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Special Article

The PREVENNT randomised, double-blind, controlled trial of preoperative intravenous iron to treat anaemia before major abdominal surgery: an independent discussion

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Abstract

Anaemia is a common finding in patients presenting for major elective surgery and is associated with poor outcomes including death and complications. Iron deficiency is the leading cause of perioperative anaemia. Intravenous (i.v.) iron is considered to be an effective and safe treatment for iron deficiency anaemia and is recommended by expert opinion for treatment of preoperative anaemia, although evidence from clinical trials is lacking. The PREVENTT trial was a large multicentre trial investigating the effects of i.v. iron on red cell transfusion, death, complications and quality of life in 487 patients undergoing major abdominal surgery. The principal finding of this multicentre randomised placebo controlled trial was that there was no difference in the co-primary outcomes of blood transfusion or death, or the number of transfusion episodes, within 30 days after surgery, in patients that received preoperative i.v. iron therapy compared to placebo. The major inferential differences in this independent discussion relate to the limitations of the PREVENTT trial and its implications for future practice. Although PREVENTT represents the best evidence available to guide perioperative use of i.v. iron, it is likely that the study was underpowered. In the context of already widespread adoption of preoperative i.v. iron therapy, many clinicians may have felt they lacked equipoise. In light of the PREVENTT study routine use of i.v. iron in patients undergoing elective abdominal surgery cannot be recommended. Further research should define the optimum red cell transfusion strategy for patients undergoing surgery and idenify other surgical groups who may benefit from this intervention.

Keywords: anaemia; blood transfusion; independent discussion; inferential reproducibility; iron; red cells; surgery

Editor's key points

- Intravenous (i.v.) iron is recommended for treatment of preoperative anaemia, although evidence from clinical trials is lacking.
- The PREVENTT trial is the largest multicentre trial investigating the effects of i.v. iron in patients undergoing major abdominal surgery.
- There was no difference in the co-primary outcomes of blood transfusion or death, or the number of transfusion episodes, within 30 days after surgery, with preoperative i.v. iron therapy compared to placebo.
- Routine use of preoperative i.v. Iron in elective abdominal surgery cannot currently be recommended.

Anaemia is a common finding in patients presenting for major elective surgery and is associated with a range of poor outcomes, including death, postoperative complications, and increased duration of hospitalisation.[1] Iron deficiency is the leading cause of anaemia and may be caused by nutritional

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factors, impaired absorption, or chronic blood loss associated with underlying disease.[2,3]

The causal relationship between anaemia and poor outcomes remains unclear, and anaemia may simply reflect other comorbidities or severity of underlying disease. Despite the association between anaemia and poor outcomes, guidance supports restrictive transfusion practice. Blood transfusion may be associated with increased risk of infection, tumour recurrence, fluid overload, or transfusion reactions. Patient blood management (PBM) approaches focus on the early detection and treatment of preoperative anaemia with the aim of reducing the requirement for blood transfusion, improving patient outcomes.[4]

Intravenous iron is considered to be an effective and safe treatment for iron deficiency anaemia and is recommended by expert opinion for treatment of preoperative anaemia in patients where oral iron is not tolerated or is ineffective, or where there is insufficient time for treatment with oral iron before surgery.[5] Intravenous iron has widespread recommendation in PBM guidelines, although there is minimal high-quality evidence to support this. The Preoperative Intravenous Iron to Treat Anaemia in Major Surgery (PREVENTT) trial was a large multicentre trial investigating the effects of i.v. iron on red cell transfusion, death, complications, and quality of life in patients undergoing major abdominal surgery.[6]

Main finding

Original discussion

The use of i.v. iron in patients with anaemia before major open elective abdominal surgery increased haemoglobin concentrations before surgery, but did not reduce the frequency of blood transfusion or mortality in the perioperative period relative to placebo.

Independent discussion

The principal finding of this multicentre randomised placebo controlled trial was that there was no difference in the co-primary outcomes of blood transfusion or death, or the number of transfusion episodes, within 30 days after surgery, in patients that received preoperative i.v. iron therapy compared with placebo.[6] The incidence of blood transfusion or death was 67/237 (28.3%) in the i.v. iron group and 69/237 (29.1%) in the placebo group. The mean (standard deviation) number of transfusion episodes was 0.47 (0.9) in the i.v. iron group compared with 0.44 (0.9) in the placebo group. There were no differences in the secondary or safety outcomes between treatment groups, and there was no effect in any of the prespecified subgroup analyses. The results of this trial do not support the routine use of preoperative i.v. iron therapy in clinical practice.

Commentary

The original and independent discussions agree on the principal findings of this trial: administration of i.v. iron therapy did not reduce a composite outcome of transfusion or death when compared with placebo. Although i.v. iron therapy appears to be safe, this trial does not support its routine use in the treatment of preoperative anaemia in major abdominal surgery.

Relationship of main finding to previous studies

Original discussion

The PREVENTT trial reduces the uncertainty created by two previous small trials on the use of preoperative i.v. iron. The Intravenous Iron in Colorectal Cancer Associated Anaemia (IVICA) trial from Nottingham, UK looked at 116 patients with anaemia undergoing colorectal cancer surgery and found that i.v. iron had no effect on blood transfusion use, whereas a smaller trial of 72 patients in Australia found that i.v. iron for patients with iron-deficiency anaemia (ferritin <300 $\mu g\ L^{-1}$; transferrin saturation <25%) did reduce perioperative blood transfusion (12% *vs* 31%). The PREVENTT trial suggests that preoperative i.v. iron has no significant effect on blood transfusion use in all patients with anaemia before major surgery.

Independent discussion

The relationship between preoperative anaemia and increased risk of postoperative morbidity and mortality is well described.[1] However, there is limited evidence to support clinical strategies to increase haemoglobin concentration and consequently improve perioperative clinical outcomes. Amongst cardiac surgical patients, a meta-analysis of 8886 patients found that a liberal red cell transfusion strategy did not reduce mortality or morbidity (pulmonary, cardiac, infective, renal, or cerebrovascular complications) compared with a restrictive strategy.[7] However, in noncardiac surgery patients, a meta-analysis of 7552 patients from 17 randomised trials suggested that a liberal transfusion strategy was associated with lower mortality compared with a restrictive strategy.[8] Amongst patients undergoing hip fracture repair, a liberal transfusion strategy was associated with increased risk of stroke, whilst a restrictive strategy was associated with higher risk of acute coronary syndrome.[9] As patients with preoperative anaemia are more likely to receive perioperative red cell transfusion, it seems intuitive that increasing the preoperative haemoglobin concentration would reduce the incidence of blood transfusion.[1] In a meta-analysis of eight studies (two randomised trials and six observational studies), including 812 patients undergoing noncardiac surgery, the rate of transfusion was lower amongst patients that received i.v. iron.[10] However, this was evident only amongst observational studies and randomised trials, suggesting the positive result may be influenced by bias.[11,12] A similar story is seen in cardiac surgery, where a meta-analysis of pooled data from four randomised trials suggests that preoperative i.v. iron therapy does not reduce the incidence of mortality, hospital length of stay, or renal injury, but there was a reduction in the rate of blood transfusion. The results of the PREVENTT trial support evidence from previous small trials that preoperative i.v. iron therapy does not reduce perioperative red cell transfusion amongst patients undergoing noncardiac surgery.[11–13] This calls into question the increasingly common practice of preoperative iron infusion for patients with anaemia, which has crept into perioperative practice with only very limited supporting evidence. Patient blood management strategies to reduce the need for allogenic red cell transfusion are very important, but clinicians should carefully

consider whether to continue offering preoperative iron infusions for patients with anaemia.[14]

Commentary

Perioperative anaemia is common, and the practice of i.v. iron administration before elective surgery has been adopted widely despite limited evidence to support its use. Both the original discussion and independent discussion agree that until the PREVENTT trial, i.v. iron has only been investigated in small randomised trials with conflicting results. Red cell transfusion is the most commonly studied clinical outcome in trials of i.v. iron, but the optimal red cell transfusion strategy is not defined in the surgical population, particularly if there is coexisting cardiac disease. Systematic reviews of clinical trials suggest that in noncardiac surgery, restrictive strategies may be associated with increased risk of death or myocardial infarction. Whilst more research is required to resolve the controversy surrounding perioperative red cell transfusion threshold, the findings from PREVENTT suggest not only that i.v. iron administration does not influence the requirement for red cell transfusion, but that like liberal red cell transfusion, another strategy aimed at increasing haemoglobin in the perioperative period has not translated to clinical benefit for patients.

Additional (secondary) findings and relationship to other studies

Original discussion

There was no reduction in the risk of postoperative in-hospital complications or length of hospital stay, and no benefits to quality of life. However, there was a reduced risk of readmission to a hospital for complications in those patients who received i.v. iron.

Independent discussion

In the PREVENTT trial, patients who received i.v. iron therapy had higher mean haemoglobin concentrations compared with placebo, an effect that lasted for at least 6 months.[15] This supports previous trials that have demonstrated the efficacy of i.v. iron therapy to treat iron-deficiency anaemia. The outcomes of patients with i.v. iron were not significantly different from patients treated with placebo in almost all domains. Patients treated with i.v. iron were less likely to be readmitted to a hospital within 8 weeks after their surgical procedures. However, this did not persist up to 6 months after surgery and may represent a chance finding. Importantly, the incidence of serious adverse events and serious unexpected adverse reactions was similar in each treatment group, with only 4.6% of patients experiencing some form of reaction to i.v. iron therapy. This suggests that i.v. iron is generally a safe therapy.

Commentary

The independent discussion highlights that in the PREVENTT trial, participants treated with i.v. iron had higher haemoglobin concentrations at 6 months and that the incidence of adverse reactions was similar between groups. This would suggest that i.v. iron is a safe and effective treatment for iron-deficiency anaemia. Intravenous iron did not, however, reduce postoperative complications, duration of hospitalisation, or quality of life. Those treated with i.v. iron were significantly less likely to be readmitted to a hospital within the first 8 weeks after surgery. The reasons for this are unclear and appear to be as a result of what the authors define as surgical complications. It is possible that this could represent a chance finding, as it is difficult to link anaemia and surgical complications with a biologically plausible hypothesis. Aside from this, there were no differences between groups in any of the other secondary outcome domains.

Strengths

Original discussion

The trial has several strengths, including allocation concealment, double blinding, placebo control, high levels of adherence to the trial intervention (481/487), and low levels of attrition, with 474 of 487 participants providing data for the primary intention-to-treat analyses. 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. The study included patients with a range of anaemia profiles, including mild anaemia. These strengths, along with the broad inclusion criteria, clear documentation of process, and absence of effectiveness across a range of primary and secondary outcomes, support the validity and generalisability of the trial results.

Independent discussion

This multicentre, randomised, placebo-controlled trial has several strengths. First, the use of a placebo addresses limitations of previous trials, which have often compared i.v. iron with either oral iron supplementation or standard clinical care, risking the introduction of bias. Second, the multicentre design makes the results of this trial widely generalisable to the majority of patients undergoing major noncardiac surgery. Third, the co-primary outcomes of allogenic red cell transfusion or death and number of units of red cells transfused are clinically relevant outcomes. That there is no difference in these outcomes between the treatment groups is an important, potentially practice-changing result.

Commentary

Optimal use of i.v. iron is an important clinical question regarding an intervention in widespread use with low-quality evidence to support it. A large, pragmatic, multicentre, placebo-controlled trial with clinically relevant endpoints was required, and PREVENTT has the validity needed to answer this question. The vast majority of the patients enrolled in the trial received the study intervention. The broad inclusion criteria mirrored the population likely to receive the intervention and widely generalisable to clinical practice. The study results will change clinical practice in patients with anaemia undergoing noncardiac surgery, and allow resources to be prioritised into other more effective treatments for patients undergoing surgery.

Limitations

Original discussion

One limitation was that preoperative iron deficiency was not defined as an inclusion criterion, although a predefined subgroup analysis was performed for those patients with ferritin <100 ng ml^{-1} and transferrin saturations <20% in line with current guidelines for preoperative iron deficiency, 14 of whom 57% had ferritin <100 ng ml^{-1} and 76% had transferrin saturations <20% at inclusion and randomisation to the trial. There was no evidence of interaction between treatments in these predefined subgroups for the co-primary endpoints of the study.

Independent discussion

This trial also has limitations. First, patient recruitment (n=487) did not meet the target sample size (n=500) and the rate of blood transfusion (29.1%) is less than the expected 40% used in the sample size calculation. Whilst it is possible that the trial is statistically underpowered, this is unlikely to make a difference in the interpretation of the primary analysis. Second, because of the complex pathway for patients undergoing surgery, the care of one in five participants deviated from the trial protocol. Whilst this is not unexpected for trials of complex intervention amongst surgical patients, it is possible that this may have introduced bias and reduced the magnitude of any differences between groups. Third, as a result of the requirement for a preoperative clinic visit for the iron infusion, patients requiring urgent surgery may not have been enrolled in the trial because of concerns about actual or perceived delays in care. Therefore, it is possible that the sample may not represent patients with very severe surgical disease that may have benefitted the most from i.v. iron therapy.

Commentary

The independent discussion identifies several notable limitations not highlighted in the original discussion. Most importantly, the study is likely to be underpowered, as it did not meet the predefined sample size and the incidence of red cell transfusion was considerably less than the estimate used to power the study. Bias may also have arisen from a large number of protocol deviations. Finally, concerns about delays in definitive treatment for more urgent patients, who would require additional clinic visits to receive the intervention with the potential to delay definitive treatment, may have excluded patients with more severe disease.

Directions for future research

Original discussion

Our findings have several important clinical implications. The treatment effect on mean haemoglobin values was higher after surgery than in the preoperative setting, despite no differences in type of surgery, bleeding, or transfusion volumes between the groups. The effect of preoperative i.v. iron and increased postoperative haemoglobin levels associated with reduced readmission to a hospital for surgical complications merits further investigation. This may reflect an underlying mechanism of functional or absolute iron deficiency and anaemia of chronic disease with inflammation, and subsequent stimulus of blood loss at operation. Clinically, this raises the possibility that postoperative i.v. iron, before discharge from a hospital, may be effective at boosting haemoglobin levels in surgical patients during their recovery period. Postoperative i.v. iron would be easier and less expensive than i.v. iron preoperatively because the patient would already be in the hospital, being nursed and monitored in a hospital bed, and likely has venous access *in situ*. This approach is unlikely, however, to be any more effective than preoperative i.v. iron in accruing benefits to the primary outcomes measured in our trial. Our findings are consistent with the existing evidence on iron therapy in noncardiac patients. Trials of interventions to reverse anaemia, either with iron therapy or more liberal transfusion thresholds, have failed to demonstrate important clinical benefits, despite observational evidence that anaemia is associated with poorer outcomes. This implies that treatments directed to the underlying causes of anaemia may be required to improve outcomes in this high-risk population.

Independent discussion

There is a clear and persistent increase in haemoglobin concentration in patients that received i.v. iron. However, the clinical significance of this finding is uncertain and could be explored to determine whether there is a long-term health benefit in excess of the follow-up period of the PREVENTT trial. Whilst there was no effect of preoperative i.v. iron therapy on perioperative allogenic blood transfusion or mortality, there was a reduction in hospital readmission within 8 weeks after surgery. The explanation for this is unclear and it may represent a chance finding, but this should be explored further. There is a clear relationship between preoperative anaemia and poor clinical outcomes after surgery. However, management strategies targeted at increasing haemoglobin levels, including perioperative blood transfusion, have shown variable and sometimes conflicting results. The optimum threshold of haemoglobin concentration to trigger perioperative blood transfusion after noncardiac surgery is uncertain and needs further study.

Commentary

There is a clear association between anaemia and poor outcomes after surgery. Intravenous iron is an effective treatment for iron deficiency anaemia, and in this study, its use leads to a sustained improvement in haemoglobin concentration. Whether i.v. iron use is associated with other long-term benefits is unknown. The optimum use of perioperative red cell transfusion is also unknown and requires further investigation. Whether particular surgical groups (e.g. cardiac surgery, orthopaedic surgery, or older surgical patients) may benefit from i.v. iron is the subject of ongoing clinical trials. The finding of reduced hospital readmission may also warrant further study.

Conclusion

Original discussion

In conclusion, PREVENTT showed that i.v. iron was not superior to placebo when administered to patients with anaemia 10–42 days before elective major abdominal surgery with respect to reducing blood transfusion or death in the perioperative period.

Independent discussion

Intravenous iron infusion was not associated with a reduction in perioperative allogeneic red cell transfusion or death within 30 days after surgery. These results do not support the routine use of preoperative i.v. iron infusion.

Commentary

The PREVENTT trial suggests that i.v. iron is a safe and effective treatment for perioperative anaemia; however, its use in patients with anaemia having major abdominal surgery did not reduce the incidence of red cell transfusion, death, or a range of other outcomes, including complications, hospitalisation, or quality of life. Routine use of i.v. iron in patients having noncardiac surgery cannot be recommended and should be reconsidered until further evidence is available.

Inferential reproducibility

The major inferential differences relate to some of the limitations of the PREVENTT trial and its position within the contextual landscape of PBM. Although PREVENTT represents the best evidence available to guide perioperative use of i.v. iron, it is likely that the study was underpowered and this is not acknowledged prominently in the original discussion. However, we acknowledge that in the context of already widespread adoption of preoperative i.v. iron therapy, this trial was likely very difficult to conduct, as many clinicians may have felt they lacked equipoise. More research is required to define the optimum red cell transfusion strategy for patients undergoing surgery. Finally, the original discussion does not consider that there may be other surgical groups (e.g. emergency or cardiac surgery) who may benefit from this intervention. Nonetheless, in most aspects, the independent and original discussions are in agreement, particularly in the interpretation of the study findings and their implications. This is an important study that should change clinical practice and reminds us of the pitfalls of implementing new therapies at scale before high-quality clinical evidence is available.

Authors' contributions

Writing of independent discussion: TEFA
Writing of commentary on discussions: MG
Both authors agreed with the article's results and conclusions, approved the final version of this article, and have read and confirm that they met the International Committee of Medical Journal Editors criteria for authorship.

Declarations of interest

TEFA is a member of the associate editorial board of the *British Journal of Anaesthesia*. MG is a Chief Scientist Office, Scotland NHS Research Scheme clinician.

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