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

Andrew J Ghio

To the Editor: The planned IRONMAN trial described by Litton and colleagues is a randomised investigation focused on the impact of intravenous (IV) ferric carboxymaltose on the mean number of red blood cell units transfused into anaemic intensive care unit patients.[1] The authors discussed the issue of the secondary effects of iron on disease processes causing admission of a patient to the ICU. A possible elevation in infections was discussed and it was suggested that IV iron will not alter the outcome of disease. However, many of the major causes for admission to ICUs are associated with or directly result from a disruption in iron homeostasis. The provision of iron in the IRONMAN trial is predicted to have an impact on the outcome of these diseases, and infections including sepsis and pneumonia show worsening of outcomes with supplementation of iron.[2-4] Indices of iron homeostasis predict the outcome of acute respiratory distress syndrome, with increased ferritin being associated with elevations in mortality.[5] Similarly, mortality due to neoplasms can be increased by greater iron availability.[6] It is anticipated that the provision of IV iron to patients admitted to ICUs will increase mortality in these diseases. The IRONMAN trial should be commended for its intent on investigating use of IV iron to decrease the need for red blood cell transfusion, but the study population must be closely followed for secondary effects of iron provision. Any evidence showing worsening of outcomes (ie, mortality) after IV iron in the trial must demand immediate attention.

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Edward Litton

In reply: We thank Ghio for his letter about the IRONMAN study investigating whether intravenous (IV) iron, compared with placebo, for critically ill patients, with anaemia but without sepsis, admitted to the intensive care unit reduces red blood cell transfusion requirements.[1]

We agree with Ghio that the role of IV iron in critical illness is uncertain, hence the need for a rigorously planned and conducted randomised controlled trial (RCT) to assess safety and efficacy. Ghio suggests that supplementation of iron is associated with worsening of outcome in sepsis, citing two preclinical observational studies. However, other preclinical studies have contradicted this.[2] Further, an association between iron and infection is biologically plausible, but the single RCT of IV iron in trauma patients admitted to the ICU did not show an increase in infection, and the majority of RCTs have not included infection as a predefined end point.[3,4] The IRONMAN trial will explicitly exclude patients with sepsis at baseline and will include important infectious complications as end points.

Ghio suggests that the provision of IV iron is predicted to have negative impacts on outcomes in patients with acute respiratory distress syndrome, on the basis of an association with raised ferritin. Ferritin is a marker of iron stores and an acute-phase reactant, so an association with adverse outcomes would be entirely anticipated in any condition associated with severe inflammation. In this setting, ferritin has minimal utility as a marker of iron stores or response to IV iron.[3,5]

Red blood cell (RBC) transfusion involves the use of a scarce and costly resource and is associated with substantial morbidity and mortality in the critically ill. Despite high concordance with conservative transfusion guidelines, RBC transfusion remains common in the ICU. Novel interventions to reduce transfusion requirements are therefore a research priority. We believe that IV iron may plausibly reduce transfusion requirements and improve patient-centred outcomes in selected patients admitted to the ICU, hence we have designed and implemented the IRONMAN RCT.

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Ventilator autotriggering in brain death: still a trap for the unwary?

Michael J O'Leary, Elena Cavazzoni and Maria P Gomez

To the Editor: As part of an audit process to document the potential brain death pool in a major teaching hospital over a 1-year period, we identified two patients for whom we considered that brain death had almost certainly occurred but was not recognised by the treating intensive care specialist on the basis of the apparent presence of continuing spontaneous respiration.

Both patients were men aged 72 years. In the first patient, accelerated intracranial hypertension occurred despite decompressive craniectomy after blunt head trauma. All brainstem reflexes were documented as absent but an apnoea test was not conducted, as the patient was claimed to have "low volume (150 mL) spontaneous breaths on pressure support ventilation (PSV)". As the patient was over the age limit for organ donation after circulatory death (DCD), he underwent palliative extubation. A nursing entry in the clinical notes included a comment that he did not take any spontaneous breaths after extubation. The second patient had presented with a massive spontaneous intracerebral haemorrhage and neurosurgical opinion was that surgery would be futile and that palliation was indicated. The patient's family mentioned that he was registered for organ donation, so he was admitted to the intensive care unit to facilitate this. After 48 hours' support and observation in the ICU, the absence of all brainstem reflexes was noted (occulocaloric testing was not performed) except for the presence of "spontaneous respiratory efforts on the ventilator, shallow breaths". This patient's age also precluded DCD and he underwent palliative extubation and was certified dead 10 minutes later. There was no documentation regarding the presence or absence of spontaneous breaths after extubation.

We were particularly concerned by these cases, as recently there have been two additional patients in the same department for whom brain death was excluded on the basis of the presence of spontaneous respiration on PSV, who were then recognised to actually be apnoeic when disconnected from the ventilator.

Organ donation coordinators at the New South Wales Organ and Tissue Donation Service suggest, anecdotally, that they are aware of some DCD donors who have been apnoeic on withdrawal of ventilatory support when it had been claimed that brain death had not occurred. We are concerned that the failure to recognise the phenomenon of ventilator autotriggering in brain death in Australian ICUs may be having an impact on our apparently low incidence of brain death when compared with some other countries.[1]

Autotriggering of the ventilator in brain death is well recognised.[2-4] It is important to note that the respiratory rate during auto-triggering is variable and is frequently not coordinated with cardiac activity, as is sometimes assumed. Furthermore, autotriggering is not always abolished by adjusting the ventilator trigger threshold, whether by pressure or by flow, and can only be reliably excluded by disconnecting the patient from the ventilator and observing for spontaneous breaths.

The failure to recognise the phenomenon of autotriggering and thus correctly diagnose the presence of brain death could be an important impediment to optimising organ donor numbers in Australia. In younger patients, opting for DCD instead of donation after brain death will result in fewer recipients benefiting from a single donor.

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