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Cardiovascular

Randomised open-label trial comparing intravenous iron and an erythropoiesis-stimulating agent *versus* oral iron to treat preoperative anaemia in cardiac surgery (INITIATE trial)

Robert Kong[1,*], Nevil Hutchinson[1], Andrew Hill[1], Fiona Ingoldby[2], Nicola Skipper[2], Christopher Jones[3], Stephen Bremner[3], Chloe Bruce[3], Juliet Wright[4], Michael Lewis[5], Stanton Newman[6], Timothy Chevassut[7] and David Hildick-Smith[8]

[1]Department of Anaesthesia, Royal Sussex County Hospital, Brighton, UK, [2]University Hospitals Sussex NHS Foundation Trust, Clinical Research Facility, Cardiac Research, Brighton, UK, [3]Brighton and Sussex Clinical Trials Unit, Brighton & Sussex Medical School, University of Sussex, Brighton, UK, [4]Brighton and Sussex Medical School, Brighton, UK, [5]Department of Cardiac Surgery, Royal Sussex County Hospital, Brighton, UK, [6]School of Health Sciences, University of London, London, UK, [7]Department of Haematology, Royal Sussex County Hospital, Brighton, UK and [8]Department of Cardiology, Royal Sussex County Hospital, Brighton, UK

*Corresponding author. E-mail: robert.kong@nhs.net

Abstract

Background: Preoperative anaemia is a risk factor for adverse postoperative outcomes after cardiac surgery. Iron deficiency is a frequent cause of low preoperative haemoglobin. An effective treatment for preoperative anaemia associated with iron deficiency has not been determined.

Methods: We conducted a single-centre, open-label, pragmatic randomised trial, enrolling 156 elective cardiac surgery patients who had low preoperative haemoglobin (100–130 g L^{-1}) with iron deficiency (serum ferritin <100 μg L^{-1} or transferrin saturation <30%) to compare intravenous ferric derisomaltose 1000 mg and darbepoetin 200 μg subcutaneously (intervention group) with oral ferrous sulphate 600 mg daily (control group). The primary outcome was transfusion of at least one unit of allogeneic red cells during surgery and within the following 5 days. Secondary outcomes included the change in haemoglobin concentration between randomisation and surgery, red cell transfusion volume, postoperative blood loss, pre-specified postoperative complications, length of hospital stay, and in-hospital death.

Results: The odds of red cell transfusion were lower in the intervention group compared with the control group (adjusted odds ratio=0.33; 95% confidence interval [CI], 0.15–0.75; P=0.008). Of the secondary outcomes, the only significant difference was the increase in haemoglobin between randomisation and surgery, intervention *vs* control 9.5 g L^{-1} (95% CI, 6.8–12.2; P<0.001).

Conclusions: In patients with a low preoperative haemoglobin and iron deficiency, preoperative treatment with a single dose of ferric derisomaltose and darbepoetin decreased the proportion of participants who received a perioperative blood transfusion as a consequence of a greater increase in haemoglobin compared with treatment with oral ferrous sulphate.

Clinical trial registration: ISRCTN Number: 41421863; EUDRACT number: 2011-003695-36.

Keywords: anaemia; cardiac surgery; darbepoetin; intravenous iron; iron deficiency; preoperative; transfusion

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Editor's key points

- The effectiveness of preoperative iron treatment for anaemia is unclear.
- A strong haemoglobin response could reduce postoperative complications and improve speed of recovery.
- This trial identified some beneficial effects of preoperative parenteral iron and darbepoeitin compared to oral iron requiring further study.
- To date, there is no evidence of improved patient outcomes.

Preoperative anaemia is associated with worse perioperative outcomes.[1] It was suggested 50 yr ago that a randomised trial could be undertaken to determine whether outcomes could be improved by preoperative correction of anaemia.[2] This hope remains an open question, although several investigators have looked at ways to correct anaemia preoperatively. Correction of preoperative anaemia is considered to be one of the pillars of Patient Blood Management.[3,4] Unfortunately, the evidence to guide such recommendations remains scant or inconclusive.[5]

First reported in 2007,[6] the association between preoperative anaemia in cardiac surgery and increased postoperative complications has since been confirmed from large registries.[7,8] Preoperative anaemia is reported in approximately 20–30%, and blood loss and red cell transfusion rates are higher in cardiac surgery than in other types of surgery.[9]

Serious wound and systemic infections,[10] renal failure, prolonged ventilation, low cardiac index, myocardial infarction, stroke, and mortality[11] have all been associated with transfusion after cardiac surgery, with mortality remaining significant after 5 yr.[12]

We examined whether patients presenting for elective cardiac surgery with a haemoglobin between 100 and 130 g L^{-1} treated with a combination of intravenous iron and a single dose of an erythropoiesis-stimulating agent can reduce the likelihood of requiring a transfusion of red blood cells (RBCs) compared with the common practice of treating iron deficiency anaemia with oral iron tablets.

Methods

Trial design and setting

This was a pragmatic, single-centre, open-label, randomised, superiority trial. It was conducted at an NHS hospital which undertakes, annually, approximately 650 adult cardiac surgery procedures requiring cardiopulmonary bypass. We compared the treatment of low preoperative haemoglobin with reduced iron reserves in participants undergoing elective cardiac surgery, using either intravenous iron (ferric derisomaltose) plus an erythropoiesis-stimulating agent (darbepoetin) or oral iron supplementation alone with ferrous sulphate.

Participants

Patients undergoing first-time, elective cardiac surgery requiring standard median sternotomy were recruited. We screened blood results from samples taken at the initial outpatient consultation with the surgical team. Samples with haemoglobin in the range of 100–130 g L^{-1} (inclusive) were highlighted to the laboratory to measure ferritin and transferrin saturation (TSAT).[13] Reduced iron reserves was defined as serum ferritin <100 μg L^{-1} or TSAT <30% provided the ferritin concentration was <800 μg L^{-1}. By adopting a broader definition of iron deficiency, we aimed to capture all patients who might have benefitted from iron supplementation.

Patients were not eligible if they were unable to give informed consent; pregnant; participating in another clinical trial; receiving renal replacement therapy; receiving chemotherapy; suspected to have significant hepatic disease; had a contraindication to receive the study drugs, including active infection at the time of randomisation; or intending to refuse any blood transfusion.

We did not recruit patients if the procedure was planned to be minimally invasive; hypothermic circulatory arrest was likely to be needed; or surgery was scheduled to be performed within 2 weeks of the outpatient attendance. Study information was posted to eligible patients who were then contacted by telephone, and those willing to participate in the trial were enrolled and asked to attend the hospital for randomisation.

Randomisation

After written informed consent was obtained, participants were randomly assigned to one of two groups – Intervention or Control. We used a web-based service[14] to provide a concealed, computer-generated sequence of randomly permuted blocks of length 2–6, stratified by sex (male or female) and haemoglobin concentration (100–115 or 116–130 g L^{-1}).

Procedures

Blood was taken to measure haemoglobin concentration (this value was used as the baseline to calculate the change between randomisation and surgery), reticulocyte count, electrolytes, creatinine, liver enzymes, C-reactive protein (CRP), thyroid function, serum vitamin B_{12}, folate, and erythropoietin. Serum was stored in liquid nitrogen and batched for duplicate measurements with the Hepcidin 25 (bioactive) HS ELISA RUO enzyme-linked immunosorbent assay (EIA 5782R; DRG Instruments, Marburg, Germany) according to the manufacturer's instructions.

Interventions

On the day of randomisation, patients in the Intervention arm were given ferric derisomaltose (previously known as iron isomaltoside, Monofer®) 1000 mg (or 20 mg kg^{-1} if the patient weighed less than 50 kg) by intravenous infusion over 60 min. Darbepoetin (Aranesp®) 200 μg was given subcutaneously.

Participants in the Control group were supplied with ferrous sulphate tablets and advised to start at a dose of 200 mg daily, increasing to 200 mg three times daily over several days, and reduce dosage to lessen any side-effects. We asked the participants' general practitioner (GP) to manage the treatment of abnormal thyroid function or low serum vitamin B_{12} (<220 pmol L^{-1}) or folate (<7 nmol L^{-1}) and renew the prescription for ferrous sulphate (control participants only). The research nurse telephoned participants to confirm medication adherence and monitor any treatment side-effects.

Timing of surgery

Scheduling of surgery was determined by the surgical team, but we anticipated that this would be 2–10 weeks after randomisation and adjusted according to clinical priority.

Masking

Participation in the trial was denoted by a sticker on the outside of the patient's medical records folder. Drugs administered at randomisation, and clinical observations and correspondence relating to the trial were filed inside the folder. Neither the participants nor the clinical staff were masked to the treatment allocation, but transfusion decisions were made according to departmental protocols by staff not involved in the study.

Intraoperative management

Participants received comparable anaesthetic and surgical management as other patients not in the study. Clinical practices (e.g. intraoperative cell-salvage, tranexamic acid usage, red cell transfusion trigger, or fluid management) did not change throughout the duration of the trial.

In the haemodynamically stable, non-bleeding patient, the trigger for transfusion of allogeneic red cells was Hb $\leq$70 g L^{-1}. The practice of 'single unit transfusion' – only one unit of red cells was transfused at a time – was used throughout. The haemoglobin concentration was recorded before the transfusion of each unit of red cells. In actively bleeding patients, both the transfusion trigger and treatment were left to the discretion of clinicians. Administration of other blood products to manage coagulopathy during and after surgery was guided by point-of-care viscoelastic test of whole blood (ROTEM®) according to a locally agreed algorithm.

Outcomes

The primary outcome was the transfusion of at least one unit of allogeneic red cells from the start of surgery until the end of the fifth postoperative day.

Secondary outcomes are listed in Supplementary Table S1. We also recorded patient-reported adverse symptoms after starting the randomised treatment (Supplementary Table S5).

Sample size

Local audit data revealed that in patients with preoperative haemoglobin concentration of 100–130 g L^{-1}, up to 80% were transfused at least one pack of red cells. We considered that a reduction in the absolute transfusion risk of 15% would be the minimum required to be clinically meaningful. To detect this difference with 80% power, we calculated that 302 participants were required, based on a two-tailed *z*-test, significance level

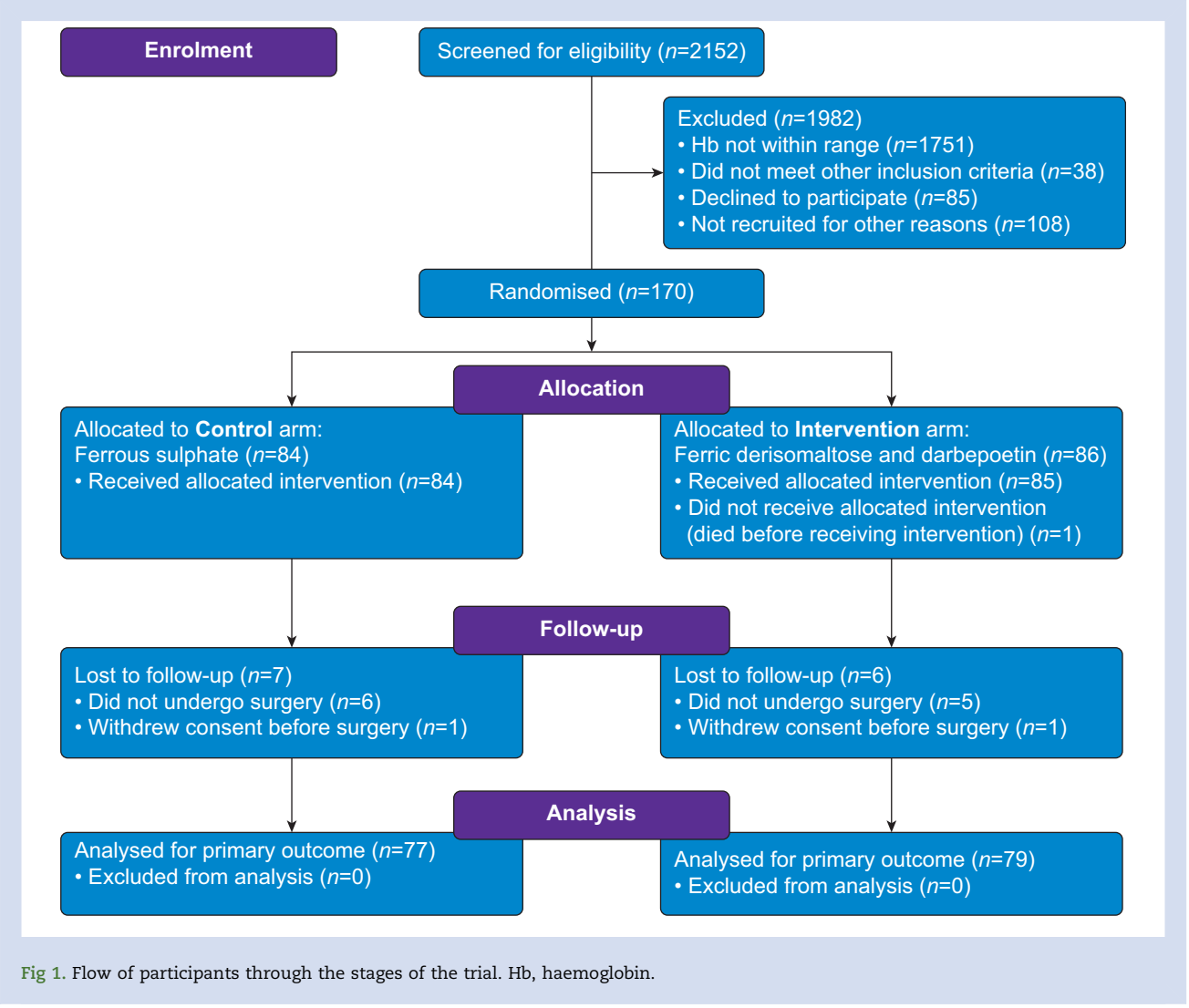

Fig 1. Flow of participants through the stages of the trial. Hb, haemoglobin.

0.05, and 1:1 allocation. To account for dropouts, we planned to randomise 330 patients to each group.

Interim analyses

To compare rates of serious adverse events, *a priori* planned interim analyses were defined in the trial protocol to be performed after 100 and 200 participants had completed surgery. There were no meaningful differences in the rates of serious adverse events between the two groups after 100 patients. Because of a slower-than-predicted recruitment rate, we submitted a protocol amendment to perform an interim analysis after 150 participants had completed surgery. In accordance with Consolidated Standards of Reporting Trials (CONSORT) recommendations for binary outcomes in pragmatic trials,[15] we calculated the relative risk (RR) of transfusion and planned to halt the study if the odds ratio (OR) for transfusion in the Intervention group *vs* the Control group was 0.46 or lower.

Statistical analysis

The statistical analysis plan (see Data Availability below) was agreed and signed off by the Chief Investigator before analysis. Baseline, surgical, and outcome variables were summarised using appropriate descriptive statistics. The primary outcome was analysed using a multivariable logistic regression model with intervention group, adjusted for the following covariates at baseline: CRP concentration, ferritin concentration, TSAT, and glomerular filtration rate. All 156 participants who underwent surgery were included in the model on an intention-to-treat basis. The adjusted OR is presented as Intervention *vs* Control with its 95% confidence interval (CI). The adjusted RR with its 95% CI is also presented. The adjusted RR was obtained by fitting a Poisson regression model with robust standard errors with the same dependent variable and covariates.[16]

Appropriate multivariable regression models were fitted for the secondary outcomes (Supplementary Tables S1 and S2) for which sufficient data were available: logistic for secondary outcome 8; negative binomial for 2a, 3a, 4a, and 5a; Cox for 12; and linear for 1, 2b, 3b, 4b, 5b, 6a, and 6b. Secondary outcomes 7, 9, 10, 11, and 13 were relevant to an insufficient number of participants to fit any models. Covariates for the secondary outcome models were the same as for the primary outcome model. Specific model assumptions were checked and where the assumption of normality of residuals in linear regression was inappropriate, bootstrapping was used to calculate appropriate 95% CIs and *P*-values. All secondary outcome models were fitted for the 156 participants who underwent surgery, except 6a and 6b, which were fitted for 155 participants, because of missing data.

Patient and public involvement

The study design and protocol were informed by a series of meetings with local GPs and patient groups. We will share the study results with the Sussex Heart Charity to disseminate to relevant patient groups.

Results

Between April 2013 and September 2017, 2151 outpatients were listed to undergo elective cardiac surgery, of whom 363 (16.9%) were eligible for the trial. The trial was stopped after the interim analysis showed that the OR for transfusion in the Intervention group *vs* the Control group was lower than 0.46. A total of 170 participants were randomised: 86 (50.6%) to the Intervention group and 84 (49.4%) to the Control group; 156 completed the trial.

There were 193 eligible patients who did not participate in the trial: 85 declined; 43 were in another study; 34 consulted the surgeon fewer than 2 weeks before surgery; 18 received treatment for anaemia off-study; 8 lacked sufficient capacity to give informed consent; and 5 could not be contacted in time to recruit into the study. The flow of participants through the stages of the trial is shown in Figure 1.

Baseline characteristics

Baseline patient, surgery, and haematological characteristics are shown in Table 1. The two groups were comparable with respect to major co-morbidities, baseline haemoglobin, iron status, haematinics, and indicators of erythropoiesis. The interval between randomisation and surgery, operative risk (as measured by European System for Cardiac Operative Risk Evaluation [Euroscore] II), types of surgery, and duration of cardiopulmonary bypass were also similar.

Primary outcome

The primary outcome could be evaluated in 156 participants who underwent surgery. The odds of receiving a blood transfusion were significantly lower in the Intervention group compared with the Control group (adjusted OR=0.33; 95% CI, 0.15–0.75; *P*=0.008). The adjusted risk ratio was 0.77 (95% CI, 0.63–0.94; *P*=0.010).

The proportion of participants who received any red cell transfusion was lower in the Intervention group with an absolute difference in transfusion rate of 14.7% (Table 2).

Based on this difference, the number needed to treat with the intervention to have one less participant require transfusion is 6.8 (95% CI, 3.5–80).

Secondary outcomes

Blood transfusion

Transfusion of red cells and other blood products are summarised in Table 2. Although a greater proportion of control group participants received a transfusion of red cells within the first 5 days after surgery, there was no difference between the two groups for the number of packed RBCs given per participant. There was some evidence for a reduction in the volume of packed RBCs given in the Intervention group, mean −212.2 ml (95% CI, −422.1 to −2.3 ml; *P*=0.047) (Supplementary Table S2, secondary outcome 2b).

Change in haemoglobin concentration

The median (inter-quartile range [IQR]) haemoglobin increase in the Intervention group was 12.0 (7.0–17.0) g L^{-1} compared with 0.0 (−5.0 to 6.0) g L^{-1} in the control group (Table 3). The adjusted difference between the groups was 9.5 g L^{-1} (95% CI, 6.8–12.2; *P*<0.001). Despite treatment, haemoglobin concentration had dropped by the time of surgery in about 10% of participants in the Intervention group and 50% in the Control group (Fig 2). More participants attained a haemoglobin increase of ≥10 g L^{-1} after intravenous iron and darbepoetin (48/79; 61%) compared with oral iron (11/77; 14%). Ferritin and TSAT increased after both treatments, although the increase was less after oral iron (Supplementary Table S3). Deficiency of

Table 1 Patient, surgery and haematological baseline characteristics. Data are reported as median (inter-quartile range) or number (%). CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; Euroscore II, European System for Cardiac Operative Risk Evaluation; TSH, thyroid stimulating hormone.

	Control (*n*=77)	Intervention (*n*=79)
Patient characteristics		
Age (yr)	73 (69–78)	75 (67–79)
BMI (kg m^{-2})	27.3 (24.8–30.7)	27.3 (24.7–31.2)
Sex		
Female	37 (48.1)	41 (51.9)
Male	40 (51.9)	38 (48.1)
Left ventricular ejection fraction		
>50%	63 (81.8)	63 (79.7)
30–50%	13 (16.9)	15 (19.0)
<30%	1 (1.3)	1 (1.3)
Diabetes mellitus		
Not diabetic	56 (72.7)	59 (74.7)
Diet–controlled	1 (1.3)	2 (2.5)
Oral therapy	7 (9.1)	6 (7.6)
Insulin therapy	13 (16.9)	12 (15.2)
Renal function, eGFR (ml min^{-1} 1.73 m^{-2})		
>60	67 (87.0)	71 (89.9)
30–60	10 (13.0)	8 (10.1)
<30	0 (0.0)	0 (0.0)
Euroscore II	2.04 (1.35–3.10)	2.33 (1.47–3.89)
Surgical characteristics		
Surgery within 2–10 weeks of randomisation		
No	22 (28.6)	26 (32.9)
Yes	55 (71.4)	53 (67.1)
Time between randomisation and surgery (days)	38 (24–77)	48 (29–84)
Type of surgery		
CABG	27 (35.1)	33 (41.8)
CABG + valve	14 (18.2)	13 (16.5)
Valve	36 (46.8)	33 (41,8)
Cardiopulmonary bypass time (min)	92 (71–127)	88 (67–112)
Haematological characteristics		
Haemoglobin at randomisation (g L^{-1})	124 (117–129)	120 (112–125)
Reticulocyte count ($\times 10^9$ L^{-1})	60 (50–74)	54 (46–67)
Ferritin (μg L^{-1})	66 (26–123)	60 (35–121)
Transferrin saturation (%)	16 (11–20)	17 (14–22)
Hepcidin (ng ml^{-1})	21.5 (7.8–34.2)	17.0 (7.5–35.3)
Erythropoietin (U L^{-1})	15.3 (12.2–18.6)	12.8 (9.2–19.2)
Vitamin B_{12} (pg ml^{-1})	379 (291–470)	358 (284–485)
Folate (ng ml^{-1})	9.0 (6.8–12.2)	8.3 (6.0–11.6)
TSH (mIU L^{-1})	1.7 (1.3–2.7)	1.6 (1.2–2.7)
Thyroxine (pmol L^{-1})	16.0 (14.3–18.4)	15.6 (14.1–17.2)
C-reactive protein (mg L^{-1})	3.0 (1.6–7.0)	2.4 (1.0–5.3)
Creatinine (μmol L^{-1})	88 (77–109)	85 (76–102)

vitamin B_{12} (serum concentration <200 pg ml^{-1}) or folate (<24 ng ml^{-1}) was found in 5.8% and 1.9% of the patients, respectively (Supplementary Table S4).

The haemoglobin concentrations of the participants at the time of routine measurement are shown in Figure 3.

Postoperative complications

There were no differences in pre-specified clinical outcomes between the groups, although some endpoints were too infrequent to allow meaningful analysis. There were no thrombotic complications in either group, although four patients in the Intervention group had perioperative embolic strokes. These were reviewed by the Safety Committee and considered to be related to the surgery. Three had severely atheromatous ascending aortas, and the fourth had an unusually calcified aortic annulus making surgery to replace the valve difficult. Patient-reported symptoms and other adverse events are shown in Supplementary Table S5.

Discussion

We found that in a cohort of patients with routine cardiac surgery who have anaemia and iron deficiency, red cell transfusion rate was lower after preoperative treatment with ferric derisomaltose and darbepoetin compared with oral ferrous sulphate. A combination of intravenous iron and erythropoiesis-stimulating agent resulted in a median 12.0 g L^{-1} increase, whereas the group receiving oral iron showed no overall change in haemoglobin concentration.

Many studies have adopted the WHO definition of anaemia to target interventions for preoperative anaemia. We disagree with this approach in practice and in the design of this trial: clinical decisions to transfuse red cells are not influenced by

Table 2 Transfusion of red blood cells or other blood products. Data are reported as median (inter-quartile range) or number (%). RBC, red blood cell.

	Control (*n*=77)	Intervention (*n*=79)
Any RBC transfusion (days 0–5)		
No	14 (18.2)	26 (32.0)
Yes	63 (81.8)	53 (67.1)
In transfused patients		
Number of RBC units	2 (2–4)	2 (1–4)
RBC volume (ml)	604 (566–1145)	597 (314–1089)
Fresh frozen plasma volume (ml)	0 (0–0)	0 (0–0)
Cryoprecipitate volume (ml)	0 (0–400)	0 (0–400)
Platelets volume (ml)	0 (0–205)	0 (0–289)

patient sex, and transfusion triggers used in routine clinical practice are not gender-specific.[17] Our decision to do this has been supported by subsequent consensus recommendations.[18] We adopted a liberal definition of iron deficiency. In the context of predictable surgical blood loss of 500 ml or more, this seemed reasonable.

Oral iron

Oral iron is widely regarded as the standard treatment of iron deficiency anaemia for patients in the community. Yet, in several clinical scenarios, a greater increase in iron stores, haemoglobin concentration, or both is achieved after replacement with intravenous compared with oral iron.[19,20] Oral iron supplementation relies on intestinal absorption of iron, which is reduced when hepcidin concentration is elevated.[21] Despite this, oral iron is cheaper, logistically simpler, and remains the standard therapy for iron deficiency.

The distribution of baseline hepcidin concentration was comparable in both groups in this trial, with median hepcidin values at the upper limit of the non-anaemic reference range for this assay.[22] This suggests that the underlying cause of anaemia in about half of the patients is likely to have been caused by inflammation or a combination of inflammation and iron deficiency.[23] Impaired iron absorption could explain the differences in ferritin and TSAT increases from baseline. The relationship between hepcidin concentration and the erythropoiesis response requires further evaluation.

A higher incidence of side-effects, which were predominantly gastrointestinal, was reported by patients who received iron orally (68% *vs* 45%). This is in keeping with the known side-effect profile of oral iron therapy. Based on the change in ferritin and TSAT, oral iron was able to increase iron stores, albeit only very slightly compared with giving iron intravenously. Newer formulations of oral iron may be more effective than ferrous sulphate and warrants wider recognition.[24]

Intravenous iron

We administered a dose of 1000 mg of ferric derisomaltose, which was – on average – 60–70% (higher for women) of the licensed maximal dose of 20 mg kg^{-1} for a single infusion. Although the fixed dose approach has its merits for simplicity in a trial context, dosing according to an individual's calculated iron deficit might be a better approach to replenish iron stores.[25] Since we embarked on our trial, other investigators have evaluated intravenous iron alone to treat preoperative anaemia and found mean increases in haemoglobin (<10 g L^{-1}) that we would not consider clinically important.[26,27]

Erythropoiesis-stimulating agent

Erythropoiesis would be expected to be enhanced by the addition of an erythropoiesis-stimulating agent. When we planned this trial, our aim was to enhance erythropoiesis in the Intervention group. At the time, the proposal to combine an erythropoiesis-stimulating agent with intravenous iron was rather unique as a treatment strategy for preoperative anaemia. The use of erythropoietin to treat anaemia in chronic kidney disease had been associated with thrombotic risks, and we therefore planned to use only a single and relatively low dose of an erythropoiesis stimulating agent.[28]

We chose darbepoetin, an agent that has not been reported for the treatment of preoperative anaemia by other

Table 3 Secondary outcomes. Data are reported as median (inter-quartile range) or number (%). *n=76 for control group. Note: inferential testing (for P values) of these outcomes was not part of our statistical analysis plan.

	Control (*n*=77)	Intervention (*n*=79)
Haemoglobin change between randomisation and surgery (g L^{-1})	0.0 (–5.0 to 6.0)	12.0 (7.0–17.0)
Postoperative blood loss* after 12 h (ml)	425 (308–658)	450 (325–675)
Postoperative blood loss* after 24 h (ml)	600 (450–930)	650 (450–905)
Significant postoperative myocardial injury	2 (2.6)	3 (3.8)
Acute kidney injury	18 (23.4)	15 (19.0)
Re-sternotomy for bleeding within 24 h of surgery	5 (6.5)	1 (1.3)
Delirium	6 (7.8)	7 (8.9)
Cerebral events <24 h	0 (0.0)	2 (2.5)
Length of postoperative hospital stay (days)	8 (5–13)	8 (6–11)
Composite adverse events	3 (3.9)	10 (10)
Death	2 (2.6)	2 (2.5)
Stroke	0 (0.0)	4 (5.1)
Renal replacement therapy	2 (2.6)	3 (3.8)
Intra-aortic balloon pump	1 (1.3)	2 (2.5)
Surgical debridement	0 (0.0)	3 (3.8)

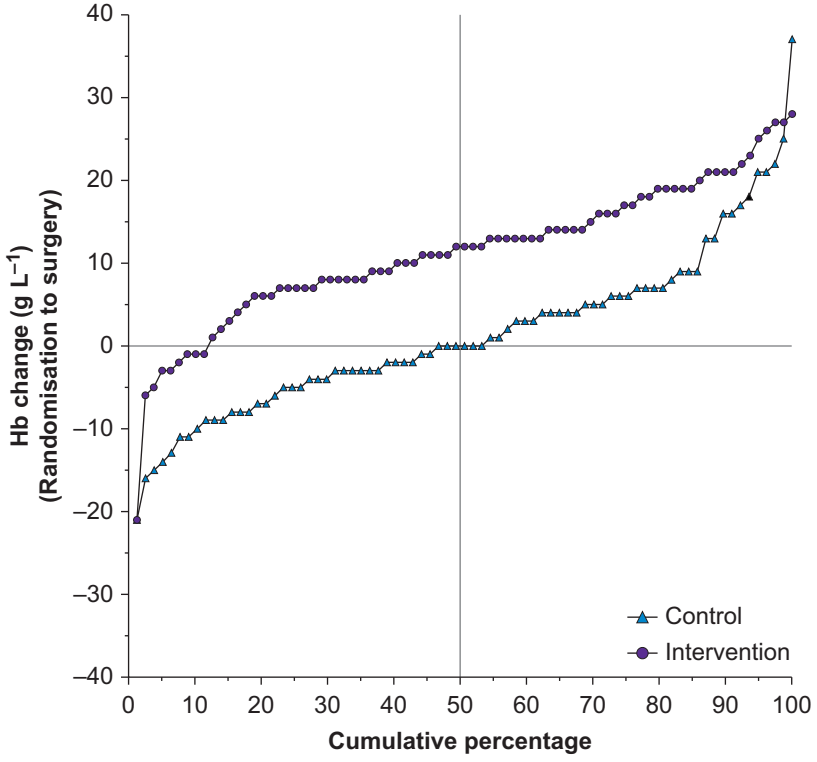

Fig 2. Cumulative percentage plot showing the change in haemoglobin (Hb) between randomisation and surgery for participants in the intervention and control groups. Hb concentration increased for less than 50% of participants in the Control group compared with an increase in more than 85% of participants in the Intervention group. This increase was greater than 10 g L^{-1} for more than 50% of participants in the Intervention group, whereas only around 15% of participants in the Control group show an increase this large.

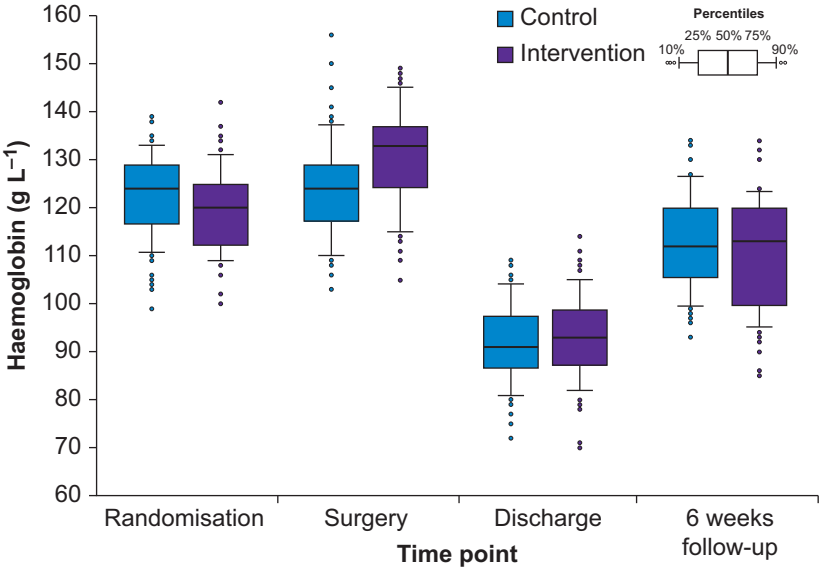

Fig 3. Haemoglobin at randomisation, surgery, discharge and at 6 week follow-up by treatment groups. Box and whisker plots showing haemoglobin distribution at four time points.

groups. The longer half-life of darbepoetin compared with epoetin allowed us to simplify the treatment by administering a single dose and avoid multiple hospital visits by the patients.

Biboulet and colleagues[29] showed that the addition of erythropoietin to either intravenous or oral iron increased haemoglobin concentration in anaemic patients awaiting major orthopaedic surgery. As their patients were iron-replete before the start of treatment, the haemoglobin increase after oral iron could be attributed largely to their use of three preoperative doses of erythropoietin. Spahn and colleagues[30] used only a single dose of erythropoietin and intravenous iron, which were given the day before cardiac surgery. Although this approach reduced the number of red cell units transfused after surgery, there was no significant difference between treatment and control groups in the proportion of patients who avoided any red cell transfusion.

In our study, haemoglobin concentration decreased between randomisation and surgery in 50% of patients in the oral iron group and 10% of the Intervention group. Data from other trials also show that in a subset of patients receiving placebo or oral iron, haemoglobin concentration can decrease further after randomisation.[31,32]

Adverse surgical outcomes

The link between preoperative anaemia and poor operative outcomes remains to be clearly elucidated despite numerous observational studies demonstrating a correlation.[33–36] Our study was not designed to examine this association. There were more strokes in the Intervention group, but our Safety Committee deemed these were unlikely to be caused by the study drugs. We did identify an increased incidence of the composite of serious complications in the Intervention group, but this was one of many secondary endpoints.

Strengths and limitations of this study

The main strength of this study lies in its pragmatic design, comparing the standard treatment of low haemoglobin associated with iron deficiency with a treatment that could be implemented in most cardiac surgery units using drugs that have a good safety record. We chose a primary endpoint that is clinically appealing – the odds of avoiding any red cell transfusion.

Conducted in a single centre, the study has limited generalisability. However, we recruited more than half of the patients who were eligible, and the broad inclusion criteria enabled us to randomise most of the patients who presented with a low haemoglobin for routine cardiac surgery.

The study was stopped after an interim analysis after just over half of the planned number of participants. Stopping the trial early poses the risk that the effects of the intervention on transfusion rate could be overestimated. The open-label design could introduce a bias and exaggerate the benefits of the intervention. However, we think this is unlikely, as clinical decisions that could influence red cell transfusion were based on objective criteria and taken by clinicians who were not involved with the trial. Moreover, the participants comprised a minority of the caseload of the surgical unit over several years and their clinical management during and after surgery was indistinguishable from that of other patients. The haemoglobin values before the transfusion of each unit of red cell were comparable in both groups (Supplementary Table S6), providing reassurance that bias was not a major problem.

We have not carried out a cost–benefit analysis. It might be argued that the costs of the intervention would not be offset by the savings from reduced transfusion rates. Furthermore, it could be argued that it was clinically irrelevant, at least in cardiac surgery, where recent prospective studies have not detected adverse outcomes as a result of more allogeneic transfusion.[37,38] However, the latest guidelines from the Society of Thoracic Surgeons continues to recommend a restrictive rather than a liberal approach to transfusion as the latter confers no long-term benefits.[39] These criticisms would be more potent if at 1 yr from surgery, such a treatment strategy for this group rendered no important benefits.[40]

Conclusions

We have shown that it is possible to increase preoperative haemoglobin concentrations and reduce the risk of requiring blood transfusion in patients presenting for elective cardiac surgery who have low haemoglobin concentrations associated with low iron reserves. Administration of single doses of intravenous iron and subcutaneous darbepoetin can achieve this; oral iron supplements cannot. Whether, ultimately, the association of preoperative anaemia with poor postoperative outcomes can be ameliorated by interventions such as these remains unanswered.[2]

Authors' contributions

Study concept and design: RK, NH, ML, JW, SN.
Data acquisition: FI, NS, CB, TC.
Data analysis and interpretation: RK, NH, CJ, SB, JW, AH, TC, DHS.
Statistical analysis: CJ, SB.
Drafting of the manuscript: RK, NH, CJ, SB.
Guarantors and approved the final version: RK, NH.
RK is the corresponding author and attests that all listed authors meet the authorship criteria and no others meeting the criteria have been omitted.
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Declarations of interest

All authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 yr, and no other relationships or activities that could appear to have influenced the submitted work. Pharmacosmos A/S (Holbaek, Denmark) supplied the ferric derisomaltose administered to participants in the study and funded the salary of a research nurse at the Clinical Research Facility at the Royal Sussex County Hospital for the duration of the study.

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Ethics and regulatory approval

Ethical and regulatory approval for the trial was given by the NHS Research Authority (London Bentham Committee, 2011) and the Medicines and Healthcare Regulatory Authority (2012). This trial was registered with EudraCT (2011-003696-36) and ISRCTN (41421863).

Data availability

The study protocol, de-identified participant data, and statistical analysis plan can be shared upon request. Please contact the lead investigator (ORCID: 0000-0002-8598-9991).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.01.034.

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