

## REVIEW ARTICLE

**Perioperative anaemia management: consensus statement on the role of intravenous iron****P. Beris<sup>1\*</sup>†, M. Muñoz<sup>2</sup>, J. A. García-Erce<sup>3</sup>, D. Thomas<sup>4</sup>, A. Maniatis<sup>5</sup>† and P. Van der Linden<sup>6</sup>**

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A multidisciplinary panel of physicians was convened by Network for Advancement of Transfusion Alternatives to review the evidence on the efficacy and safety of i.v. iron administration to increase haemoglobin levels and reduce blood transfusion in patients undergoing surgery, and to develop a consensus statement on perioperative use of i.v. iron as a transfusion alternative. After conducting a systematic literature search to identify the relevant studies, critical evaluation of the evidence was performed and recommendations formulated using the Grades of Recommendation Assessment, Development and Evaluation Working Group methodology. Two randomized controlled trials (RCTs) and six observational studies in orthopaedic and cardiac surgery were evaluated. Overall, there was little benefit found for the use of i.v. iron. At best, i.v. iron supplementation was found to reduce the proportion of patients requiring transfusions and the number of transfused units in observational studies in orthopaedic surgery but not in cardiac surgery. The two RCTs had serious limitations and the six observational limited by the selection of the control groups. Thus, the quality of the available evidence is considered moderate to very low. For patients undergoing orthopaedic surgery and expected to develop severe postoperative anaemia, the panel suggests i.v. iron administration during the perioperative period (weak recommendation based on moderate/low-quality evidence). For all other types of surgery, no evidence-based recommendation can be made. The panel recommends that large, prospective, RCTs be undertaken to evaluate the efficacy and safety of i.v. iron administration in surgical patients. The implementation of some general good practice points is suggested.

*Br J Anaesth* 2008; **100**: 599–604

**Keywords:** blood, transfusion; complications, anaemia; surgery, cardiac, orthopaedic; surgery, postoperative period; surgery, preoperative period

Allogenic blood transfusion is commonly used to rapidly and effectively increase haemoglobin levels and avoid the deleterious effects of acute severe anaemia, especially in elderly patients whose compensatory mechanisms may be limited.<sup>5</sup> However, although increasingly more safe, allogenic blood transfusion can never be risk-free, nor can drugs and other interventions intended to reduce exposure to donor blood. In addition, the impact of new illnesses and infections on blood safety cannot be predicted.<sup>26</sup> Thus, concerns about adverse effects of allogenic blood transfusion have prompted a review of transfusion practice, with implementation of restrictive transfusion criteria, and the search for a safer and more biologically rational treatment

of anaemia, such as pharmacological treatment, in order to reduce patient risks and improve patient outcomes.<sup>22 26</sup>

Perioperative anaemia has been linked to increased postoperative morbidity and mortality, and decreased quality of life.<sup>35</sup> Depending on the procedures and the definitions of anaemia, from 11% to 76% of surgical patients may present with preoperative anaemia,<sup>35</sup> which is one of the major predictive factors for allogenic blood transfusion

†*Declaration of interest.* Prof. P.B. has received lecture honoraria from Vifor International and has participated in a clinical trial approved by the institutional ethical committee and funded by Vifor International. Prof. A.M. has received lecture honoraria from Pharmacosmos.

related to surgery with moderate to high blood loss.<sup>12 13</sup> The limited physiological reserve and the higher incidence of unrecognized cardiovascular disease may make the elderly population more vulnerable to milder degrees of anaemia when undergoing surgery. In a retrospective analysis of 310 311 patients aged  $\geq 65$  yr, who underwent major non-cardiac surgery, it was found that the adjusted risk of 30 day postoperative mortality and cardiac morbidity started to increase when preoperative haematocrit levels decreased below 39%.<sup>44</sup> Anaemia may be due to iron deficiency, chronic inflammation, or both. Folic acid or vitamin B<sub>12</sub> deficiencies may also be present, especially in elderly patients.<sup>18</sup>

A recent retrospective observational study<sup>34</sup> evaluating the prevalence and characteristics of preoperative anaemia in patients undergoing elective major joint arthroplasty in a specialized Scottish orthopaedic hospital found that 224 of 1142 patients (19.6%) presented with preoperative anaemia (defined as a haemoglobin concentration  $<13$  g dl<sup>-1</sup> in males and  $<11.5$  g dl<sup>-1</sup> in females). The type of anaemia was assessed based on mean cell volume and mean cell haemoglobin. Of those with anaemia, 64.3% had normocytic normochromic anaemia, consistent with the anaemia of chronic disease, 23.3% had hypochromic anaemia, potentially responsive to iron therapy alone, and 12.4% had other types of anaemia. Overall, 21.3% of patients required perioperative allogenic blood transfusion, compared with 42% of patients with preoperative anaemia.<sup>34</sup>

Postoperative anaemia, which may be present in up to 90% of patients undergoing major surgery,<sup>35</sup> is mainly caused by perioperative blood loss and may be aggravated by blunting of erythropoiesis by inflammatory responses, especially through decreased iron availability (i.e. hepcidin-dependent down-regulation of intestinal absorption and impaired mobilization from body stores).<sup>30 39 42</sup> A study of patients who had undergone hip arthroplasty showed evidence of increased erythropoiesis by postoperative day 7 and approximately two-thirds of the postoperative haemoglobin deficit was corrected by day 28.<sup>40</sup> However, in more than 25% of patients, the recovery of haemoglobin levels was still incomplete on postoperative day 56 and ferritin levels were significantly decreased in patients who were not transfused. The authors concluded that this was mainly due to functional or (more frequently) true iron deficiency; the main predictors for postoperative iron deficiency are perioperative blood loss and preoperative iron stores.

The currently available evidence does not support the efficacy of *postoperative* oral iron supplementation: in five randomized controlled trials (RCTs) (four after orthopaedic surgery and one after cardiac surgery), postoperative administration of oral iron failed to increase haemoglobin levels.<sup>7 29 37 41 45</sup> It has been suggested that both minor and major surgery induce distinctive changes in iron metabolism, similar to those observed in the anaemia of chronic disease, which may explain the ineffectiveness of

oral iron supplementation during the postoperative period.<sup>39</sup> In contrast, *preoperative* oral iron supplementation in patients undergoing colorectal resection was found to increase haemoglobin levels immediately before surgery and to reduce the proportion of patients requiring intraoperative allogenic blood transfusions in comparison with a control group (9.4% vs 27.4%,  $P<0.05$ ).<sup>33</sup> However, there were no significant differences in postoperative haemoglobin levels or volume transfused between the two groups.<sup>33</sup> A recent prospective RCT in patients undergoing elective colorectal resections showed that preoperative oral iron therapy (with a median length of treatment of 14 days) significantly reduced the number of patients requiring red blood cell transfusions from 59% to 26% ( $P=0.031$ ).<sup>23</sup> In an RCT of patients undergoing orthopaedic surgery, preoperative oral iron administration was found to prevent postoperative decreases in haemoglobin levels,<sup>1</sup> and oral iron combined with a restrictive transfusion protocol was associated with a reduction in transfusion requirements in an observational study.<sup>11</sup>

Although oral administration is the conventional route for iron because of its convenience and low cost, i.v. iron has emerged as a safe and effective alternative for perioperative anaemia management. This takes into consideration factors such as intolerance of or contraindications to oral iron (e.g. inflammatory bowel disease), short time to surgery, severe preoperative anaemia, or the use of erythropoiesis-stimulating agents.

## Methods

A multidisciplinary panel of physicians with expertise and experience in perioperative anaemia management was convened by the Network for Advancement of Transfusion Alternatives (NATA), in January 2007, in Barcelona, Spain. The panel's aim was to review the available evidence on i.v. iron administration as a means of increasing haemoglobin levels and reducing the need for allogenic blood transfusion in patients undergoing surgery. Its goal was also to develop a consensus statement on perioperative use of i.v. iron as an alternative to blood transfusion (Table 1). The use of i.v. iron in the settings of preoperative autologous blood donation and preoperative administration of recombinant human erythropoietin (rHuEPO) or other alternatives to allogenic blood transfusion were included in the discussion. The Medline database was searched using the MESH keywords 'anemia', 'surgery', 'iron', and 'blood transfusion', and the abstracts of the retrieved references were reviewed to identify the studies with at least one patient group given i.v. iron alone for the treatment of perioperative anaemia. The search was restricted to English- and French-language articles. A critical evaluation of the evidence was then performed and recommendations were formulated according to the method proposed by the Grades of Recommendation

**Table 1** Summary of expert panel's remit

Target population	Patients undergoing surgery and expected to develop severe postoperative anaemia requiring allogenic blood transfusion
Question	How to increase haemoglobin in the perioperative period?
Proposed intervention	Administration of i.v. iron
Relevant outcome	Reduction in the perioperative transfusion rate and the volume of blood transfused

Assessment, Development and Evaluation (GRADE) Working Group (Table 2).<sup>3</sup>

## The evidence base

### Summary of relevant evidence

A more detailed analysis of the studies can be found in the Appendix, online at <http://www.bja.oxfordjournals.org.uk>.

#### Preoperative

There were two observational studies with control groups in patients undergoing hip fracture repair.<sup>8 9</sup> In patients with hip fracture who were operated on 2–4 days after admission, preoperative use of i.v. iron alone (2–3×100 mg, starting on admission) was effective in reducing the transfusion rate when compared with historical control patients.<sup>8 9</sup> In addition, there was a significant reduction in the postoperative infection rate and in hospital stay and 30 day postoperative mortality.<sup>9</sup>

#### Perioperative

In one observational study, perioperative i.v. iron administration (3×200 mg in 48 h, starting on admission), alone or in combination with a single-dose rHuEPO (40 000 IU on admission) if preoperative haemoglobin concentration was <13 g dl<sup>-1</sup>, plus a restrictive transfusion trigger

**Table 2** Criteria for assigning grade of evidence according to the GRADE Working Group<sup>3</sup>

Levels of evidence: high, moderate, low, and very low
Types of evidence
Randomized controlled trial, high
Observational study, low
Any other evidence, very low
Decrease grade if
Serious (–1) or very serious (–2) limitation to study quality
Important inconsistency (–1)
Some (–1) or major (–2) uncertainty about directness
Imprecise or sparse data (–1)
High probability of reporting bias (–1)
Increase grade if
Strong evidence of association—significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
Very strong evidence of association—significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2)
Evidence of a dose–response gradient (+1)
All plausible confounders would have reduced the effect (+1)

(8 g dl<sup>-1</sup>), reduced allogenic blood transfusion in hip fracture patients who underwent surgery 2–6 days after admission.<sup>14</sup> There was also a significant reduction in the postoperative infection rate.<sup>14</sup> In addition, a similar protocol reduced the proportion of patients requiring allogenic blood transfusions (<5%) in total knee replacement, in comparison with a previous series from the same institution in which the transfusion rate was 30%.<sup>10</sup>

#### Postoperative

There were two prospective, randomized trials<sup>21 25</sup> and three observational studies with control groups.<sup>4 20 32</sup> RCTs: in cardiac surgery patients and in a small group of orthopaedic patients, postoperative administration of i.v. iron, alone or in combination with rHuEPO, was not associated with a greater increase in haemoglobin concentration than placebo.<sup>4 25</sup> Similar results were obtained in one of the observational studies in cardiac surgery patients.<sup>32</sup> In contrast, in one observational study of orthopaedic patients, i.v. iron resulted in higher haemoglobin concentrations compared with oral iron.<sup>20</sup> In the third observational study, postoperative administration of i.v. iron (3×100 mg per day, starting on the first postoperative day) in patients undergoing total hip replacement resulted in a reduction in the transfusion rate and volume compared with a historical control group.<sup>6</sup>

#### Safety

Although no serious life-threatening adverse events or increment in postoperative infection rate were reported, the number of patients included in these studies is not large enough to draw definitive conclusions regarding the safety of i.v. iron agents. However, data from the US Food and Drug Administration suggest that the total number of reported parenteral iron-related adverse drug events (ADEs) was 1141 from approximately 30 million doses given (approximately 38 ADEs per million).<sup>36</sup> The rates of life-threatening events were 0.6, 0.9, 3.3, and 11.3 per million for iron sucrose, sodium ferric gluconate complex, low-molecular-weight iron dextran, and high-molecular-weight iron dextran, respectively, and the death rates were 0.11, 0.25, 0.75, and 0.78 per million, respectively.<sup>36</sup> Therefore, the rates of life-threatening ADEs associated with iron (2.2 per million), including iron-related deaths (0.4 per million), are lower than those of transfusion-related severe side-effects (10 per million) and transfusion-related deaths (4 per million).<sup>19 36</sup> In addition, several studies suggested that previously observed associations between iron administration and higher infection and mortality rates may have been due to confounding variables.<sup>28 38</sup>

#### Quality of evidence

Of the studies evaluating the efficacy of i.v. iron to reduce perioperative allogenic blood transfusion, the two RCTs have serious limitations (small number of patients, randomization bias, inconsistency, etc.), whereas the six

observational studies appear to have been well conducted, but are limited by the selection of the control groups. Thus, the level of evidence is considered moderate,<sup>4</sup> low,<sup>6</sup> 8 10 14 25 32 and very low.<sup>20</sup>

#### Best estimates

Pre- and perioperative i.v. iron administration may reduce both the proportion of patients requiring blood transfusions and the volume of blood transfused.

#### Judgement of benefits vs risks, burden, and cost

The available information suggests benefits of pre- and perioperative i.v. iron administration, especially for patients with anaemia, but the quality of evidence is low.

#### Recommendation

For patients undergoing elective and non-elective orthopaedic surgery and expected to develop severe postoperative anaemia, we currently suggest i.v. iron administration during the perioperative period. This is a weak recommendation based on moderate- and low-quality evidence. For all other surgeries, no evidence-based recommendation can be made.

We strongly recommend that large, prospective, RCTs be undertaken in surgical patients expected to develop severe postoperative anaemia.

### General good practice points

In addition to the recommendations stated above, the following points based on the experience of the panel members can be considered good clinical practice for surgical patients.

- Patients at risk of receiving perioperative transfusions should be identified based on the patient's red blood cell mass, the transfusion trigger, and the expected blood loss, for example, using Mercuriali's algorithm.<sup>28</sup>
- Whenever clinically feasible, patients undergoing elective surgery with a high risk of severe postoperative anaemia should have their haemoglobin concentration<sup>15</sup> and iron status (serum iron, serum ferritin, transferrin saturation, and C-reactive protein) tested, preferably at least 30 days before the scheduled surgical procedure. For patients >60 yr old, vitamin B<sub>12</sub> and folic acid should also be measured.<sup>18</sup>
- Patients with preoperative anaemia due to iron deficiency or chronic disease may receive preoperative treatment with oral or i.v. iron, depending on the timescale before surgery, tolerance of oral iron, and iron status.<sup>15</sup> In addition, i.v. iron rather than oral iron should be given to improve response to rHuEPO and might allow for a reduction in rHuEPO dose requirements.<sup>2 16 21 31</sup> Total i.v. iron dose (TID) can be calculated according to the formula: TID (mg)=(Hb<sub>target</sub>-Hb<sub>actual</sub>) (g dl<sup>-1</sup>)×weight (kg)×2.4. After operation, 150 mg of i.v. iron per g dl<sup>-1</sup>

of haemoglobin drop should be added to compensate iron loss due to perioperative bleeding.

- Unexplained anaemia should always be considered as secondary to some other process and, therefore, elective surgery, especially for non-malignant disease, should be deferred if possible until the anaemia is adequately evaluated and treated.<sup>17</sup>
- Non-anaemic patients with a serum ferritin level <100 ng ml<sup>-1</sup> (or ferritin 100–300 ng ml<sup>-1</sup> and transferrin saturation <20%) undergoing surgical procedures with an expected blood loss >1500 ml (haemoglobin drop of 3–5 g dl<sup>-1</sup>) may benefit from preoperative oral or i.v. iron administration, depending on the presence of co-morbidities and on the timescale before surgery, as they may not have enough stored iron to replenish their perioperative haemoglobin loss and maintain normal iron stores (serum ferritin ≥30 ng ml<sup>-1</sup>).<sup>3 7 11 40</sup>
- Administration of i.v. iron should be avoided in patients with pre-treatment ferritin values >300–500 ng ml<sup>-1</sup> and transferrin saturation >50%.<sup>24</sup> Moreover, despite the absence of definitive clinical data, as all i.v. iron agents have the potential to release biologically active iron, it seems reasonable to avoid i.v. iron administration in the setting of acute infection.<sup>43</sup>
- Finally, it must be borne in mind that the goal of performing major surgical procedures without the use of allogenic blood transfusion and without placing the patient at risk for anaemia-related complications may be better accomplished by combining several blood-saving techniques into a defined algorithm such as those proposed recently<sup>27 43</sup> in orthopaedic surgery.

### Conclusion

A recommendation on the perioperative use of i.v. iron to increase haemoglobin levels and reduce allogenic blood transfusion can only be made for orthopaedic surgical patients based on moderate- to low-quality evidence. Therefore, the panel strongly recommends that large, prospective, RCTs be undertaken in patients expected to develop severe postoperative anaemia before routine use of i.v. iron can be recommended. The outcomes to be evaluated in such studies should also include length of hospital stay, postoperative morbidity and mortality, postoperative recovery, costs, etc. Meanwhile, the implementation of the suggested good clinical practice points is proposed.

### Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

### Acknowledgements

The development of this consensus statement was initiated and coordinated by NATA. The authors thank François Christory and LMS Group

for their support in preparing and organizing the expert meeting, and are very grateful to Dr Catriona Connolly and Dr Peter Tomasulo for critically reviewing a draft version of the manuscript and providing valuable suggestions.

## Funding

The costs associated with the preparation and organization of the meeting were supported by an unrestricted educational grant from Vifor (International) Inc. The sponsor had no influence on the discussions during the meeting or the preparation of the manuscript.

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