# CLINICAL STUDY SUMMARY REPORT

Preoperative Treatment Of A Low Haemoglobin In Cardiac Surgery: Pragmatic Open-Label Randomised Controlled Trial To Compare Treatment Using Intravenous Iron Plus Darbepoetin Versus Standard Care (INITIATE Study)

| Persons contributing to this report | |
|---|---|
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**Trial ID:**

**EudraCT Number: 2011-003695-36**

**GCP Sponsor: Brighton & Sussex University Hospitals NHS Trust**

**Trial initiation (FSFV): 18 April 2013**

**Trial completion (LSLV):** 7 December 2018

**Date of report:** 11 November 2019

**Title of trial**

Preoperative treatment of a low haemoglobin (Hb) in cardiac surgery: pragmatic open-label randomised controlled trial to compare treatment using intravenous iron plus darbepoetin versus standard care (INITIATE Study)

**Name of trial centres**

Royal Sussex County Hospital, Brighton, UK

**Trial period**

First subject's first visit (FSFV): 18 April 2013

Last subject's last visit (LSLV): 7 December 2018

**Objectives and endpoints**

Primary objective

Compare treatment of low Hb in patients undergoing elective cardiac surgery using either intravenous iron and darbepoetin or oral ferrous sulphate.

Primary endpoint

Proportion of participants that receive one or more packed red cell transfusions between the start of surgery and the end of the fifth postoperative day.

Secondary objectives

Evaluate the relationships between treatment strategies and patient outcomes, specifically - preoperative fatigue, Hb increase after treatment, blood product usage, postoperative adverse events and quality of life after surgery.

Secondary endpoints

1. Hb increase (between randomisation and surgery) after intervention or standard care.
2. Total number and volume of packed red cells given to each participant during the hospital stay for surgery.
3. Total number of packs and volume of fresh frozen plasma, platelets and cryoprecipitate given to each participant during the hospital stay for surgery.
4. Postoperative blood loss at 12 and 24 hours after surgery
5. Significant postoperative myocardial injury - Troponin T 18-24h after surgery
6. Acute kidney injury (RIFLE-R criteria) – greater than 1.5x increase in creatinine concentration to above baseline levels (creatinine value measured on the day before surgery or closest date).
7. Composite in-hospital adverse events
    a. In-hospital death
    b. Stroke – any new, persistent (>24h) and focal neurological deficit after surgery and confirmed by CT scan

c. Need for postoperative renal replacement therapy

d. Need for postoperative IABP to treat low cardiac output state (clinically defined)

e. Return to theatre for debridement of sternal or graft harvest site wound

8. Re-sternotomy for bleeding within 24h of surgery
9. Occurrence of postoperative delirium (clinically defined) or ischaemic, focal cerebral events lasting less than 24h (TIA).
10. Length of hospital stay - from day of operation to the day the participant is medically fit for discharge.
11. Patient-reported outcomes: changes in FACIT-fatigue, SF36, STAI, CES-D quality of life and fatigue."

**Methodology and trial design**

Pragmatic, single centre, open-label, randomised, controlled, superiority trial to compare the treatment of low preoperative Hb concentration with iron deficiency in participants undergoing elective cardiac surgery, using either intravenous iron plus darbepoetin or oral iron supplementation.

Participants were assigned 1:1 to one of two strategies - Intervention or Standard Care. Web-based service provided a concealed, computer-generated block randomisation sequence, stratified by gender (male or female) and Hb concentration (100 - 115 or 116 - 130 g/L).

We anticipated that participants would be scheduled for surgery between 2 and 10 weeks after randomization. However, the date of surgery was determined by clinical considerations and bed capacity.

Decisions to transfuse red cells and other blood products were left to the discretion of the clinical team to follow current departmental protocols.

**Number of subjects**

1. Intervention group analysed: 79
2. Standard care group analysed: 77
3. Total randomised: 170
4. Eligible: 364
5. Screened: 2799

**Diagnosis and main criteria for inclusion and exclusion**

All patients undergoing elective cardiac surgery at the centre were screened for eligibility. The following features were required for inclusion:

1. Hb concentration between 100 and 130 g/L (inclusive)
2. and **either** serum ferritin concentration less than 100µg/L **or** transferrin saturation less than 30% with ferritin concentration less than 800µg/L.
3. 18 years of age or older, undergoing first-time, elective cardiac surgery requiring median sternotomy.

Exclusion criteria

1. Scheduled to be performed less than two weeks after the clinic appointment at which the patient is placed on the list for surgery.
2. Re-operation (i.e. not first-time surgery).
3. Anticipated to be via a minimally-invasive approach.
4. Likely to require hypothermic circulatory arrest.
5. At risk of pregnancy.
6. Participating in another clinical trial.
7. Receiving renal replacement therapy or chemotherapy for cancer.
8. Unable to give informed consent due to language or mental capacity.

**Test product and comparator, dose, mode of administration,**

Intervention

Given to participant on the same day as randomisation.

1. Iron isomaltoside (MonoFer®) 1000 mg or 20mg/kg if the patient weighed less than 50kg. Administered as an intravenous infusion over 60 minutes.
2. Darbepoetin (Aranesp®) 200µg of by subcutaneous injection.

Standard care

To be taken by participant from the day of randomisation until the day before surgery.

Ferrous sulphate 600mg daily, in 3 divided doses, taken orally - or the maximum tolerable dose if side effects preclude taking 600mg daily.

**Duration of treatment**

Intervention: Study drugs given once only.

Standard care: Participant instructed to take study drug continuously from randomisation until the day before surgery.

**Statistical methods**

Analysis was according to intention to treat principles. A secondary analysis of the primary outcome following per-protocol principles was planned if any of the participants who underwent surgery did not adhere to their assigned intervention. However, all participants who underwent surgery adhered to their assigned intervention, so this secondary per-protocol analysis was not required.

Primary outcome analysis

The study was planned to detect a difference in the proportion of participants meeting the primary outcome as follows (from the Study protocol):

*Assuming transfusion rates of 65% in the intervention group and 80% in the routine care group, the sample size is calculated to be 151 participants in each group: two-sided significance level (alpha) of 0.05 and 80% power to detect a 15% difference"*

However, due to slow recruitment, the ethics committee approved a protocol amendment to undertake a modified analysis once 150 participants had reached the primary endpoint.

The adjusted analysis was performed using logistic regression with 'Did participant receive one red cell transfusion on days 0-5? (Yes/No)' as the dependent variable. This model included the stratification variables (Gender and Hb concentration). Effect estimates were presented with 95% confidence intervals and p-values.

To increase the power of the test of the treatment effect, the following variables were included in the model in order of priority.

- Treatment group
- Baseline C reactive protein concentration
- Baseline serum ferritin
- Baseline transferrin saturation
- Baseline estimated glomerular filtration rate

Secondary outcomes analysis:

Appropriate regression models were fitted, where possible, for each secondary outcome with the same predictor variables as for the primary analysis. Outcomes were described descriptively if modelling was not possible.

**Results**

Ninety percent (71/77) of participants in the Intervention group and 92% (71/77) in the Standard care group underwent surgery within 2 -10 weeks after randomisation - a median of 49 and 40 days respectively between randomisation and surgery.

There was no difference in the median pre-transfusion Hb concentration between the 2 groups for the first through to the eight unit of red cell transfused.

Primary outcome

The odds ratio for the Intervention group vs the Standard care group is 0.42 (95% CI: 0.19 to 0.91, p=0.027), indicating that the odds of receiving a blood transfusion in the Intervention group are 0.42x the odds of receiving a blood transfusion in the Standard care group. Alternatively, the odds of receiving a blood transfusion are 2.39 (95% CI: 1.10 to 5.19) times greater in the Standard group.

Fifty-three (67.1%) participants in the intervention group received any red cell transfusion within the first 5 days after surgery against 63 (81.8%) participants in the Standard care group.

Secondary outcomes

Patient-reported outcomes have not been analysed yet.

Due to low numbers of events, models could not be fitted for these outcomes:

1. Significant postoperative myocardial injury - Troponin T 18-24h after surgery
2. Composite in-hospital adverse events
3. Re-sternotomy for bleeding within 24h of surgery

4. Occurrence of postoperative delirium (clinically defined) or ischaemic, focal cerebral events lasting less than 24h (TIA).

Sufficient data were available to fit models for the remaining secondary outcomes. Normality of residuals was checked for each linear regression model and the residuals were not normally distributed from any of these. Bootstrapping (5000 replicates with seed 695674803) was used for these models to calculate appropriate 95% CIs and p-values.

For secondary outcome "Hb increase (between randomisation and surgery) after intervention or standard care", there is strong evidence against the null hypothesis of no difference between intervention and standard groups. The median Hb increase in the Intervention group was 12.0g/L (IQR 7.0 – 17.0) compared to 0.0g/L (IQR -5.0 -6.0) in the Standard care group.

There was no evidence against any of the other null hypotheses of no difference between intervention and standard groups for any of the other secondary outcomes.

**Conclusion**

In patients with a low Hb and iron deficiency before elective cardiac surgery, treatment with a single dose of intravenous iron and darbepoetin reduced postoperative red cell transfusion. In contrast to treatment with intravenous iron and darbepoetin, oral ferrous sulphate did not increase preoperative Hb.

**Date and version of this report**

11 November 2019 (v1.1)