

The IRONMAN trial: a protocol for a multicentre randomised placebo-controlled trial of intravenous iron in intensive care unit patients with anaemia

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Red blood cell (RBC) transfusion is common in critically ill patients in Australia and worldwide, with 17%–45% of all patients admitted to an intensive care unit, and more than 70% of those staying longer than 7 days, receiving one or more RBC units.^{1–3} Transfused critically ill patients receive a mean of four RBC units in the ICU, accounting for nearly 20% of all RBC transfusions in Australia.⁴

In a recent systematic review of observational studies, RBC transfusion in the critically ill was an independent predictor of death (pooled odds ratio, 1.7; 95% CI, 1.4–1.9), nosocomial infection, multiorgan dysfunction syndrome and acute respiratory distress syndrome.⁵ The blood supplies needed for allogeneic RBC transfusion are also an increasingly costly and scarce resource.⁶

Transfusion in the ICU remains common despite extremely high concordance with current restrictive transfusion guidelines.¹ More than 75% of RBC units transfused in the ICU are given for anaemia, rather than for major haemorrhage,^{1,2} and anaemia itself is also associated with adverse outcomes.⁷ There is therefore an unmet need for novel interventions that reduce the incidence of anaemia and subsequent transfusion.

Iron-restricted erythropoiesis is extremely common in patients who are critically ill and may occur through absolute iron deficiency, functional iron deficiency or iron sequestration.⁸ Enteral administration of iron is ineffective in critically ill patients due to gastrointestinal intolerance, decreased iron absorption from routine use of gastric acid suppression, physiological limits to maximal enteral iron absorption and inhibition of absorption due to high hepcidin levels that occur in critical illness.⁹ Intravenous (IV) administration of iron overcomes these disadvantages and has been shown to be superior to enteral iron for correcting iron-restricted erythropoiesis in a number of patient populations.^{10,11} The diagnosis and management of iron deficiency and suboptimal iron stores in the critically ill has been identified as an important evidence gap by the National Blood Authority.¹²

Iron is essential for bacterial growth, and exogenous iron is therefore associated with a theoretical increased risk of infection. However, most randomised controlled trials (RCTs) to date have not included infection as a prespecified end point, and the risk in critically ill patients remains

ABSTRACT

Background: Allogeneic red blood cell (RBC) transfusion is associated with significant increases in mortality and major morbidity in patients admitted to the intensive care unit, and the blood supplies it requires are an increasingly scarce and costly resource. Despite high levels of compliance with recommended transfusion thresholds in the ICU, RBC transfusion remains common. Novel interventions to reduce the incidence of RBC transfusion are required.

Objective: To describe the study protocol for a randomised controlled trial, the Intravenous Iron or Placebo for Anaemia in Intensive Care (IRONMAN) trial, comparing intravenous (IV) iron with placebo in patients who are admitted to an ICU and are anaemic.

Design, setting, participants and intervention: A Phase IIb multicentre, randomised, placebo-controlled trial. Patients admitted to the ICU with a haemoglobin (Hb) level < 100 g/L and predicted to require critical care beyond the next calendar day will be randomly assigned in a 1 : 1 ratio to receive IV ferric carboxymaltose (500 mg) or placebo.

Main outcome measures: The primary end point will be the mean number of RBC units transfused from study enrolment to discharge from hospital. Secondary end points will include change in Hb level and incidence of nosocomial infection.

Results and conclusions: The IRONMAN trial is designed to determine whether IV iron administered to patients admitted to an ICU and who are anaemic is associated with a reduction in RBC transfusion, compared with placebo in addition to standard care. The results of this trial may determine whether a Phase III trial of IV iron in ICUs is feasible.

Trial registration: Australian New Zealand Clinical Trials Registry (ACTRN12612001249842).

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uncertain.^{10,13} In an animal model of sepsis, IV iron improved haemoglobin (Hb) levels and was not associated with increased risk of death.¹⁴ An RCT by Pieracci et al of

Table 1. Trial end points**Primary outcome**

Mean number of red blood cell (RBC) units transfused from study enrolment to discharge from hospital

Secondary outcomes

Proportion of participants who receive RBC transfusion from enrolment to discharge from ICU

ICU and hospital mortality

Duration of admission to ICU and hospital

Organ-failure support-free days between enrolment and ICU discharge

Proportion of patients who develop nosocomial infection in the ICU, including all-cause incident infection, confirmed bloodstream infection and incident infection associated with new organ failure

Number of serious adverse events (SAEs) and proportion of patients who develop an SAE

Mean number of RBC units transfused and proportion of patients transfused from study enrolment to discharge from hospital adjusted for baseline haemoglobin (Hb) level, pre-enrolment transfusion, ferritin level, transferrin saturation, hepcidin level, soluble transferrin receptors and renal replacement therapy

Secondary outcomes in subgroups

Mean number of RBC units transfused and proportion of patients transfused from study enrolment to discharge from hospital in patients with baseline transferrin saturations <20%

Mean number of RBC units transfused and proportion of patients transfused from study enrolment to discharge from hospital in patients with baseline ferritin levels <200 ng/mL

Mean number of RBC units transfused and proportion of patients transfused from study enrolment to discharge from hospital in patients receiving more than one dose of the study drug

Mean Hb level on discharge from ICU and hospital in patients not receiving RBC transfusion in ICU after study enrolment

Duration from enrolment to time of first RBC transfusion in patients receiving at least one RBC unit after enrolment

ICU = intensive care unit.

Table 2. Trial eligibility criteria**Inclusion criteria**

Admitted to an ICU for less than 48 hours

Anticipated to require ICU care beyond the next calendar day

Haemoglobin (Hb) level less than 100 g/L at any time in the preceding 24 hours

Aged 18 years or older

Exclusion criteria

Suspected or confirmed severe sepsis (two or more systemic inflammatory response syndrome criteria, suspected or confirmed infection, and one or more organ system failures)

Serum ferritin level greater than 1200 ng/mL or transferrin saturation greater than 50%

History of haemochromatosis or aceruloplasminaemia

Known administration of intravenous (IV) iron in the preceding 3 months

Jehovah's Witness or other documented exclusion to receiving blood products

Receiving an erythropoiesis-stimulating agent (eg, epoetin or darbepoetin) in the preceding 3 months

Known hypersensitivity to IV iron

Pregnancy

Palliative treatment intent

Death is imminent and inevitable

Weight less than 40 kg

Participating in a competing study

ICU = intensive care unit.

more severe anaemia (Hb <100 g/L versus Hb <120 g/L) and administering an alternative and higher dose of IV iron (500 mg ferric carboxymaltose versus 100 mg iron sucrose), which is associated with greater erythropoietic response.¹⁶

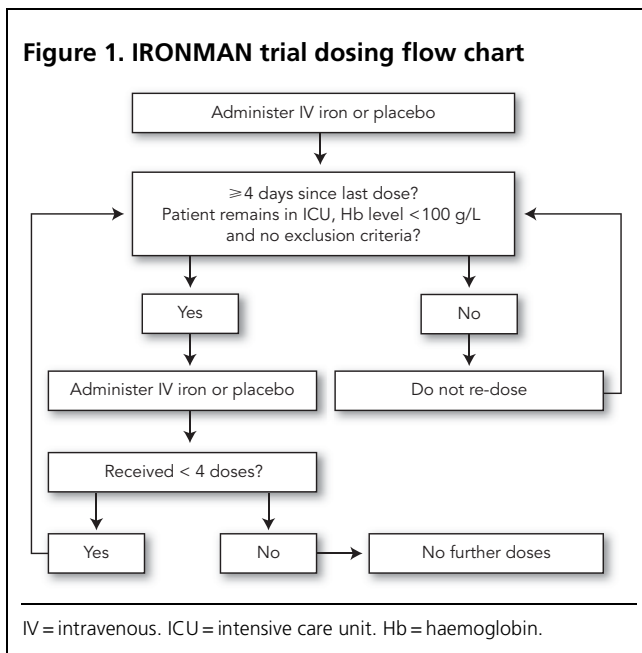
Study design

The IRONMAN trial is a multicentre, Phase IIb, randomised, placebo-controlled, parallel group trial comparing IV iron in addition to standard care with standard care alone in patients admitted to the ICU who are anaemic. The primary end point is the mean number of RBC transfusions from study enrolment to discharge from hospital. Secondary end points include the proportion of patients transfused, and ICU and hospital mortality and infection. A full list of outcome measures is shown in Table 1.

The IRONMAN trial will enrol 140 participants across four centres. Adult patients admitted to the ICU (or a high-dependency area under the supervision of an intensivist) within the previous 48 hours and predicted to remain in the ICU beyond the next calendar day, with an Hb concentration <100 g/L in the preceding 24 hours and not fulfilling any exclusion criteria will be eligible for enrolment after prospective consent is obtained. A complete list of inclusion and exclusion criteria is provided in Table 2.

low-dose iron sucrose in trauma patients found no significant difference in infection between the groups, but it also found no significant difference in Hb concentration or RBC transfusion requirement associated with IV iron.¹⁵

We hypothesise that IV iron supplementation is effective in reducing RBC transfusion in critically ill patients who are anaemic but do not have severe sepsis. A reduction in the mean RBC transfusion requirement may lead to a reduction in mortality and major morbidity, as well as substantial health care cost savings. Here, we describe the study protocol for an RCT, the Intravenous Iron or Placebo for Anaemia in Intensive Care (IRONMAN) trial, to compare IV iron with placebo in patients who are admitted to an ICU and are anaemic. In comparison with the Pieracci trial,¹⁵ the IRONMAN trial will enrol a broader population of critically ill patients, the study drug will be blinded to bedside clinicians responsible for prescribing RBC transfusion, and the study has been designed to optimise IV iron efficacy by only including patients with

Figure 1. IRONMAN trial dosing flow chart**Figure 2. Blinding kit**

Participants

Patients admitted to the ICU will be assessed by trained study personnel including the research coordinators and medical staff (including investigators) at each study site. Patients will be eligible for enrolment if they fulfil all of the inclusion criteria and none of the exclusion criteria (Table 2).

Participants will be allocated to the treatment arm using a randomly generated sequence. Randomisation will be in variable block size and stratified by site. Allocation concealment will be maintained by using sequentially numbered, sealed, opaque envelopes containing the numeric code of the study arm to which the participant has been assigned. The randomisation code will be documented in the participant's notes and the case report form (CRF) and provided to the ICU nursing shift coordinator with access to the unblinding code for preparation of the intervention.

Study medication and procedures

Active medication and re-dosing

Participants randomly assigned to the intervention arm will receive 500 mg of ferric carboxymaltose (Ferinject; Vifor Pharma) as an IV infusion. Ferric carboxymaltose is an iron-carbohydrate complex licensed in Australia.¹⁷ It can be safely administered as a short IV infusion, without the need for a test dose, and provides controlled release of iron with a low risk of acute toxicity, infusion reaction or immediate hypersensitivity. Previous large multicentre RCTs have used ferric carboxymaltose in similar doses and reported efficacy, with a low adverse event rate comparable to placebo.^{16,18} The dosing schedule will be 500 mg ferric carboxymaltose prepared in 100 mL of sodium chloride 0.9% infused over a total of 60 minutes.

Patients will be re-dosed with study medication if they remain in the ICU (or high-dependency unit that is under the supervision of an intensivist), are at least 4 days beyond their previous dose, their Hb level has been less than 100 g/L in the preceding 24 hours and they continue not to fulfil any of the exclusion criteria. Initial study eligibility and re-dosing are dependent on excluding potential iron overload (ferritin level > 1200 ng/mL or transferrin saturations > 50%). Previous RCTs demonstrating the safety and efficacy of IV iron have used similar ferritin and transferrin saturation thresholds.^{18,19} Assessment for re-dosing will continue according to these criteria until death, discharge from the ICU or a maximum of four doses of study drug (total 2000 mg IV iron or equivalent volume of placebo) have been administered, whichever occurs first (Figure 1).

Placebo

Participants randomly assigned to the placebo arm will receive 100 mL of sodium chloride 0.9% delivered by an identical infusion pump over a total of 60 minutes, in addition to standard care. All aspects of patient management other than the specific study-related procedures will be at the direction of the treating clinician. Open-label oral or IV iron and open-label erythropoiesis-stimulating agents will not be permitted in patients participating in the

IRONMAN trial. Clinicians will be encouraged to follow the National Blood Authority critical care transfusion guidelines, including a restrictive transfusion trigger.¹²

Blinding

Study treatment will be blinded using an opaque sleeve covering the syringe and giving set (Figure 2). An unblinded research nurse or pharmacist will draw up the study medication, and the bedside nurse will deliver the infusion. The efficacy of blinding will be assessed according to a substudy questionnaire asking the clinicians responsible for the patients whether they were aware of the study allocation.

Discontinuation of study treatment

Participants will be discontinued from receiving further study treatment on discharge from the ICU or after the fourth dose of study treatment, whichever occurs first. Any participant who develops sepsis (as defined by two or more systemic inflammatory response syndrome criteria plus antibiotics started or changed by the treating clinician for suspected or confirmed infection) will be discontinued from receiving further study treatment for the duration of the period of sepsis. Participants experiencing a suspected or confirmed immediate hypersensitivity reaction temporally related to delivery of the study intervention will have delivery of the study treatment ceased immediately.

Statistical considerations

Sample size

Assuming a mean of four RBC transfusions in eligible patients remaining in the ICU > 2 days, a standard deviation in the intervention and control groups of 2 and a loss to follow-up or incomplete data rate of 10% (including those participants initially enrolled by their next of kin and subsequently declining to provide ongoing participant consent), a study of 140 patients would have 80%

Table 3. Data to be collected in the IRONMAN trial

Baseline

Age and sex
 Dates of hospital and ICU admission
 Number of red blood cell (RBC) units transfused between arrival in hospital and ICU admission
 First haemoglobin (Hb) level and mean corpuscular volume on arrival in hospital
 Episode of bleeding before ICU admission
 Source of ICU admission
 APACHE II score and diagnostic code on ICU admission
 SOFA score and components on ICU admission
 Hb level closest to but before enrolment in study
 Organ support on enrolment in study: mechanical ventilation, vasopressors, renal replacement therapy
 Iron studies: serum iron, transferrin, transferrin saturation, ferritin, soluble transferrin receptors
 Heparin and C-reactive protein levels

Daily

SOFA score and components
 Hb level
 Heparin and C-reactive protein levels
 Number of RBC units for which transfusion commenced during calendar day
 Indication for transfusion
 Organ support during calendar day: mechanical ventilation, vasopressors, renal replacement therapy
 New infection
 Organ failure associated with infection
 New episode of bacteraemia
 Re-dosing of study drug
 Iron studies on days eligible for re-dosing: serum iron, transferrin, transferrin saturation, ferritin
 Adverse events, including anaphylaxis

Discharge

Dates of discharge from ICU and hospital
 Readmission to ICU
 Survival status at ICU and hospital discharge
 Number of RBCs transfused after ICU discharge
 Received non-study drug-related iron
 Hb level on hospital discharge
 Discharge destination

ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = Sequential Organ Failure Assessment.

power to detect a decrease in the mean number of RBC transfusions of 1 unit at a significance level of 5%.

Statistical analysis

All analyses will be conducted on an intention-to-treat basis. Differences in outcome variables will be compared using the *t* test and χ^2 test, as appropriate, if normally distributed, and using non-parametric equivalents if not normally distributed. Analysis will primarily be conducted using Stata version 10.2 (StataCorp). Data will be censored at 60 days after study enrolment for Hb level, RBC transfusion and vital status.

Data management

All data will be collected by trained staff at each study site using a paper source document developed by the management committee. Data will then be entered into a secure, password-protected web database (<http://www.savant.net.au>). Data queries will be automatically generated via the electronic database. Participants will be followed up to death or hospital discharge. A "day" in the ICU will be defined as commencing at midnight. The study data to be collected are shown in Table 3.

Safety monitoring

The drug safety and monitoring board (DSMB) will be comprised of three experienced researchers based in Western Australia: two intensivists not associated with the study and a senior emergency clinician. Serious adverse events (SAEs) will be reported according to the Good Clinical Practice guidelines²⁰ and the requirements of the institutions in which the study will take place. The DSMB will receive notification of all SAEs. No interim analysis is planned; however, the DSMB will reserve the right to request an interim analysis on the basis of unblinded SAEs. In keeping with the advice of Cook et al, events that are part of the natural history of the primary disease process or expected

complications of critical illness will not be reported as SAEs in this trial unless thought to be causally related to the study intervention or otherwise specified in the CRF.²¹

Ethics issues

The study will not proceed at any site until approval has been gained from the responsible human research ethics committee. Prospective informed consent will be sought from eligible patients who retain capacity. However, the proportion of critically ill patients retaining capacity is likely to be extremely low and not representative of the patient population most likely to benefit from the intervention under investigation. For eligible patients who are unable to provide consent, prospective informed consent will be obtained before study enrolment from the designated next of kin. Consent for ongoing participation will then be sought from the participants as soon as practicable.

Funding and support

This study has been funded by a grant from the Western Australian State Health Research Advisory Council. The study drug will be supplied by Vifor Pharma according to a letter of understanding reviewed and agreed upon by Royal Perth Hospital and adhering to the principles of scientific independence in the conduct and reporting of the trial. The study is endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group and is part of the Centre of Research Excellence for Patient Blood Management in Critical Illness and Trauma.

Summary

RBC transfusion is associated with increased morbidity and mortality in critically ill patients. Blood supplies needed for RBCs are also an increasingly costly and scarce resource. In the ICU, RBC transfusion occurs predominantly for anaemia, and despite high levels of compliance with recommended transfusion thresholds, the incidence of RBC transfusion remains high. The aim of the IRONMAN randomised controlled trial is to determine whether IV iron administered to patients admitted to the ICU who are anaemic results in a decrease in the mean RBC transfusion requirement.

Competing interests

The study drug for the IRONMAN study is supplied by Vifor Pharma according to a letter of understanding. Toby Richards is Chief Investigator on PREVENTT, a trial sponsored by the United Kingdom National Institute for Health Research Health Technology Assessment Programme to investigate the use of preoperative IV iron in treating anaemia in major surgery. His university (University College, London) has received educational grant funding from Vifor Pharma

and fees from Vifor Pharma and Pharmacosmos. Shannon Farmer has received lecture travel support and honoraria from Vifor Pharma.

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