Preoperative intravenous iron for anaemia in elective major open abdominal surgery: the PREVENTT RCT

Toby Richards,[1,2,3*] Ravishankar Rao Baikady,[4] Ben Clevenger,[3,11] Anna Butcher,[3] Sandy Abeysiri,[2,3] Marisa Chau,[2,3] Rebecca Swinson,[5] Tim Collier,[5] Matthew Dodd,[5] Laura Van Dyck,[5] Iain Macdougall,[6] Gavin Murphy,[7] John Browne,[8] Andrew Bradbury[9] and Andrew Klein[10]

[1]Division of Surgery, University of Western Australia, Perth, WA, Australia
[2]Institute of Clinical Trial and Methodology, University College London, London, UK
[3]Division of Surgery, University College London, London, UK
[4]The Royal Marsden NHS Foundation Trust, London, UK
[5]Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK
[6]Department of Renal Medicine, King's College Hospital, London, UK
[7]NIHR Leicester Biomedical Research Centre, Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
[8]School of Public Health, University College Cork, Cork, Ireland
[9]University Department of Vascular Surgery (University of Birmingham), Solihull Hospital, Solihull, UK
[10]Department of Anaesthesia and Intensive Care, Royal Papworth Hospital, Cambridge, UK
[11]Department of Anaesthesia, Royal National Orthopaedic Hospital, Stanmore, UK

*Corresponding author toby.richards@uwa.edu.au

Declared competing interests of authors: Andrew Klein reports grants and personal fees from Pharmacosmos A/S (Holbaek, Denmark) and Fisher and Paykel (Auckland, New Zealand), personal fees from Vifor Pharma (Glattbrugg, Switzerland) and Masimo (Irvine, CA, USA), and grants from Haemonetics® (Braintree, MA, USA) and HemoSonics (Charlottesville, VA, USA) outside the submitted work. Iain Macdougall reports grants and personal fees from Vifor Pharma outside the submitted work. Ravishankar Rao Baikady reports grants and other support from Pharmacosmos UK (Reading, UK), Vifor Pharma, Novo Nordisk A/S (Bagsværd, Denmark) and Fresenius Kabi (Bad Homburg, Germany) outside the submitted work. Gavin Murphy reports grants from Zimmer Biomet (Warsaw, IN, USA) and other from Terumo Corporation (Tokyo, Japan) outside the submitted work, and is part of Clinical Trials Units (CTUs) funded by the National Institute for Health Research (NIHR) CTU Standing Advisory Committee. Toby Richards reports grants from NIHR Health Technology Assessment (HTA) during the conduct of the study, grants, personal fees and non-financial support from Pharmocosmos and Vifor Pharma, and personal fees from Tiash Ltd (Republic of Singapore) outside the submitted work. Sandy Abeysiri reports grants from NIHR HTA during the conduct of the study and has been working on PREVENTT as part of her PhD at University College London. She has also worked at

The Iron Clinic (London, UK), which provides intravenous iron therapy. Andrew Bradbury reports membership of the NIHR HTA Interventional Procedures Panel, NIHR HTA Prioritisation Group, NIHR HTA Remit and Competitiveness Committee and NIHR HTA Hospital Based Care Methods Group (2014–2020).

Published February 2021
DOI: 10.3310/hta25110

Scientific summary

The PREVENTT RCT

Health Technology Assessment 2021; Vol. 25: No. 11
DOI: 10.3310/hta25110

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Preoperative anaemia is common in patients undergoing major surgery and increases the need for perioperative blood transfusion. There are now well-recognised associations between preoperative anaemia and increased patient postoperative complications, length of hospital stay and worse overall patient outcomes. These may be compounded by the need for blood transfusion at operation, as patients receiving a blood transfusion have similarly been associated with increased complications and adverse clinical outcomes.

Iron deficiency is aetiologically the most common cause of anaemia in the setting of surgery. Iron deficiency can develop directly from blood loss, due to the underlying disease for which the patient is having surgery (e.g. gastrointestinal cancer) or indirectly due to inflammation from the disease process or secondary to patient comorbidities. In the preoperative setting, oral iron has a limited role, as there is little time before the operation to replenish iron stores, and oral iron can be ineffective because of the presence of inflammation that impairs iron absorption and iron transport.

The NHS England Commissioning for Quality and Innovation (CQUIN) scheme for 2020–21 set targets for patients undergoing surgery with an expected blood loss of $\geq$ 500 ml to be screened for anaemia at least 2 weeks prior to surgery, and treatment recommended with iron therapy. However, this was based on the National Institute for Health and Care Excellence Guideline 24, which reported only 'very low quality of evidence' [National Institute for Health and Care Excellence (NICE). *Blood Transfusion. NICE Guideline (NG24)*. 2015. URL: www.nice.org.uk/guidance/ng24 (accessed 1 April 2020)].

Therefore, it is important to assess whether or not intravenous iron given, in the preoperative setting, to patients with anaemia can correct the anaemia and, furthermore, whether or not this reduces the clinical risk of preoperative anaemia on associated outcomes such as blood transfusion, postoperative outcomes and complications, as well as patient quality of life.

Aim

To assess if intravenous iron given to patients with anaemia before major surgery reduces the need for perioperative blood transfusion or the risk of death and improves the patient's recovery from their operation.

Primary objective

To determine if a single dose of intravenous iron given to patients with anaemia prior to major open abdominal surgery reduces the need for blood transfusion or the risk of death, in the period from randomisation until 30 days following the operation. Thus, the co-primary end points were the risk of blood transfusions or death, and the number of blood transfusions from randomisation to 30 days post operation.

Secondary objectives

- To evaluate the effect of intravenous iron compared with placebo on change in haemoglobin levels.
- To evaluate the effect of intravenous iron compared with placebo on postoperative morbidity, intensive care unit and total hospital length of stay, hospital re-admission and mortality.
- To evaluate the effect of intravenous iron compared with placebo on health-related quality of life.
- To evaluate resource use and costs associated with the treatment with intravenous iron compared with placebo.
- To evaluate the tolerability and safety of intravenous iron compared with placebo from randomisation until study termination.
- To evaluate the effect of intravenous iron compared with placebo on:
    - complications of the intervention itself
    - complications from blood transfusion or blood products.

Methods

The preoperative intravenous iron to treat anaemia in major surgery (PREVENTT) trial was a randomised, double-blind, parallel-group, placebo-controlled, multicentre, Phase III study comparing placebo (normal saline) with intravenous iron (intravenous ferric carboxymaltose 1000 mg). Adult patients who were planning to undergo major elective open abdominal surgery were included if they were found to have anaemia (haemoglobin < 130 g/l for men and haemoglobin < 120 g/l for women) and could be randomised and receive the intervention 10–42 days before their planned operation date.

Exclusions were those patients who were not anaemic or who were undergoing keyhole or laparoscopic surgery. Other exclusions were those with a known history of acquired iron overload, family history of haemochromatosis or thalassaemia or transferrin saturation > 50%, known cause of anaemia (other than iron deficiency), known chronic liver disease, concurrent infection or body weight < 50 kg.

Protocol changes included removing an additional hospital visit for preoperative assessment, reducing the timeline to surgery from 14 days to 10 days, revising the description for major surgery and adjusting the diagnosis of anaemia in line with World Health Organization definitions.

Following informed consent, patients were randomised 1 : 1 in a double-blind manner to either intravenous iron therapy or placebo. As iron is a dark-brown liquid, both the iron therapy and the placebo were administered in a covered saline bag through black opaque tubing so that the patient was blinded to the intervention. Similarly, the staff involved in the infusion were not part of the reporting team. All subsequent operations and patient and trial assessments were undertaken by staff blinded to the intervention.

Results

PREVENTT was conducted across 46 hospitals in England, Scotland and Wales between September 2013 and September 2018. A total of 487 patients were randomised (243 given placebo and 244 given intravenous iron). At randomisation, haemoglobin levels were well balanced between the placebo and intravenous iron groups. Time from administration of the intervention to the day of surgery was similar in the two groups, with the median (interquartile range) being 14 (12 to 20.5) days and 15 (12 to 22) days in the placebo and intravenous iron groups, respectively.

At the time of surgery, mean (standard deviation) haemoglobin was significantly higher in the intravenous iron group than in the placebo group [113.5 (13.2) g/l compared with 108.2 (13.2) g/l; mean difference 4.7 g/l, 95% confidence interval 2.7 to 6.8 g/l; $p < 0.0001$]. Anaemia was corrected in 42 (21%) patients in the intervention group compared with 21 (10.2%) patients in the placebo group ($p = 0.002$). There was an even distribution of operations performed through gynaecology, upper gastrointestinal, colorectal, hepatobiliary and pancreatic, urological and general surgery with a median (interquartile range) total procedure time of 250 minutes (175 to 355 minutes) and the median (interquartile range) total hospital length of stay was 9 days (6 to 14 days).

The co-primary end point of blood transfusion or death from randomisation to 30 days following index operation was reached in 136 patients. There was no difference in the risk of transfusion or death at 30 days between those who received preoperative intravenous iron and those who received placebo (69/243 vs. 67/244; risk ratio 1.03, 95% confidence interval 0.78 to 1.37; $p = 0.84$). There was no difference in rate of blood transfusion between those who received preoperative intravenous iron and those who received placebo (rate ratio 0.98, 95% confidence interval 0.68 to 1.43; $p = 0.93$; absolute rate difference 0.00, 95% confidence interval −0.14 to 0.15).

There was no difference between the groups in postoperative complications, with 24 out of 237 patients in the placebo group and 22 out of 237 patients in the treatment group experiencing significant postoperative complications. Similarly, there was no difference in length of intensive care unit or hospital stay.

Haemoglobin levels were significantly higher in the intravenous iron group at 8 weeks (mean difference 10.7 g/l, 95% confidence interval 7.8 to 13.7 g/l; $p < 0.0001$) and at 6 months (mean difference 7.3 g/l, 95% confidence interval 3.6 to 11.1 g/l; $p < 0.001$). There was a reduction in the number of patients re-admitted to hospital for postoperative complications in the intravenous iron group at 8 weeks [51/234 (22%) vs. 31/234 (13%), risk ratio 0.61, 95% confidence interval 0.40 to 0.91; $p = 0.015$). However, there were no significant between-group differences in health-related quality of life, fatigue or overall condition improvement at any time point up to the 6-month assessment.

Conclusions

In patients undergoing major open abdominal surgery, intravenous iron was not superior to placebo in the preoperative period in reducing the need for blood transfusion. There was no difference seen in patient postoperative complications or hospital stay. However, there was an associated reduced re-admission rate to hospital with postoperative complication seen in those patients who received intravenous iron.

Trial registration

This trial is registered as ISRCTN67322816 and ClinicalTrials.gov NCT01692418.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 11. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/104/06. The contractual start date was in September 2012. The draft report began editorial review in November 2019 and was accepted for publication in July 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).