

**Evidence cornered: Preoperative intravenous iron to treat anaemia before major abdominal surgery
(PREVENTT trial)**

Louise Aaron¹, James Day², Akshay Shah^{2,3}

1. Foundation Doctor, Health Education Thames Valley, NHS
2. Nuffield Department of Anaesthesia, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
3. Radcliffe Department of Medicine, University of Oxford, Oxford, UK

Correspondence to:

Akshay Shah, Radcliffe Department of Medicine, University of Oxford, Leve 4 Academic Block, John Radcliffe Hospital, Oxford, OX3 9DU, UK

Email address:

Dr Louise Aaron: louiseaaron@hotmail.co.uk

Dr James Day: james.day@ouh.nhs.uk

Dr Akshay Shah: akshay.shah@linacre.ox.ac.uk

Running title: Preoperative intravenous iron before major surgery

Key words: intravenous iron; anaemia; major surgery; transfusion

Word count: 847 (excluding Summary)

Summary

Clinical question: Does intravenous iron given to anaemic patients (haemoglobin (Hb) <130 g/L for men and 120 g/L for women) before major elective open abdominal surgery reduce the need for blood transfusions or death within 30 days of surgery?

Evidence from trial: There were no significant differences in the rates of blood transfusion or death at 30 days after the index operation between anaemic patients who received intravenous iron preoperatively and those who did not.

International guidelines¹ recommend that patients undergoing major surgery with an expected blood loss of greater than 500 mL or more should be screened for anaemia at least 6-8 weeks before surgery and if less than 4 weeks, intravenous iron therapy should be offered as first-line therapy for patients with iron deficiency anaemia. These guidelines are based on low-quality evidence largely from small randomised controlled trials (RCTs) and observational studies. A Cochrane meta-analysis² published in December 2019 concluded that preoperative intravenous iron did not show a clinically significant reduction in allogeneic blood transfusions (risk ratio (RR) 1.21; 95% Confidence Interval (CI): 0.87 to 1.70; four RCTs; 200 participants, moderate certainty of evidence). The timing of administration of intravenous iron in the included studies ranged from between 48 hours to up to 3 weeks prior to surgery. PREVENTT aimed to increase the certainty of the evidence and is the first, large, double-blind RCT that has evaluated the clinical effectiveness of preoperative intravenous iron.³ This Transfusion Evidence Synopsis summarises the paper describing this RCT in The Lancet (Box 1).

Summary of the results of the study

Primary outcome

Preoperative intravenous iron did not result in a reduction in the risk of the composite endpoint of blood transfusion, death or the number of blood transfusion episodes between randomisation to 30

days after index operation (**Table 1**). There was also no evidence of an effect on any of the prespecified subgroup analyses, including patients with iron deficiency defined as ferritin <100 ng/mL and/or transferrin saturation <20%.¹ This finding supports evidence from previous small trials that preoperative iron therapy does not reduce perioperative transfusion requirements.

Secondary outcomes

There were no significant differences between the groups for the total number of blood components transfused at 30 days; postoperative complications until 6 months; intensive care unit stay and total hospital length of stay. There was also no difference between groups for days alive and out of hospital at 30 days after index operation or any of the health-related quality of life outcomes.

Preoperative intravenous iron did result in a statistically significant increase in haemoglobin concentration from randomisation to index operation at 8 weeks (mean difference 10.7 g/L; 95% Confidence Interval (CI): 7.8-13.7) and 6 months (mean difference 7.3 g/L; 95% CI: 3.6-11.1) when compared with placebo. There was a significant reduction in hospital readmissions at 8 weeks following the index operation in the intravenous iron group when compared with placebo. This is likely to be a chance finding; but could also reflect the actual time period required to elicit any effects from intravenous iron, including effects independent of erythropoiesis such as improved cardiopulmonary function, exercise capacity and immunity.^{4,5} These findings should inform future hypothesis-testing studies. There were no significant differences in any of the pre-specified safety endpoints.

Limitations of the trial

The blood transfusion rate observed in the placebo arm of the trial was 29%, which is less than the 40% used in the original sample size calculation. Therefore, it is possible that the study may have been underpowered. The observed reduction in transfusion rates could be attributed to the widespread adoption of patient blood management principles^{4,6} which occurred during the time period of this study. Approximately 1 in 5 patients deviated from the study protocol, which can be expected for interventions being tested in complex perioperative pathways. Patients did not require a confirmed diagnosis of iron deficiency to enter the study with no clear diagnostic pathway defined. Only 29% in included participants had known iron deficiency. These factors may introduce bias and reduce the magnitude of the observed effect in a study which was already underpowered. The inclusion criteria defined that preassessment should occur a minimum of 10 days before surgery. This may miss some urgent cancer patients for whom surgery is a priority and preassessment is less

than 10 days before surgery. These patients, with more severe surgical disease, may have benefitted the most from iron therapy. There was no standardised transfusion protocol for participating hospitals.

Evidence in context

This is the first large RCT of preoperative intravenous iron therapy to treat anaemia before major elective abdominal surgery. The findings support evidence from previous small trials² that routine preoperative iron therapy does not reduce perioperative transfusion requirements in this cohort of patients.

Implications for research

Preoperative intravenous iron resulted in a sustained improvement in haemoglobin that lasted up to 6 months postoperatively. There was also a reduction in hospital readmissions in the same timeframe. These require further study including the potential role of postoperative iron therapy. Future studies should aim to include patients with diagnosed iron deficiency and evaluate patients who may have other indications for intravenous iron, other than reducing transfusion requirements, such as cardiopulmonary disease. Whether other surgical groups, such as those undergoing orthopaedic surgery, emergency surgery, or older surgical patients, may benefit from intravenous iron is the subject of current research.

Implications for practice

Routine use of preoperative intravenous iron to treat anaemia in patients scheduled to undergo elective open major abdominal surgery, without laboratory confirmed iron deficiency, should not be recommended. Current clinical guidelines should be updated accordingly.

Conflicts of interest

The authors have no competing interests.

Funding

No external funding was required for this work. A.S. is currently supported by an NIHR Doctoral Research Fellowship (NIHR-DRF-2017-10-094)

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Outcomes	Placebo	Intravenous iron	Relative risk (95% CI)
Blood transfusion or death at 30 days	67/237 (28%)	69/237 (29%)	1.03 (0.78 to 1.37)
- Transfusion	67/237 (28%)	68/237 (92%)	
- Death	2/237 (1%)	2/237 (1%)	
Anaemia correction at time of surgery	21/243 (10%)	42/244 (21%)	2.06 (1.27 to 3.35)
Postoperative complications	24/227 (11%)	22/233 (9%)	0.89 (0.52 to 1.55)
ICU length of stay (median days)	1 (0-3)	2 (0-3)	-
Hospital length of stay (median days, IQR)	9 (5-14)	9 (7-14)	-
Days alive and out of hospital within 30 days (mean, SD)	19.8 (7.5)	19.7 (7.0)	-0.1 (-1.5 to 1.2)
Any hospital readmission from discharge to:			
- 8 weeks	51/234 (22%)	31/234 (13%)	0.61 (0.40 to 0.91)
- 6 months	73/223 (32%)	58/227 (26%)	0.78 (0.58 to 1.04)
Safety outcome: adverse reaction to trial therapy	5/240 (2%)	11/240 (5%)	2.20 (0.78 to 6.24)

Table 1. Outcomes from the PREVENTT trial

ICU, Intensive care unit; IQR, Interquartile range; SD, Standard deviation

Box 1

BOX 1: EVIDENCE BOX

- **Study design:** Double-blind, parallel-group randomised controlled trial
- **Study dates:** Jan 6, 2014, to Sept 28, 2018
- **Location:** United Kingdom, 46 tertiary care centres
- **Setting:** Elective, major open abdominal surgery
- **No. Of patients:** 487 randomised (474 intention to treat analysis, 388 per-protocol analysis)
- **Demographics**
 - Median age 66 years; Female 267/487 (54.8%); predominantly American Society of Anesthesiologists grade II (288/472 (61.0%)) and III ((121/472 (25.6%))
- **Inclusion criteria**
 - Age >18 years, Anaemia defined as haemoglobin <130 g/L for men and <120 g/L for women, major surgery lasting >1 hour coded major, major plus or complex major, no specific requirement for preoperative iron deficiency
- **Exclusion criteria**
 - Laparoscopic surgery, bodyweight <50kg, chronic liver disease, concurrent infection, other cause for anaemia, acquired iron overload, family history haemochromatosis or thalassaemia, transferrin saturation >50%
- **Comparison:** Single 1000 mg dose of ferric carboxymaltose in 100 mL 0.9% saline versus blinded placebo (100 mL 0.9% saline).
- **Co-primary outcomes:**
 - Risk of the composite endpoint of blood transfusion or death, and number of blood transfusion episodes (≥1 red blood cell unit or any other blood component in a 24hr period) from randomisation until 30 days after the index operation
- **Secondary outcomes:**
 - total number blood components transfused at 30 days and 6 months after surgery, change in haemoglobin concentration from randomisation to day of the index operation and at 8 weeks and 6 months after surgery, postoperative complications, intensive care unit and total hospital length of stay, days alive and out of the hospital at 30 days after the index operation, hospital readmission at 8 weeks and 6 months postoperatively, and health-related quality of life