability, and malnutrition.[3] Hip fracture patients often present with multiple pre-existing comorbidities[4,5] that further increase their risk of postoperative complications. One common associated risk factor is anaemia,[6] which is associated with worse perioperative outcomes,[7–18] whereas postoperative anaemia is associated with impaired rehabilitation.[19]

Hip fracture patients are often anaemic on presentation, commonly sustain blood loss from their injury and subsequent surgical intervention, resulting in the frequent administration of blood transfusions.[20] Normal clinical practice is for patients to undergo urgent surgical reduction and fixation to reduce pain, facilitate early mobilisation, and shorten hospital stay.[21] Although anaemia is common, the liberal use of blood transfusions to increase haemoglobin concentration has not been shown to improve patient outcomes.[22,23]

The most common underlying cause of anaemia is iron deficiency.[24] In hip fracture patients, iron deficiency can occur preoperatively because of poor nutrition or from inflammation associated with chronic disease, which disrupts normal pathways of both iron transport and metabolism.[25–28] This is compounded by the trauma of the hip fracture, which causes blood loss and inflammation. Cytokines, notably interleukin-6 (IL-6), upregulate the release of hepcidin, which inhibits dietary iron absorption and blocks cellular iron export into plasma, with retention of iron within macrophages. Reduced circulating concentrations of iron contribute to a state of functional iron deficiency and anaemia. As a result of this inflammatory iron metabolism blockade, treatment of anaemia in surgical patients with oral iron is considered ineffective.[25,29–32]

In contrast, the use of i.v. iron can rapidly correct iron stores and increase haemoglobin concentration by bypassing the hepcidin-compromised gastrointestinal absorption pathway.[33] The efficacy of i.v. iron has been demonstrated in both surgical patients[34,35] and those in critical care.[36,37] The use of i.v. iron to correct anaemia in patients presenting for hip fracture surgery is plausible and would ideally attenuate the associated risks to the patient. The correction of iron deficiency in these patients could reduce the need for blood transfusions, and improve postoperative recovery and quality of life.[38]

The IRON NOF study was a double-blind, placebo-controlled, randomised trial designed to assess the clinical effects of i.v. iron therapy on blood transfusion rates, postoperative haemoglobin concentration, and patient recovery in hip fracture patients with preoperative anaemia. We hypothesised that patients treated with i.v. iron would show better outcomes compared with placebo-treated patients in terms of reduced blood transfusion.

Methods

Study design

The IRON NOF trial was a phase III double-blind 1:1 randomised, controlled trial undertaken at seven Australian hospitals—three of which were in Western Australia (Fiona Stanley Hospital, Fremantle Hospital, and Royal Perth Hospital), three in Queensland (Nambour General Hospital, The Prince Charles Hospital, and Princess Alexandra Hospital), and one in Victoria (The Alfred Hospital). Ethics approval was from the Western Australia, South Metropolitan Health Services Human Research Ethics Committee (HREC approval number 12/202). The trial was registered on ANZCTR on the 19 April 2012 (ACTRN12612000448842).

Participants

Patients >60 yr old presenting with neck of femur (NOF) or subtrochanteric fracture were reviewed at daily morning multidisciplinary team meetings. Patients with anaemia were included (haemoglobin <120 g L^{-1} in females or <130 g L^{-1} in males) if they had not already received a blood transfusion during the current hospital episode. Patients provided written informed consent, or written consent from next of kin where patients were unable to consent, most commonly because of delirium or dementia. Exclusions included: weight <40 kg; previous adverse reaction to i.v. iron; those with known haemochromatosis or a serum ferritin concentration >800 μg L^{-1}; and those with renal failure, defined as a creatinine clearance <30 ml min^{-1} 1.73 m^{-2} (eGFR), or on dialysis.

Important changes to the protocol

The study commenced in 2013 with participants included if they had iron deficiency anaemia, defined as a serum ferritin <30 μg L^{-1} with normal C-reactive protein or ferritin <100 μg L^{-1} with an elevated C-reactive protein. However, many patients did not meet these initial inclusion criteria as their injury produced acute trauma-induced inflammation, which consequently elevated ferritin ≥100 μg L^{-1}. As a result, the trial steering committee broadened the inclusion criteria to include any patient presenting with anaemia as defined by WHO (haemoglobin <120 g L^{-1} in females or <130 g L^{-1} in males) (HREC 30 March 2014).

In 2017, the Project Management Group reviewed patient recruitment to the trial, which was found to have slowed because of implementation of the state-wide patient blood management programme and observed reductions in blood transfusion outside of the trial.[25,39] The use of i.v. iron had become common in clinical practice, (e.g. Fiona Stanley Hospital adopted routine use of i.v. iron and tranexamic acid as part of the NOF pathway), and the trial steering committee stopped the trial before achieving target recruitment numbers of participants. The last patient was enrolled in May 2017 and final data were collected in January 2018.

Procedures

The infusion preparations were delivered in a single session, i.v., over 15 min. The intervention group received a dose of iron carboxymaltose up to 1000 mg, based on patient body weight and haemoglobin concentration,[40] in 50 ml of normal saline, while the placebo group received only 50 ml of normal saline. The study drug was given following surgical fixation at commencement of skin closure. Participants were monitored for adverse events or signs of hypersensitivity during the infusion for at least 30 min after treatment or, if longer, until the end of the anaesthetic period. There were no other changes to the patient's normal surgical or rehabilitation pathway. Clinical assessments and patient-reported outcomes were recorded by blinded research team members.

Standard patient perioperative management was in accordance with the Australian and New Zealand Hip Fracture

Registry (ANZHFR) guidelines.[41] This includes multidisciplinary orthogeriatric team review with the objective to minimise time to surgery (standard within 48 h); suitable pain relief such as use of femoral nerve blockade; and minimisation of functional decline. At operation, the anaesthetic technique was as per local hospital practice, including the use of perioperative tranexamic acid and regional blockade in addition to general or spinal anaesthesia. Surgical fixation was either dynamic hip screw, hemiarthroplasty or total hip replacement. Blood transfusion practice was guided by local practice and the Australian National Blood Authority perioperative guidelines[42] with a non-mandatory transfusion trigger haemoglobin concentration of 80 g L^{-1}.

Outcome measures

The primary endpoint was the number of patients who received a blood transfusion from randomisation to 30 days after the day of operation. Blood transfusion was defined as administration of all or part of a unit of packed red blood cells, and a large blood transfusion was defined as more than four units transfused in one 24-h period. Secondary endpoints were the number of units of blood transfused, postoperative complications and infections, length of hospital and rehabilitation stay, home to home return after hip fracture and haemoglobin concentrations preoperatively, nadir (lowest recorded) and at 6 weeks after operation. Mortality follow-up at 6 months was gathered from hospital databases, the Western Australian Cemetery Board database, and from similar state-based resources. A predefined sub-study was performed at one site (Fiona Stanley Hospital) to assess functional recovery as measured by a modified Katz Activities of Daily Living score preoperatively and at 6-week follow-up.

Power calculation

From historical data, of 451 patients who underwent surgery for fractured NOF at one centre (Fremantle Hospital), 156 patients required blood transfusion, with a total of 340 units of blood administered. For a clinically significant (35%) reduction in blood transfusion following intervention by i.v. iron, we calculated that 230 patients would provide 85% power at an alpha error of 5% to detect an absolute reduction of 13% for the primary endpoint of blood transfusion by 30 days after surgery, allowing for 10% loss to follow-up.

Randomisation and masking

Randomisation was conducted in a 1:1 ratio, facilitated by an online web-based server (random.org) with block stratified computer-generated groups of 20. After informed consent, randomisation took place by an unblinded intervention team before commencement of the surgery. Allocation concealment was by sequentially numbered opaque envelopes. As i.v. iron is a dark brown solution that is easily distinguishable from the saline placebo, dedicated unblinded study personnel were responsible for the preparation of the drug, with administration masked using an opaque syringe (BD Plastipak 800369) via opaque tubing (BD Alaris MFX1641) in theatre. These unblinded personnel had no further involvement in the trial. The

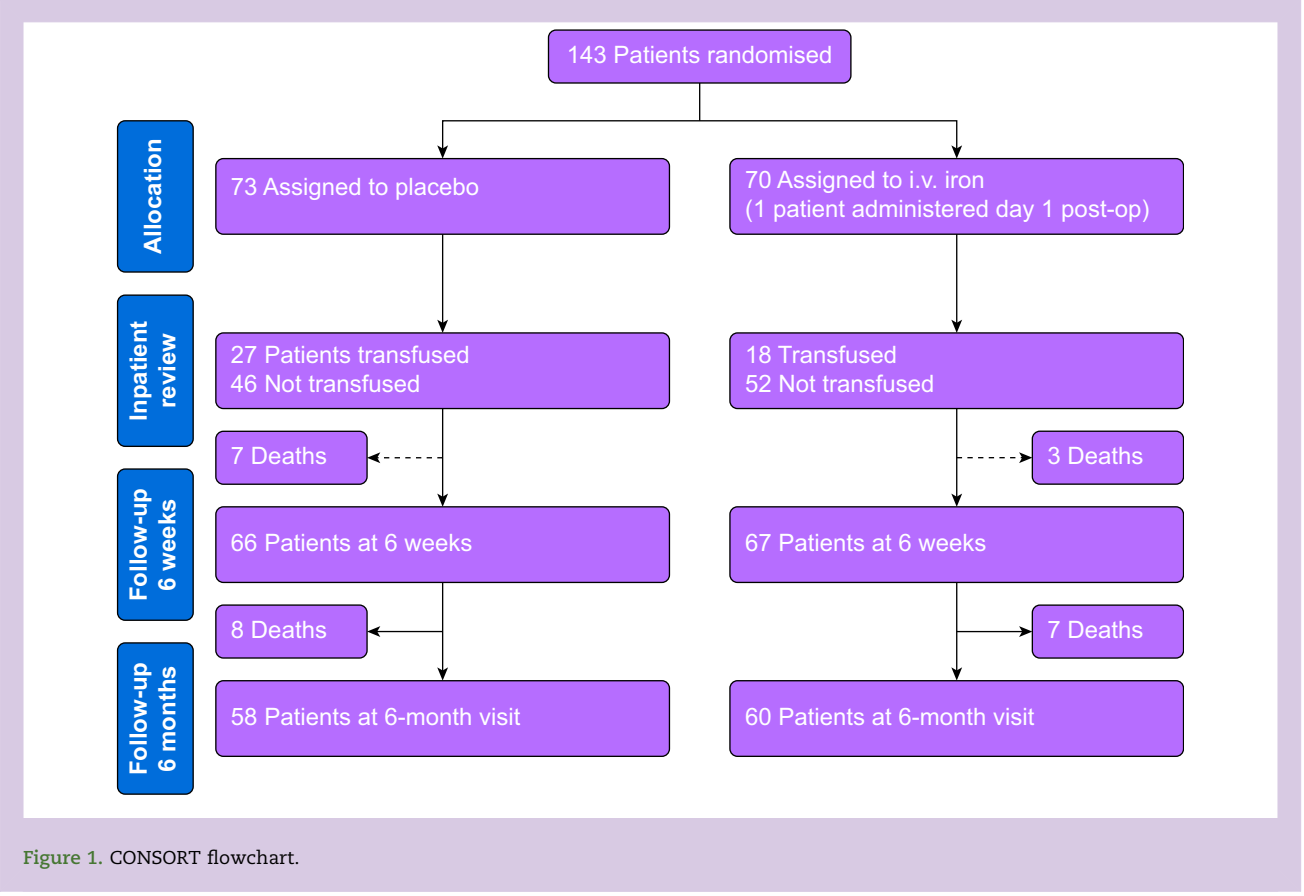

Figure 1. CONSORT flowchart.

Table 1 Baseline characteristics and surgical characteristics by intervention group. The data from the intervention groups (i.v. iron or placebo) are reported as median (inter-quartile range) or number of observations (%).

	I.V. iron (n=70)	Placebo (n=73)	Total (n=143)
Characteristics			
Age (yr)	86 (12)	85 (10)	85 (11)
≤80	22 (31)	23 (32)	45 (31)
>80	48 (69)	50 (68)	98 (69)
Male	23 (33)	24 (33)	47 (33)
Female	47 (67)	49 (67)	96 (67)
Stay at home	45 (64)	46 (63)	91 (64)
Stay at hostel or nursing home	25 (36)	27 (37)	52 (36)
Medical history			
Body mass index (kg m^{-2})	22 (7.2)	22.5 (6.7)	22.1 (6.4)
<30	51 (73)	49 (67)	100 (70)
≥30	19 (27)	24 (33)	43 (30)
Ischaemic heart disease	29 (41)	37 (51)	66 (46)
Congestive cardiac failure	3 (4)	7 (10)	10 (7)
Lung disease	14 (20)	16 (22)	30 (21)
Anaemia requiring transfusion within past 12 months	2 (3)	1 (1)	3 (2)
Cancer treatment	10 (14)	7 (10)	17 (12)
Preoperative blood results			
Haemoglobin (g L^{-1})	111.5 (16)	109 (18.5)	110 (16)
<100	13 (19)	21 (29)	34 (24)
≥100	57 (81)	51 (71)	108 (76)
Ferritin (μg L^{-1})	108 (230)	117 (288)	113 (243)
<100	29 (41)	29 (40)	58 (41)
≥100	41 (59)	44 (60)	85 (59)
Transferrin saturation (%)	13 (6)	11 (9)	12 (8)
<20	58 (87)	58 (87)	116 (87)
≥20	9 (13)	9 (13)	18 (13)
Creatinine (μmol L^{-1})	72 (31)	75.5 (35.5)	73 (34)
C-reactive protein (mg L^{-1})	16 (64.4)	37 (69)	31 (68.8)
Nadir haemoglobin (g L^{-1})	90 (22)	83 (14)	86 (19)
Planned type of surgery			
Internal fixation	48 (69)	41 (56)	89 (62)
Hemiarthroplasty	17 (24)	21 (29)	38 (27)
Total hip	5 (7)	11 (15)	16 (11)
KATZ score	6 (4)	7 (4)	7 (4)

remaining clinical and research staff involved in outcome assessment were blinded throughout the duration of the trial, from index hospital admission until 6 months after the index surgery.

Statistical analyses

Analyses were performed according to the intention-to-treat principle whereby the randomly assigned patients with data available were included in the analysis. For both intervention groups, the baseline characteristics and surgical characteristics were reported as median and inter-quartile range (IQR) or number of observations (%).

The primary endpoint, blood transfusion incidence, was reported for each intervention group as the number of transfusion events and percentage of each group receiving transfusion. Adjusted odds ratio and 95% confidence interval (CI) were calculated using binomial regression, adjusting for preoperative haemoglobin concentration (g L^{-1}), age (yr), and surgical procedure. The median (IQR) length of acute stay and rehabilitation stay were reported by the intervention groups for all patients. Number and percentage of additional secondary endpoints (postoperative infection by 6 weeks, home to return home by 6 weeks, haemoglobin concentration at 6 weeks, and mortality at 6 weeks and 6 months) were reported by the intervention groups. Adjusted odds ratio and 95% CI were calculated by logistic regression after adjusting for preoperative haemoglobin concentration (g L^{-1}), age (yr) and surgical procedure. All statistical analyses were performed using Stata 14.2 (StataCorp, College Station, TX, USA).

The secondary endpoint of average number of units of blood transfused was analysed using negative binomial regression models. Number and percentage of transfusion units, mean and standard error of units transfused were reported by intervention groups. Adjusted incidence rate ratio and 95% CI were reported after adjusting for preoperative haemoglobin concentration (g L^{-1}), age (yr), and surgical procedure.

Subgroup analyses for blood transfusion and the number of units transfused were carried out based on age (≤80 *vs* >80 yr old), preoperative haemoglobin concentration (<100 *vs* ≥ 100 g L^{-1}), sex (male *vs* female), body mass index (<30 *vs* ≥ 30 kg m^{-2}), preoperative ferritin (<100 *vs* ≥100 μg L^{-1}), and preoperative transferrin saturation (<20 *vs* ≥20 %). The effect of excluding those patients with significant blood loss ('major bleeding' four or more units of blood transfused in a 24-h period) was also explored.

Results

Participant characteristics

A total of 143 patients were enrolled at seven sites over a 4-yr period from February 2013 to May 2017, of whom 70 were randomly allocated to receive i.v. iron and 73 to receive placebo (Fig 1). All patients received their intended randomised treatment at operation, except for one patient who received their treatment immediately postoperatively for logistical reasons. At 6 months, 10 patients from the i.v. iron group and 15 from the placebo group were deceased.

The patients were well matched regarding baseline characteristics (Table 1). Most patients were female (67%), >80 yr old (69%), and more than a third were admitted from a hostel or nursing home (36%). The median body mass index was 22.1 kg m^{-2} (25th–75th percentile: 19.6–26.0) and 70% of the patients had body mass index <30 kg m^{-2}. Approximately half of the patients (46%) had a history of cardiac disease and about one-fifth had lung disease. Pre-admission KATZ scores were similar between the groups (sub-study *n*=82). Preoperative ferritin, transferrin saturation, creatinine, and C-reactive protein levels were comparable between the intervention groups. The median preoperative haemoglobin concentration was similar between the treatment groups and 24% of the patients had preoperative haemoglobin concentration <100 g L^{-1}. There was no difference in the type of operative fixation for the hip fracture with internal fixation being the most common procedure; i.v. iron group 69% and placebo group 56% (Table 1).

Effect of i.v. iron on blood transfusion

Across all 143 patients in the cohort, 45 (31%) received blood transfusions from randomisation to 30 days. There was no difference between intervention groups (treatment group 18/70; placebo group 27/73; odds ratio (for transfusion if receiving placebo): 1.70; 95% CI 0.83–3.47; *P*=0.15; Table 2) and after adjustment for preoperative haemoglobin concentration, age, and surgical procedure (adjusted odds ratio 2.07; 95% CI 0.95–4.48; *P*=0.07; Table 2). Among the 45 transfused patients, the median preoperative haemoglobin concentration was 101 g L^{-1} (min–max: 67–125) (i.v. iron group: 102.5 g L^{-1}, min–max: 83–119; placebo group: 99 g L^{-1}, min–max: 67–125). The observed transfusion trigger (nadir haemoglobin) in those transfused was in line with guidelines with a median of 75 g L^{-1} (min–max: 51–106) (i.v. iron group: 74 g L^{-1}, min–max: 58–106; placebo group: 75 g L^{-1}, min–max: 51–85).

In total, 39 units of packed red cells were administered to the i.v. iron group and 62 units were administered to the placebo group (incidence rate ratio [placebo *vs* iron]1.52; 95% CI 0.77–3.00; *P*=0.22; Table 3). A large blood transfusion (four or more units transfused within 24 h) occurred in four patients in the i.v. iron group (three patients received four units and one patient received five units) and in three patients in the placebo group (respectively receiving five, seven, and nine units). Exclusion of these cases had no meaningful impact on the transfusion incidence between the groups (incidence rate ratio

Table 2 Primary endpoint (blood transfusion) from randomisation to 30 days after operation. The data are reported per intervention group (iron or placebo) as odds ratio, 95% confidence interval, interaction *P*-value (*n*=143), with subgroup analyses. CI, confidence interval. * Adjusted for age, pre-operative haemoglobin and planned surgery. † Missing data from one patient from the placebo group.

	I.V Iron (*n*=70)	Placebo (*n*=73)	Placebo *vs* iron: odds ratio (95% CI), *P*-value	Interaction *P*-value	Placebo *vs* iron: adjusted odds ratio (95% CI)*, *P*-value	Interaction* *P*-value
Had blood transfusion, *n* (%)	18/70 (26)	27/73 (37)	1.70 (0.83–3.47), P=0.15	N/A	2.07 (0.95–4.48), P=0.07	N/A
Subgroup analyses, *n* (%)						
Age (yr)						
≤80	4/22 (18)	10/23 (43)	3.46 (0.89–13.51), P=0.07		3.75 (0.69–20.3), P=0.13	
>80	14/48 (29)	17/50 (34)	1.25 (0.53–2.94), P=0.61	0.22	2.17 (0.80–5.91), P=0.13	0.45
Preoperative haemoglobin concentration (g L^{-1})						
<100	7/13 (54)	14/21 (67)	1.71 (0.41–7.08), P=0.46		1.08 (0.22–5.25), P=0.93	
≥100	11/57 (19)	12/51 (24)	1.29 (0.51–3.23), P=0.59	0.74	2.15 (0.74–6.27), P=0.16	0.88
Sex						
Male	5/23 (22)	7/24 (29)	1.48 (0.39–5.58), P=0.56		1.56 (0.37–6.63), P=0.55	
Female	13/47 (28)	20/49 (41)	1.80 (0.77–4.25), P=0.18	0.81	1.76 (0.65–4.73), P=0.26	0.59
Body mass index (kg m^{-2})						
<30	12/51 (24)	16/49 (33)	1.58 (0.65–3.80), P=0.31		1.82 (0.63–5.21), P=0.27	
≥30	6/19 (32)	11/24 (46)	1.83 (0.52–6.44), P=0.35	0.85	1.98 (0.51–7.73), P=0.32	0.85
Preoperative ferritin concentration (μg L^{-1})						
<100	9/29 (31)	12/29 (41)	1.57 (0.53–4.62), P=0.41		0.91 (0.25–3.28), P=0.88	
≥100	9/41 (22)	15/44 (34)	1.84 (0.70–4.84), P=0.22	0.83	2.97 (0.98–9.03), P=0.06	0.69
Preoperative transferrin saturation (%)†						
<20	16/58 (28)	23/58 (40)	1.73 (0.79–3.76), P=0.17		1.67 (0.66–4.22), P=0.28	
≥20	2/9 (22)	3/9 (33)	1.75 (0.22–14.22), P=0.60	0.99	1.39 (0.11–17.09), P=0.80	0.81

Table 3 Secondary endpoint (number of units transfused) from randomisation to 30 days after operation. The data are reported per intervention group (iron or placebo) as odds ratio, 95% confidence interval, interaction P-value (n=143), with subgroup analyses. * CI, confidence interval; SE, standard error. *Adjusted for age, preoperative haemoglobin concentration and planned surgery. † Missing data from one patient from the placebo group.

	I.V. iron (n=70)	Placebo (n=73)	Placebo vs iron: incidence rate ratio (95% CI), P-value	Interaction P-value	Placebo vs iron: adjusted incidence rate ratio (95% CI), P-value	Interaction P-value
Number of units transfused, n (%)						
0	52/70 (74)	46/73 (63)	—	N/A	—	N/A
1	7/70 (10)	11/73 (15)	—	N/A	—	N/A
2	6/70 (9)	9/73 (12)	—	N/A	—	N/A
3	1/70 (1)	4/73 (5)	—	N/A	—	N/A
4	3/70 (4)	0	—	N/A	—	N/A
5	1/70 (1)	1/73 (1)	—	N/A	—	N/A
6	0	0	—	N/A	—	N/A
7	0	1/73 (1)	—	N/A	—	N/A
8	0	0	—	N/A	—	N/A
9	0	1/73 (1)	—	N/A	—	N/A
Mean number of units transfused (SE)	0.56 (0.14)	0.85 (0.19)	1.52 (0.77–3.00), P=0.22	N/A	1.69 (0.88–3.25), P=0.11	N/A
Subgroup analyses						
Age (yr)						
≤80	0.4 (0.2)	0.7 (0.2)	2.03 (0.67–6.19), P=0.21		2.26 (0.69–7.44), P=0.18	
>80	0.6 (0.2)	0.9 (0.3)	1.39 (0.60–3.23), P=0.44	0.62	1.72 (0.80–3.73), P=0.17	0.63
Preoperative haemoglobin concentration (g L^{-1})						
<100	1.0 (0.3)	1.7 (0.5)	1.67 (0.70–3.96), P=0.25		1.16 (0.49–2.70), P=0.74	
≥100	0.5 (0.1)	0.5 (0.2)	1.12 (0.41–3.06), P=0.83	0.59	2.17 (0.77–6.11), P=0.14	0.60
Sex						
Male	0.5 (0.2)	0.8 (0.4)	1.60 (0.38–6.64), P=0.52		1.79 (0.44–7.23), P=0.41	
Female	0.6 (0.2)	0.9 (0.2)	1.49 (0.70–3.19), P=0.30	0.93	1.13 (0.54–2.36), P=0.74	0.95
Body mass index (kg m^{-2})						
<30	0.5 (0.2)	0.9 (0.3)	1.80 (0.73–4.46), P=0.20		1.86 (0.82–4.24), P=0.14	
≥30	0.7 (0.3)	0.7 (0.2)	1.04 (0.40–2.65), P=0.94	0.46	1.23 (0.49–3.06), P=0.66	0.47
Preoperative ferritin concentration (μg L^{-1})						
<100	0.7 (0.2)	1.1 (0.3)	1.55 (0.58–4.12), P=0.38		0.71 (0.28–1.84), P=0.49	
≥100	0.5 (0.2)	0.7 (0.2)	1.52 (0.60–3.85), P=0.38	0.98	2.18 (0.88–5.38), P=0.09	0.58
Preoperative transferrin saturation (%)						
<20	0.6 (0.1)	0.9 (0.2)	1.67 (0.81–3.42), P=0.16		1.62 (0.84–3.13), P=0.15	
≥20	0.7 (0.5)	0.7 (0.4)	1.00 (0.13–7.77), P=0.99	0.62	0.76 (0.11–5.12), P=0.78	0.34

1.94; 95% CI 0.90–4.18; P=0.09), or after adjusting for preoperative haemoglobin concentration (g L^{-1}), age (yr), and surgical procedure (adjusted odds ratio 1.80; 95% CI 0.75–4.32; P=0.19). However, in younger patients without major bleeding, the use of placebo compared with i.v. iron was associated with more units of blood transfused (incidence rate ratio [of transfusion if receiving placebo] 3.88; 95% CI 1.16–13.0; P=0.03), even after adjusting for covariates (adjusted incidence rate ratio 3.71; 95% CI 1.02–14.3; P=0.05).

Additional secondary endpoints

From index procedure to follow-up at 6 weeks, similar clinical outcomes were reported in both intervention groups, including rates of postoperative infections (36% iron *vs* 44% placebo; Table 4) and home to return home (58% iron *vs* 69% placebo; Table 4). There were eight deaths (two in the i.v. iron group and six in the placebo group). Functional recovery, as measured by change in modified Katz activities of daily living (ADLs), was similar between the groups (60 patients).

More patients from the i.v. iron group had haemoglobin concentration ≥100 g L^{-1} at 6 weeks (86%) than patients from the placebo group (68%; Table 4). Patients in the i.v. iron group were also likely to have higher haemoglobin concentration at 6 weeks (increased haemoglobin iron *vs* placebo 9.11 g L^{-1}; 95% CI 4.09–14.12; P<0.001; Table 4) (Fig 2), even after adjusting for the covariates (adjusted increase 6.89 g L^{-1}; 95% CI 2.08–11.69; P=0.01).

By follow-up at 6 months, there were a further 15 patient deaths (seven in the i.v. iron group, eight in the placebo group). The odds ratio of mortality at 6 months was also similar between the groups (odds ratio [death in placebo group *vs* iron] 1.55; 95% CI 0.65–3.73; P=0.33; Table 4). This was not different after adjusting for preoperative haemoglobin concentration (g L^{-1}), age (yr), and surgical procedure (adjusted odds ratio [placebo *vs* iron] 1.56; 95% CI 0.63–3.84; P=0.34).

Acute hospital length of stay ranged from 2 to 25 days and time in rehabilitation from 0 to 62 days, with considerable variability between study participants. The median acute length of stay was 5.5 days in the group receiving i.v. iron and 7 days in the placebo group (Table 4).

Discussion

In patients undergoing emergency surgery for hip fracture, the use of i.v. iron infusion at the time of surgery did not reduce the need for blood transfusion compared with placebo. Subgroup analysis did suggest a reduced need for blood transfusion in patients <80 yr old in the i.v. iron group, with fewer units of blood transfused compared with the placebo group. Because of implementation of routine patient blood management protocols we were required to terminate the trial before sufficient numbers were achieved to provide further precision of these point estimates.

We found that patients in the i.v. iron group had a higher mean haemoglobin concentration, and proportion with a Hb >100g L^{-1}, at 6 weeks after operation compared with the placebo group, which is consistent with the findings of PREVENTT, in which preoperative i.v. iron treatment before major abdominal surgery significantly increased haemoglobin concentration 8 weeks after intervention compared with placebo.[43] Our finding may suggest that haemoglobin concentration, and therefore the need for transfusion,

Table 4 Secondary endpoints from randomisation to 6 weeks after operation and all-cause mortality to 6 months after operation. The data are reported per intervention group (iron or placebo) (n=143). CI, confidence interval; IQR, inter-quartile range. * Incidence rate ratios (for continuous outcome variables) and odds ratios (for categorical outcome variables) were adjusted for preoperative haemoglobin concentration (g L^{-1}), age (yr), and surgical procedure. † Missing data at 6 weeks.

	I.V. iron (n=70)	Placebo (n=73)	Placebo *vs* iron (95% CI), *P*-value	Placebo *vs* iron (95% CI), *P*-value
Length of acute stay (days)			1.28 (−0.15 to 2.71); P=0.08	1.41 (−0.01 to 2.83); P=0.05
Median (IQR)	5.5 (3)	7 (4)	—	—
Range	2–24	2–25	—	—
Length of rehabilitation stay (days)			0.98 (−5.79 to 7.76); P=0.77	0.15 (−7.15 to 7.44); P=0.97
Median (IQR)	8 (16.5)	1 (22)	—	—
Range	0–49	0–62	—	—
Had any infection by 6 weeks, n (%)	24/67 (36)	30/68 (44)	1.41 (0.71–2.83), P=0.33	1.28 (0.63–2.61), P=0.50
Home to home by 6 weeks, n (%)	31/53 (58)	37/54 (69)	1.54 (0.70–3.41), P=0.28	1.96 (0.79–4.87), P=0.15
Haemoglobin concentration ≥100 (g L^{-1}) at 6 weeks, n (%)	50/58 (86)	40/59 (68)	0.34 (0.13–0.85), P=0.02	0.40 (0.15–1.09), P=0.07
Haemoglobin concentration (g L^{-1}) at 6 weeks			−9.11 (−14.12 to −4.09); P<0.001	−6.89 (−11.69 to −2.08); P=0.01
Median (IQR)	116 (21)	108 (17)	—	—
Range	87–145	87–130	—	—
Deceased at 6 months, n (%)	10/70 (14)	15/73 (21)	1.55 (0.65–3.73), P=0.33	1.56 (0.63–3.84), P=0.34

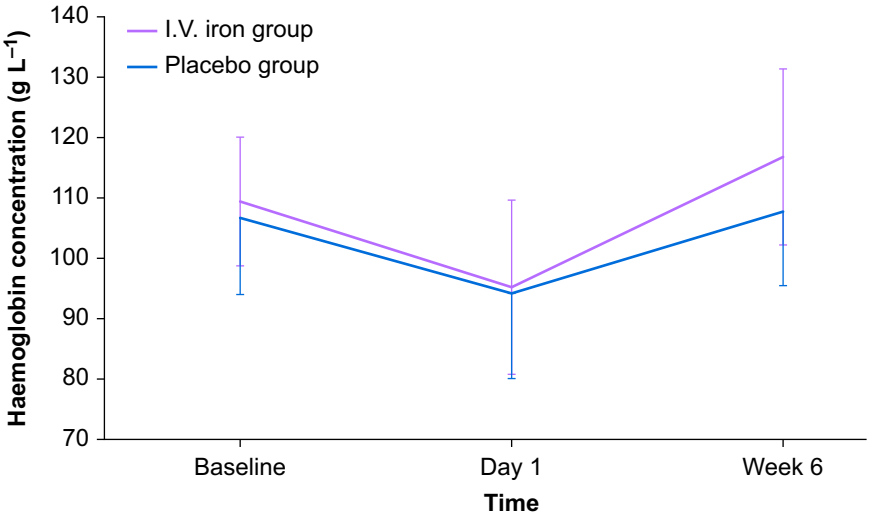

Figure 2. Haemoglobin concentration from baseline to 6 weeks. Number of patients in the i.v. iron group at baseline, Day 1 and Week 6: 70, 70, and 67 patients, respectively; number of patients in the placebo group at baseline, Day 1, and Week 6: 73, 73, and 66 patients, respectively.

following perioperative i.v. iron in fractured NOF is dependent on both iron dosing and initial haemoglobin concentration, as Bielza and colleagues[44] did not observe a similar improvement in haemoglobin concentration 3 months after randomly allocating fractured NOF patients to i.v. iron treatment on days 1, 3, and 5 of admission or placebo. In Bielza's study the initial haemoglobin concentration of the cohort was higher than IRON NOF (125 g L^{-1} *vs* 110 g L^{-1}) and Venofer 200 mg was used at each treatment interval. The work of Foss and colleagues[21] demonstrating improved early mobilisation and rehabilitation in those patients with a higher haemoglobin concentration highlights the importance of haemoglobin as a clinically important outcome worth measuring and trying to improve.

The strengths of this study include the prospective nature; allocation concealment; and patient-centred outcomes. Iron dosing was contemporary using iron carboxymaltose and not associated with adverse outcomes. Blinding was assiduously established and maintained with other care being consistent with national guidelines. Modified KATZ ADLs, for those patients at the largest site, and home to home rates were included in the study.

A central limitation to this study was the time taken to complete then publish this study and therefore its relevance to contemporary practice. Recruitment took >4 yr because of the lack of patients meeting the initial protocol inclusion criteria for iron deficiency anaemia, with many patients (60%) presenting with a ferritin concentration ≥100 μg L^{-1}. The inclusion criteria for the study were consequently modified ~1 yr after commencement to improve recruitment and better reflect the population presenting with NOF fracture. Furthermore, a large proportion of study participants had either acute or chronic cognitive impairment making recruitment involving a surrogate decision maker challenging in the acute setting. Including all anaemic patients who had not received a transfusion was a pragmatic trial design decision, but may have reduced the observed effect size of iron on transfusion by including those patients with a very low haemoglobin concentration in whom transfusion is almost unavoidable despite intervention. Over the period of recruitment, a shift in transfusion practices favouring a more restrictive transfusion threshold in this patient population in Australia occurred. Initial power calculations were based on a transfusion rate of 37%; however, by the end of the study period, the transfusion rates were around 20%, which was a larger decrease than the effect size powered for. These factors have also contributed to a significant delay in composing the manuscript after study completion.

Despite slow recruitment and a change in transfusion practice in this population necessitating the premature termination of the study, this study adds to the available knowledge in this area. Further research into the application of i.v. iron in patients <80 yr old undergoing fractured NOF surgery is required to determine whether there is a reduction in blood transfusion incidence. I.V. iron does improve haemoglobin concentration at 6 weeks and is safe and easy to administer at the time of surgery. Further work needs to be conducted to explore the optimal timing of i.v. iron administration around surgery, with preoperative iron administration of interest but logistically challenging.

Authors' contributions

Grant submission: EOL.
Trial design: EOL.
Investigation: EOL, PS, JS, GG.
Manuscript preparation and revision: BM, TR, EOL.
Trial management: EOL.
Data collection and preparation: EOL, HJC, PS, JS, GG.
Data analysis: HJC, EOL.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix 1 Modified Ganzoni iron dosing

Maximum dose=1000 mg over 15 min.

NOF, neck of femur.

NOF, neck of femur.

Body weight	Hb 60 g L^{-1}	Hb 75 g L^{-1}	Hb 90 g L^{-1}	Hb 105 g L^{-1} +
kg	mg	mg	mg	mg
40	1000	1000	800	700
45	1000	1000	800	700
50	1000	1000	900	700
55	1000	1000	900	700
60	1000	1000	1000	700
65	1000	1000	1000	800
70	1000	1000	1000	800
75	1000	1000	1000	800
80	1000	1000	1000	800
85	1000	1000	1000	800
90 +	1000	1000	1000	800

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