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Intravenous iron administered to anaemic patients before surgery and hospital readmission in the PREVENTT study: one answer, a potentially important health benefit, and new questions

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In recent observational studies encompassing thousands of surgical patients, the prevalence of preoperative anaemia varied between 10% and 50%,[1] and was associated with increased morbidity and mortality. Trials investigating more liberal allogeneic red blood cell (RBC) transfusion to reverse anaemia have failed to demonstrate substantial clinical benefits.[2] In this respect, an increasing number of guidelines recommend that patients undergoing major surgery should be screened for anaemia and treated preoperatively to improve erythropoiesis. In patients with iron-deficiency anaemia, iron substitution would ideally reduce the allogeneic blood transfusion rate and side-effects associated with blood transfusion including fluid overload, infection, and transfusion errors.

From a practical point of view, patients undergoing surgical procedures with expected blood loss >500 ml or a ≥10% probability of RBC transfusion should be screened for anaemia.[2–4] Early treatment of anaemia using an easy-to-follow diagnostic algorithm is desirable.[5] Intravenous iron is efficacious, safe[6] and should be used in patients in whom oral iron is not tolerated, or if surgery is planned within 4–6 weeks after the diagnosis of iron deficiency (anaemia).

Only a few well-designed, adequately powered RCTs assessing the effect of i.v. iron to treat anaemia in patients undergoing abdominal surgery are available. Froessler and colleagues[7] randomised 72 patients with iron-deficiency anaemia undergoing major abdominal surgery to receive either i.v. iron or usual care. Administration of perioperative i.v. iron reduced the need for allogeneic blood transfusion by 60% (31.2% *vs* 12.5%), was associated with a shorter hospital stay (9.7 *vs* 7.0 days), enhanced restoration of iron stores, and resulted in a higher increase of mean haemoglobin concentrations 4 weeks after surgery (0.9 *vs* 1.9 g dl^{-1}).

To evaluate further the clinical effectiveness of i.v. iron therapy (ferric carboxymaltose, 1000 mg) *vs* placebo (saline) in anaemic patients undergoing major open elective abdominal surgery, Richards and colleagues[8] conducted the double-blind, parallel-group, placebo-controlled, randomised PREVENTT trial at 46 centres in the UK.

Co-primary endpoints were the rate of blood transfusion or death and the number of blood transfusions from randomisation to 30 days postoperatively. Among 487 participants randomised between January 2014 and September 2018, death or blood transfusion occurred in 67/243 subjects in the placebo group (28.3%) and 69/244 subjects in the i.v. iron group (29.1%). Death (1% *vs* 1%), postoperative complications (11% *vs* 9%), hospital stay, or days alive and out of the hospital at 30 days did not differ among groups. However, both haemoglobin concentrations at the time of surgery and postoperative haemoglobin concentrations were higher in the i.v. iron treatment group, and may have led to improved postoperative recovery.

Interestingly, hospital readmissions within 8 weeks after surgery were significantly lower in the i.v. iron group (22% *vs* 13%), as these patients had fewer wound infections. These effects merit further investigation, and future studies investigating i.v. iron should also focus on the quality of patient recovery after surgery.

Importantly, PREVENTT has several strengths, including allocation concealment, double-blinding, placebo control, high levels of adherence to the trial intervention, high number of follow-ups, and low levels of attrition. There was no difference between the results of the per-protocol and intention-to treat analyses or between the predefined subgroups, suggesting that non-adherence with other components of the protocol was unlikely to have influenced the trial result. In addition, the median time from randomisation to surgery was 14 and 15 days, respectively, and the two groups were well balanced in terms of surgical complexity, with the most common operations being upper gastrointestinal (34%), gynaecologic (30%), and colorectal (15%).

There are several issues to be discussed, however. First, preoperative anaemia was corrected in 42 (21%) of 244 subjects in the i.v. iron group. Consequently, about 80% of included anaemic subjects in the intervention group still suffered from anaemia with all the associated risks at time of surgery. This aspect emphasises the high medical need for preoperative anaemia management. Haemoglobin concentrations can be increased most effectively when treatment is initiated early. Whenever possible, elective surgery should be postponed until preoperative anaemia has been appropriately classified and treated.[9] The i.v. iron group had significantly higher haemoglobin concentrations at 8 weeks (mean difference 10.7 g L^{-1}, 95% confidence level 7.8–13.7) and at 6 months after intervention (mean difference 7.3 g L^{-1}, 3.6–11.1). In this respect, a median time from intervention to surgery of 15 (inter-quartile range 12–22) days might preclude a maximum effect of i.v. iron.[10–13] Although details about the exact mechanistic basis are less known, longer time for treatment may be required based on recent clinical trials suggesting a time-dependent effect.[10–13] A short time frame between treatment and surgery could be counterbalanced with increasing iron dose or combining haematinics.

Spahn and colleagues[14] recently reported beneficial effects of ultra-short-term combination treatment with ferric carboxymaltose, erythropoietin alpha, vitamin B_{12}, and folic acid in 505 patients with anaemia or isolated iron deficiency undergoing elective cardiac surgery. The combination treatment significantly reduced RBC transfusions from a median of one unit in the placebo group (inter-quartile range 0–3) to zero units in the treatment group (0–2) during the first 7 postoperative days. Despite fewer RBC units transfused, subjects in the treatment group had a higher haemoglobin concentration, higher reticulocyte count, and higher reticulocyte haemoglobin content.

Second, preoperative iron deficiency was not defined as an inclusion criterion to facilitate feasibility of patient recruitment, but resulted in the recruitment of non-informative patients which might dilute the beneficial effects. There might be a correlation between iron deficiency level and biological response after i.v. iron substitution.[15] However, if your only tool is a hammer, everything starts to look like a nail. In this respect, patients with non-iron deficiency anaemia probably benefit less from i.v. iron substitution. Furthermore, in patients with severe iron deficiency or higher body weight, the standard iron dose of 1000 mg might reasonably be too low for a complete biological response and haemoglobin recovery.[15]

Third, primary and secondary endpoints refer to blood transfusion. However, the amount, dose, and rate of RBC transfusions vary between physicians and hospitals, even within clinical trials. Guidelines recommend different RBC transfusion triggers, and the individual indication also takes into account individual risk factors.[16] Furthermore, dosing of RBC units is reasonably crude with large steps from 0 to 1 or 2 units, thereby transfusing a full unit of RBC concentrate although a half unit might have been enough in an individual patient. Optimal clinical endpoints should have a continuous scale to discriminate between groups and to analyse effectiveness. Using the number of RBC units with a four-point scale (0, 1, 2, or more units) reasonably limits informative power and increases the risk of a masking effect. If most transfused study subjects would have received a liberal transfusion regime irrespective of group assignment, finding a group difference in RBC units would be very hard, particularly with regard to unknown haemoglobin triggers, the high number of patients with only mild anaemia, and the unknown amount of blood loss. Such underlying biases and changes in practice patterns may be even more important with respect to the 5-year recruitment period for the 487 patients randomised at 46 sites. In line with this statement, it is surprising that despite an overall significant biological response (increase in haemoglobin concentration as a result of the intervention), the effect did not correlate with indicators of iron depletion as indicated by transferrin saturation.

Fourth, in view of the planned secondary outcome measures (http://www.isrctn.com/ISRCTN67322816) in the health economics domain (health resource utilisation at each assessment time point; calculated direct, indirect, and total costs for the NHS; cost-effectiveness of treatment options using relevant effectiveness parameters), the reported absolute differences of the readmission rates of 9% at 8 weeks after surgery may turn out as a net benefit dependent on the resources allocated to the intervention. The observed absolute risk difference of 9% yields a number-needed-to-treat of only 11 for ferric carboxymaltose 1000 mg given to an unselected cohort of patients (without proper iron-deficiency diagnostics) to prevent one unplanned hospital admission.

We congratulate the authors for providing another piece of evidence with respect to improving perioperative outcomes of surgical patients, but would slightly modify the conclusion in terms of the clinical bottom line: PREVENTT showed that a standard dose of i.v. iron (1000 mg) given shortly before elective major abdominal surgery to a cohort of anaemic patients without diagnosis of iron deficiency may not reduce blood transfusion rates, but may have beneficial effects in the postoperative period leading to a clinically relevant reduction in readmission rates.

Finally, preoperative anaemia management is only one pillar of a multimodal concept to reduce and avoid unnecessary blood loss and to focus on the rational handling of blood components known as patient blood management. Successful implementation of a single pillar intervention, however, might be compromised if surgery is

scheduled short-term or if hospitals do not have the necessary resources. Patient blood management is most successful when multiple interventions are combined. We propose that clinicians and policy makers concentrate their efforts on adoption of a multi-pillar framework, to promote a step-by-step implementation of further patient blood management measures that fit best the individual conditions. Based on the possibilities to strengthen and preserve patients' own blood resources and to enable safe handling of donor blood, the World Health Assembly endorsed patient blood management in 2010 (WHA63.12).[17] Patient blood management in clinical practice follows three main pillars: (1) comprehensive preoperative anaemia management; (2) minimisation of iatrogenic (unnecessary) blood loss; and (3) harnessing and optimising patient-specific physiological tolerance to anaemia.[18] Importantly, a comprehensive patient blood management program addressing all three pillars reduces transfusion need of RBC units and decreases complication and mortality rates, thereby improving clinical outcome.[19]

Authors' contributions

Drafted, wrote, and approved the manuscript: PM, DB, PK

Declarations of interest

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