Anaemia in cardiac surgery – a retrospective review of a centre’s experience with a pre-operative intravenous iron clinic

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Summary
Pre-operative anaemia is associated with higher rates of transfusion and worse outcomes, including prolonged hospital stay, morbidity and mortality. Iron deficiency is associated with significantly lower haemoglobin levels throughout the peri-operative period and more frequent blood transfusion. Correction of iron stores before surgery forms part of the first pillar of patient blood management. We established a pre-operative anaemia clinic to aid identification and treatment of patients with iron deficiency anaemia scheduled for elective cardiac surgery. We present a retrospective observational review of our experience from January 2017 to December 2019. One-hundred and ninety patients received treatment with intravenous iron, a median of 21 days before cardiac surgery. Of these, 179 had a formal laboratory haemoglobin level measured before surgery, demonstrating a median rise in haemoglobin of 8.0 g.l$^{-1}$. Patients treated with i.v. iron demonstrated a significantly higher incidence of transfusion (60%) compared with the non-anaemic cohort (22%) during the same time period, $p < 0.001$. Significantly higher rates of new requirement for renal replacement therapy (6.7% vs. 0.6%, $p < 0.001$) and of stroke (3.7% vs. 1.2%, $p = 0.010$) were also seen in this group compared with those without anaemia, although there was no significant difference in in-hospital mortality (1.6% vs. 0.8%, $p = 0.230$). In patients where the presenting haemoglobin was less than 130 g.l$^{-1}$, but there was no intervention or treatment, there was no difference in rates of transfusion or of complications compared with the anaemic group treated with iron. In patients with proven iron deficiency anaemia, supplementation with intravenous iron showed only a modest effect on haemoglobin and this group still had a significantly higher transfusion requirement than the non-anaemic cohort. Supplementation with intravenous iron did not improve outcomes compared with patients with anaemia who did not receive intravenous iron and did not reduce peri-operative risk to non-anaemic levels. Questions remain regarding identification of patients who will receive most benefit, the use of concomitant treatment with other agents, and the optimum time frames for treatment in order to produce benefit in the real-world setting.

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Introduction

The worldwide prevalence of anaemia is estimated to be 25% [1]. Pre-operative anaemia is associated with higher rates of transfusion and prolonged hospital stay, morbidity and mortality [2–7]. This is particularly evident in cardiac surgery where blood loss and transfusion requirements are higher. Even relatively modest rates of peri-operative transfusion have been associated with increasing morbidity and mortality following cardiac surgery [8, 9]. The presence of iron deficiency, with or without anaemia, is associated with significantly lower haemoglobin (Hb) levels throughout the peri-operative period, and this group of patients receive transfusions more frequently and receive a greater total number of red cell units than non-iron-deficient patients [10, 11]. Patient blood management comprises a series of patient-centred and evidence-based preventative and reactive measures intended to reduce bleeding and blood transfusion. The international consensus guidelines on the management of peri-operative anaemia and iron deficiency recommend treatment of pre-operative iron deficiency anaemia with intravenous (i.v.) iron if the surgery is planned within 6 weeks [12]. This is also supported by the National Institute for Health and Care Excellence (NICE) quality statement of 2015 [13] and the 2020/21 Commissioning for Quality and Innovation (CQUIN) framework, which incentivises the treatment of iron deficiency anaemia before surgery. Introduction of a multimodal patient blood management programme has been associated with improved outcomes in terms of reduced rates of transfusion, morbidity and mortality [14] and it has been suggested that treatment of pre-operative anaemia may improve outcome and reduce cost [15, 16]. However, such recommendations present significant organisational challenges in an often busy setting before surgery. Additionally, a recent detailed meta-analysis of patient blood management interventions found that, while patient blood management measures reduce bleeding and requirement for transfusion, they did not significantly reduce morbidity or mortality and there was a lack of evidence of true cost effectiveness [17].

In 2010, we performed an audit of the prevalence of anaemia in our centre, a high-volume stand-alone cardiothoracic unit. Similar to national data reported [2] we found a prevalence of anaemia of 30%. As a result of this, we set up a pre-operative anaemia clinic for the diagnosis and treatment of iron deficiency anaemia. Our clinic started to see patients in late 2016. We decided to perform a retrospective review of outcomes of patients attending our service, summarising our experience from January 2017 to December 2019.

Methods

We performed a retrospective review of data from all patients undergoing elective cardiac surgery between 1 January 2017 and 31 December 2019, a proportion of whom attended for pre-operative i.v. iron treatment. All elective cardiac and aortic surgical patients at our centre with proven iron deficiency and anaemia are invited to attend for iron, according to the approach described below and in online Supporting Information Figure S1. This service evaluation was registered with our Trust research and development department; ethical approval was waived in view of its observational nature. All patients scheduled for elective cardiac surgery attended for baseline screening before surgery, including a full blood count. Where Hb was < 130 g.l⁻¹, an automatic order for the addition of further tests was made, including ferritin and transferrin saturation (TSAT), B12/folate and C-reactive protein (CRP). Patients with Hb < 130 g.l⁻¹, whether male or female, and with either a ferritin level < 30 ng.ml⁻¹, or ferritin < 100 ng.ml⁻¹ and TSAT < 20%, were identified. A review of their medical records was performed by the lead nurse for the anaemia service to assess for the presence of contra-indications to iron treatment. In the absence of any contra-indication, the patient was invited to attend pre-operatively to receive a single dose of i.v. iron isomaltoside 1000 (20 mg.kg⁻¹) (Monofer, Pharmacosmos A/S, Holbaek, Denmark). Our hospital covers a large geographical area of Merseyside and North Wales but, despite this, all patients were offered the opportunity to attend.

Our local policy now stipulates that i.v. iron should be administered 4–6 weeks in advance of surgery if possible, but during the study period iron was occasionally offered up to 2 weeks before admission for surgery. Patients were admitted to our day surgery unit and reviewed by the lead nurse for the i.v. iron service. After confirmation of the absence of any contra-indication, iron isomaltoside 1000 was administered, followed by a period of monitoring. The first six patients treated by the service received a dose of iron calculated using the Ganzoni equation; total iron deficit (mg) = patient weight (kg) × (target Hb – actual Hb in g.dl⁻¹) × 2.4 + iron stores, with target Hb of 13 g.dl⁻¹ and iron stores of 500 mg used for all patients. This was later changed so that all patients received 20 mg.kg⁻¹. Following discharge from the day surgery unit, the patient attended for surgery as planned, and their Hb was checked before surgery.

During the patient’s admission for surgery, care provided was according to the individual practice of the surgical and anaesthetic team looking after the patient. This
included routine use of tranexamic acid (at a dose chosen by the individual anaesthetist according to their routine practice); cell salvage (during off-pump coronary artery bypass grafting only); re-infusion of ‘pump’ blood in cases using cardiopulmonary bypass; use of topical haemostatic agents (according to the individual surgeon’s practice); and maintenance of normothermia throughout surgery during off-pump cases, and post-cardiopulmonary bypass in all others. Clinicians are regularly educated regarding the importance of single unit blood transfusion and the evidence behind restrictive transfusion, but there were no fixed transfusion targets; decision to transfuse was made by the individual team caring for the patient, both within the operating theatre and during postoperative recovery.

A record of all patients treated with i.v. iron was maintained. This was examined, together with data from the National Institute for Cardiovascular Outcomes Research database, in order to identify significant pre-operative comorbidities and postoperative complications.

Categorical variables were compared using Chi-squared tests or Fisher’s exact tests as appropriate. Normality for continuous data was assessed using the Kolmogorov-Smirnov test. Non-normally distributed variables compared using Wilcoxon Signed Rank tests. Analysis was carried out using the SAS system for Windows v9.3 (SAS Institute, Cary, NC, USA) software. A p value < 0.05 was considered statistically significant.

Results
Between January 2017 and December 2019, 314 patients attended for treatment with i.v. iron. Of these, 190 attended for treatment and then proceeded to surgery within 90 days. The other patients either did not proceed to surgery or underwent more complex surgery than our inclusion criteria. The median (IQR [range]) pre-treatment Hb (the ‘presenting Hb’) was 122 (113–126 [90–129]) g.l\(^{-1}\) with a median (IQR [range]) ferritin level of 49 (24–82 [4–712]) µg.l\(^{-1}\) and a median (IQR [range]) TSAT of 14 (10–18 [2–50]) %. Patient characteristics in Table 1 show anaemic patients who received i.v. iron, anaemic patients who did not receive i.v. iron and non-anaemic patients. Patients who had a presenting Hb < 130 g.l\(^{-1}\) were not treated either because they did not meet the iron deficiency inclusion criteria or were unable to attend for logistical reasons. A total of 581 patients had a presenting Hb < 130 g.l\(^{-1}\) but did not attend for i.v. iron, and 301 patients had no record of a ferritin measurement being performed. Of the 280 patients who did have their ferritin checked, 69 would have been eligible for i.v. iron treatment based on their ferritin and TSAT levels. Forty patients had a low vitamin B12 or folate level and were referred to their GP for supplementation. Patients received a median (IQR [range]) i.v. iron isomaltoside 1000 dose of 1300 (1200–1500 [600–2000]) mg. They were admitted to the hospital for cardiac surgery a median (IQR [range]) of 21 (13–34 [5–89]) days later. A total of 179 patients had a formal laboratory Hb measured before surgery, this demonstrated a median (IQR [range]) rise in Hb of 8.0 (2.3–11.0 [–14.0–55.0]) g.l\(^{-1}\). A total of 74 (39%) patients who were treated achieved a pre-operative Hb ≥ 130 g.l\(^{-1}\). Compared with patients who were not anaemic, those who were treated with i.v. iron demonstrated a significantly higher incidence of transfusion (60% vs. 22%, p < 0.001) during the peri-operative period, as shown in Table 2. Significantly higher rates of new requirement for renal replacement therapy (6.7% vs. 0.6%, p < 0.001) and of stroke (3.7% vs. 1.2%, p = 0.01) were also seen in this group, although there was no significant difference in in-hospital mortality (1.6% vs. 0.8%, p = 0.23), sternal wound infection (3.7% vs. 2.0%, p = 0.12) or requirement for re-operation (4.7% vs. 3.5%, p = 0.70). In patients where the presenting Hb was < 130 g.l\(^{-1}\), but this was not treated, there were no differences in rates of transfusion or complications compared with patients that had a similar presenting Hb who received i.v. iron (Table 2). We subdivided anaemic patients into four groups based on their presenting Hb: Hb < 100 g.l\(^{-1}\); Hb 100–109 g.l\(^{-1}\); Hb 110–119 g.l\(^{-1}\); and Hb 120–129 g.l\(^{-1}\). Table 3 shows the presenting iron studies and response to i.v. iron in each group. Patients with a lower starting Hb demonstrated an incrementally greater response to i.v. iron administration. We also subdivided anaemic patients according to the type of iron deficiency they demonstrated: true iron deficiency (ferritin < 30 µg.l\(^{-1}\) and CRP < 5 mg.l\(^{-1}\)); functional iron deficiency (ferritin < 30 µg.l\(^{-1}\), CRP > 5 mg.l\(^{-1}\)); anaemia of inflammation (ferritin > 30 µg.l\(^{-1}\), CRP > 5 mg.l\(^{-1}\)); other (ferritin > 30 µg.l\(^{-1}\), TSAT < 20%, CRP < 5 mg.l\(^{-1}\)). Table 4 shows the outcomes, requirement for transfusion and number of units transfused for each group. Figure 1 demonstrates the effect of i.v. iron on Hb level for each group.

Discussion
The main findings of our study were that, in patients with proven iron deficiency anaemia, supplementation with i.v. iron showed only a modest effect on Hb; supplementation with i.v. iron was not associated with improved outcomes compared with anaemic patients who did not receive i.v. iron, and did not reduce peri-operative risk to non-anaemic levels.

The median rise of Hb in those patients given iron supplementation was only 8 g.l\(^{-1}\) and this was despite
administration of a full replacement dose of iron a median of 3 weeks before surgery. It is possible that a larger rise in Hb would have been seen if the patients had been given more time to generate a response; however, this represents the reality of work within the constraints of the UK NHS. Our experience mirrors that of a large UK study addressing the feasibility of a larger UK-wide i.v. iron initiative [18], where iron was administered a median of 33 days before surgery, with a mean Hb rise of 8.4 g.l⁻¹. When considering the response of patients according to their presenting Hb we found that, while there was an increase in the median Hb before surgery in all groups, this was most pronounced in the cohort with the most severe anaemia, and less pronounced in those with mild anaemia (Hb of 120–129 g.l⁻¹). As expected, a greater degree of anaemia was associated with a lower median ferritin and TSAT. As the degree of anaemia reduced, both these markers improved. Our practice has been to treat all patients, regardless of sex, where Hb is < 130 g.l⁻¹, but our data suggest that the optimal benefit, in terms of Hb increase, may favour treatment where Hb is < 120 g.l⁻¹, the practice in many other centres.

Six patients received a dose of iron less than 1000 mg following dosing using the Ganzoni formula (two patients received 600 mg, three received 700 mg and one received 900 mg). This group was treated a median of 22 days before surgery and demonstrated a median rise in Hb of 10 g.l⁻¹. They were included in the overall analysis.

Anaemic patients treated with i.v. iron demonstrated significantly higher rates of transfusion, stroke and requirement for haemofiltration when compared with the non-anaemic cohort of those with a presenting Hb > 130 g.l⁻¹. The risks, which are known to be greater in

### Table 1

| Characteristics | Hb < 130 g.l⁻¹ and received i.v. iron (n = 190) | Hb < 130 g.l⁻¹ and did not receive i.v. iron/ not iron-deficient (n = 581) | Hb ≥ 130 g.l⁻¹ (n = 2093) | p value* | p value** |
|-----------------|-----------------------------------------------|------------------------------------------------------------------------|--------------------------|----------|----------|
| Isolated valve(s) | 92 (48.4%)                                    | 312 (53.7%)                                                             | 815 (38.9%)              | 0.45     | < 0.001  |
| Isolated CABG    | 62 (32.6%)                                    | 169 (29.1%)                                                             | 978 (46.7%)              |          |          |
| CABG + single valve | 36 (19.0%)                                  | 100 (17.2%)                                                             | 300 (14.3%)              |          |          |
| Age; y           | 71 (63–77)                                    | 73 (67–78)                                                              | 69 (61–75)               | 0.01     | 0.002    |
| Sex; female      | 104 (54.7%)                                   | 280 (48.2%)                                                             | 409 (19.5%)              | 0.12     | < 0.001  |
| NYHA class ≥ III | 79 (41.6%)                                    | 238 (41.0%)                                                             | 536 (25.6%)              | 0.88     | < 0.001  |
| MI within 90 days of operation | 4 (2.1%)                                | 19 (3.3%)                                                               | 63 (3.0%)                | 0.41     | 0.48     |
| Previous cardiac operation | 9 (4.7%)                           | 43 (7.4%)                                                               | 87 (4.2%)                | 0.2      | 0.70     |
| Diabetes         | 56 (29.5%)                                    | 154 (26.5%)                                                             | 386 (18.4%)              | 0.43     | < 0.001  |
| Hypertension     | 103 (54.2%)                                   | 291 (50.1%)                                                             | 1009 (48.2%)             | 0.32     | 0.11     |
| Current smoker   | 17 (9.0%)                                     | 44 (7.6%)                                                               | 157 (7.5%)               | 0.54     | 0.47     |
| Creatinine > 200 μmol.l⁻¹ | 2 (1.1%)                               | 19 (3.3%)                                                               | 6 (0.3%)                 | 0.10     | 0.14     |
| Pre-operative Hb; g.l⁻¹ | 125 (119–130)                      | 123 (116–127)                                                           | 143 (137–150)            | <0.001   | <0.001   |
| Respiratory dysfunction | 48 (25.3%)                        | 145 (25.0%)                                                             | 416 (19.9%)              | 0.93     | 0.08     |
| Previous stroke  | 27 (14.2%)                                    | 73 (12.6%)                                                              | 176 (8.4%)               | 0.56     | 0.007    |
| Neurological dysfunction | 8 (4.2%)                         | 25 (4.3%)                                                               | 43 (2.1%)                | 0.96     | 0.07     |
| PVD              | 16 (8.4%)                                     | 53 (9.1%)                                                               | 130 (6.2%)               | 0.77     | 0.23     |
| Pre-operative arrhythmia | 27 (14.2%)                        | 82 (14.1%)                                                              | 219 (10.5%)              | 0.97     | 0.11     |
| Ejection fraction 30%–50% | 38 (20.0%)                         | 93 (16.0%)                                                              | 347 (16.6%)              | 0.2      | 0.23     |
| Ejection fraction < 30% | 9 (4.7%)                         | 22 (3.8%)                                                               | 55 (2.6%)                | 0.56     | 0.09     |
| Logistic EuroSCORE | 5 (2–8) [1–48])                    | 6 (3–9) [1–60])                                                        | 3 (2–6) [1–40])          | 0.03     | <0.001   |

**p values of Hb < 130 g.l⁻¹ and received i.v. iron compared with Hb < 130 g.l⁻¹ and did not receive i.v. iron/not iron-deficient.

**p values of Hb < 130 g.l⁻¹ and received i.v. iron compared with Hb ≥ 130 g.l⁻¹.
those with iron deficiency anaemia, were not mitigated in our patient group by receiving i.v. iron. This cohort of patients also had a higher incidence of diabetes, contributing to an increased risk of renal injury, and with a higher incidence of previous stroke. This may have influenced the prescribing behaviour of clinicians, who may have had a lower threshold for transfusing red cells. In the absence of cohorts matched for comorbidity, it is unclear whether these baseline differences masked a potential beneficial reduction in risk due to i.v. iron. However, when comparing the group that attended for i.v. iron with the untreated anaemic cohort, there was no difference in the incidence of diabetes or stroke pre-operatively, and despite this, there was still no significant difference in the incidence of transfusion between those treated with i.v. iron and those who were not.

It is worth noting that only 39% of patients managed to attain a pre-operative Hb > 130 g.l\(^{-1}\). There are many

### Table 2

|                      | Hb < 130 g.l\(^{-1}\) and received i.v. iron | Pre-op Hb < 130 g.l\(^{-1}\) and did not receive i.v. iron/not iron-deficient | Pre-op Hb ≥ 130 g.l\(^{-1}\) | p value* | p value** |
|----------------------|---------------------------------------------|--------------------------------------------------------------------------------|-----------------------------|---------|---------|
| RBC transfused       | 114 (60.0%) (95 [38–92])                    | 368 (63.3%) (100 [60–108])                                               | 548 (26.2%) (100 [60–108]) | 0.41    | < 0.001 |
| Number of RBC units  | 1 (0–2 [0–17])                              | 1 (0–2 [0–17])                                                            | 0 (0–2 [0–17])              | 0.29    | < 0.001 |
| Number of RBC units  | 2 (1–3 [0–17])                              | 2 (1–3 [0–17])                                                            | 2 (1–3 [0–17])              | 0.50    | 0.24    |
| In-hospital mortality| 3 (1.6%)                                    | 14 (2.4%)                                                                | 17 (0.8%)                                                               | 0.78    | 0.23    |
| Sternal wound infection| 7 (3.7%)                                    | 16 (2.8%)                                                                | 42 (2.0%)                                                               | 0.51    | 0.12    |
| Deep sternal wound infection| 0                                         | 3 (0.5%)                                                                | 5 (0.2%)                                                                | > 0.99  | > 0.99  |
| Superficial sternal wound infection| 6 (3.2%)                           | 11 (1.9%)                                                                | 33 (1.6%)                                                               | 0.39    | 0.12    |
| Other sternal wound infection| 1 (0.5%)                                 | 2 (0.3%)                                                                | 4 (0.2%)                                                                | 0.57    | 0.35    |
| CVA                  | 7 (3.7%)                                    | 11 (1.9%)                                                                | 24 (1.2%)                                                               | 0.15    | 0.01    |
| New RRT              | 7 (6.7%)                                    | 9 (1.6%)                                                                | 13 (0.6%)                                                               | 0.08    | < 0.001 |
| Re-operation (all)   | 9 (4.7%)                                    | 24 (4.1%)                                                                | 73 (3.5%)                                                               | 0.72    | 0.36    |
| Re-operation for bleeding/tamponade | 6 (3.2%)                                      | 15 (2.6%)                                                                | 56 (2.7%)                                                               | 0.67    | 0.70    |
| Re-operation for bleeding/tamponade and ≥ 4 units blood transfused during admission | 5 (2.6%)                                      | 12 (2.1%)                                                                | 28 (1.8%)                                                               | 0.69    | 0.19    |

RBC, red blood cells; CVA, cerebrovascular accident; RRT, renal replacement therapy.

* p values of Hb < 130 g.l\(^{-1}\) and received i.v. iron compared with Hb < 130 g.l\(^{-1}\) and did not receive i.v. iron/not iron-deficient.

** p values of Hb < 130 g.l\(^{-1}\) and received i.v. iron compared with Hb ≥ 130 g.l\(^{-1}\).

### Table 3

|                      | Pre-treatment Hb (g.l\(^{-1}\)) |
|----------------------|----------------------------------|
|                      | <100 n = 9                        | 100–109 n = 24                   | 110–119 n = 41                 | 120–129 n = 116                |
| Pre-treatment Hb; g.l\(^{-1}\) | 96 (92–98 [90–99]) | 105 (100 [90–109]) | 114 (112–118 [110–119]) | 125 (123–127 [120–129]) |
| Ferritin level; μg.l\(^{-1}\) | 30 (13–51 [11–94]) | 33 (15–79 [12–172]) | 45 (21–72 [7–267]) | 56 (28–89 [4–712]) |
| TSAT level; %        | 9 (6–16 [4–50])                  | 11.5 (6.75–18 [4–20])           | 12 (8–18 [2–27])              | 14 (11–18 [5–37])             |
| Serum iron; μmol.l\(^{-1}\) | 7.9 (4.4–13.1 [2.9–32.8]) | 7.8 (4.8–9.9 [2.6–12.8]) | 8.7 (6.5–11.0 [2.1–19.4]) | 9.2 (7.3–11.5 [4.3–23.0]) |
| Intravenous iron dose; mg | 1200 (1200–1400 [1000–2000]) | 1300 (1175–1400 [1000–1600]) | 1300 (1200–1500 [700–1600]) | 1300 (1200–1500 [600–1800]) |
| Change in Hb; g.l\(^{-1}\) | 20 (11–35 [8–47]) | 10 (8–16 [5–55]) | 9 (3–14 [9–27]) | 6 (2–10 [14–29]) |

i.v., intravenous; TSAT, transferrin saturation.

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Table 4 Outcomes in patients who attended the iron clinic by iron deficiency category. Values are number (proportion) or median (IQR [range]).

| Outcome                              | True iron deficiency (ferritin < 30 µg.l⁻¹, CRP < 5 mg.l⁻¹) n = 36 | Functional iron deficiency (ferritin < 30 µg.l⁻¹, CRP > 5 mg.l⁻¹) n = 7 | Anaemia of inflammation (ferritin > 30 µg.l⁻¹, TSAT < 20%, CRP > 5 mg.l⁻¹) n = 44 | Ferritin > 30 µg.l⁻¹, TSAT < 20%, CRP < 5 mg.l⁻¹ n = 61 | CRP N/A n = 42 | p value |
|--------------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------|----------------|---------|
| Patients transfused RBCs             | 17 (47.2%)                                                    | 5 (71.4%)                                                                | 26 (59.1%)                                                                     | 42 (68.9%)                                                   | 24 (57.1%)    | 0.29    |
| Number of RBC units (transfused patients only) | 2 (2–3) [1–5])                                                | 2 (1–2) [1–17])                                                          | 2 (2–4) [1–8])                                                                 | 2 (1–5) [1–11])                                              | 2 (1, 3)    | 0.76    |
| Change in Hb; g.l⁻¹                  | 9 (0–14) [–3–55])                                             | 10 (5–16) [–5–35])                                                       | 7 (3–11) [–10–27])                                                             | 6 (2–9) [–14–28])                                            | 10 (5–14)    | 0.06    |
| Deep sternal wound infection (all)   | 1 (2.8%)                                                     | 0                                                                        | 2 (4.6%)                                                                      | 1 (1.6%)                                                     | 3 (7.1%)     | 0.63    |
| Superficial sternal wound infection  | 0 (0%)                                                       | 0                                                                        | 2 (4.6%)                                                                      | 1 (1.6%)                                                     | 2 (4.8%)     | 0.86    |
| Other sternal wound infection        | 0 (0%)                                                       | 0                                                                        | 0                                                                              | 0                                                            | –             |         |
| CVA                                  | 1 (2.8%)                                                     | 0                                                                        | 2 (4.6%)                                                                      | 3 (4.9%)                                                     | 1 (2.4%)     | 0.47    |
| New RRT                              | 0 (0%)                                                       | 0                                                                        | 2 (4.6%)                                                                      | 3 (4.9%)                                                     | 2 (4.8%)     | 0.71    |
| Re-operation (all)                   | 1 (2.8%)                                                     | 0                                                                        | 1 (2.3%)                                                                      | 5 (8.2%)                                                     | 2 (4.8%)     | 0.58    |
| Re-operation for bleeding/ tamponade | 1 (2.8%)                                                     | 0                                                                        | 1 (2.3%)                                                                      | 3 (4.9%)                                                     | 1 (2.4%)     | 0.90    |

CRP, C-reactive protein; N/A, not available; TSAT, transferrin saturation; RBC, red blood cells; CVA, cerebrovascular accident; RRT, renal replacement therapy.

Factors which may contribute to this. Our current practice does not include administration of any erythropoiesis-stimulating agent. There is concern regarding the risk of an increase in thromboembolic events in patients treated with an erythropoiesis-stimulating agent. It is unclear whether the addition of an erythropoiesis-stimulating agent would improve effectiveness of i.v. iron in the medium term before surgery, while also demonstrating an acceptable risk-benefit.

The role of hepcidin and the hepcidin-ferroportin axis in iron metabolism and the development of iron deficiency is increasingly understood [19]. Hepcidin is a hormone secreted by the liver to control the transfer of iron into the circulation via degradation of the ferroportin transporter. In physiological conditions, it is released when iron is plentiful, with the intention of preventing iron absorption and mobilisation, and secretion should conversely be reduced in the presence of iron deficiency. Despite this, in the presence of chronic inflammation, hepcidin release is frequently increased. Iron is an essential element to some pathogens, and reduction in its availability within the circulation may be protective, although ultimately leading to iron-restricted erythropoiesis and anaemia. As a consequence, many patients will receive limited benefit from oral iron supplementation, as dietary absorption is prevented by elevated hepcidin levels. It may also be true that not all patients will have a good response to i.v. iron therapy. A recent study of patients admitted to ICU showed that hepcidin levels were predictive of a response to i.v. iron [20].

There are limitations in our service that may contribute to the lack of an increase in Hb. The time period for identification and treatment of patients with iron deficiency before surgery is frequently limited. Our patients underwent treatment a median of 21 days before surgery, which may limit the time for treatment to be maximally effective. However, a recent study by Klein et al. chose a minimum time from treatment to surgery of 10 days [18], based on studies indicating time frames from infusion of 7–9 days to a
peak in ferritin levels [21], and 5–14 days to an increase in Hb [22]. While we inform the patient’s surgical consultant of the requirement for treatment with i.v. iron, the decision regarding scheduling of surgery may be dictated by the clinical urgency of their surgery. Current guidance suggests that replacement should occur 4–6 weeks before surgery, and previous studies have shown that ultra-short notice treatment is ineffective [23], although the effectiveness of treatment in the interim period is unclear. An optimal service must endeavour to identify anaemia at the earliest possible stage of the patient journey, ideally at the time of referral, in order to maximise time for identification of iron deficiency and scheduling of treatment.

There are significant barriers to overcome in order to establish and run a successful i.v. iron service. Within organisations, financial constraints may lead to business cases being rejected, and some Trusts have experienced difficulty adding i.v. iron to hospital formularies [18]. Of our patients, 581 were anaemic before surgery but did not attend the i.v. iron clinic. While a proportion of these patients were found not to be iron deficient or had a vitamin B12 or folate deficiency, 301 patients did not have a ferritin check. A large proportion of this cohort was missed during the first year of the clinic, before the addition of an automatic order set within our requesting system that would add ferritin and iron studies where Hb < 130 g.l⁻¹. This ordering system is still reliant on the requester specifically utilising the pre-operative blood test order set in order to trigger the addition of other tests, and where this has not been utilised, patients have not been fully assessed. Of those patients who did have a ferritin check, 69 would have been eligible for i.v. iron treatment. A significant barrier to treatment within this group was limited time between identification of iron deficiency and surgery, an experience echoed by other centres. Early identification of anaemia and iron deficiency is essential in order to maximise time for intervention, but, frequently, despite streamlined pathways, identification is later than ideal. The location of a service may also limit its success. As a hospital serving a large catchment area of Merseyside and North Wales, many of our patients have a significant distance to travel. Attendance of patients from a distance when they were invited for iron was not perceived to be a problem initially, as in our experience patients were keen to take all possible steps to optimise their outcome. However, blood tests identifying anaemia may have been performed close to the day of

Figure 1  Box and whisker plot demonstrating change in haemoglobin following administration of i.v. iron, according to iron deficiency category. Circles represent median change, boxes represent IQR and whiskers represent range.
surgery when patients attended pre-operative assessment clinics. Avoiding delays in diagnosis by encouraging early screening of patients for anaemia, or the development of same-day treatment clinics, is something we are pursuing and that may benefit this cohort. Community-based services could also increase the opportunity for intervention, as could regional delivery of services, allowing centralised treatment of patients from several hospital Trusts. With regional ‘buy-in’, the opportunities to assess and identify iron deficiency early, before referral, may allow optimisation of the timing of treatment.

We found that administration of i.v. iron to patients with iron deficiency anaemia before cardiac surgery was associated with no reduction in rates of transfusion; number of units transfused; incidence of sternal wound infection; cerebrovascular accident; requirement for haemofiltration; re-operation; or in-hospital mortality compared with the untreated anaemic cohort. Unfortunately, a propensity matched analysis was not possible, in part because the number of patients so far treated is modest, but also because patients with anaemia have more comorbidities in general. However, the data do present a note of caution, with the roll out of anaemia services nationwide; that the results of treating iron deficiency solely with i.v. iron may not be as positive as we had hoped, echoing the findings of other groups [17]. It has been estimated by NICE that treatment with i.v. iron in a high-dose low-frequency setting costs £220–£250 per course, when considering the costs of the iron, blood tests before treatment, consumables for infusion and staff in an appropriate location. A unit of red cells currently costs £139 ($183, Euro 155) (NHSBT pricelist 2020/21), and therefore if a reduction in transfusion or overall morbidity cannot be demonstrated, it may be challenging for commissioners to justify the additional costs of funding a service. Oral iron, by contrast, costs pennies per dose, although patient compliance may be poor due to gastrointestinal side-effects and, when absorption is limited by high hepcidin levels, it is frequently ineffective.

There are limitations to the analysis of the effectiveness of our service. This is not a powered or matched analysis. More patients in the non-anaemic group underwent coronary artery bypass grafting vs. valve surgery, or coronary artery bypass grafting and valve surgery, presenting different risks of transfusion and other postoperative complications. As expected, a significantly higher proportion of patients within the iron-deficient anaemic cohort were women, had a New York Heart Association score of 3 or more, were diabetic or had suffered a previous stroke. They were also significantly older. These are all factors that are contributors to risk of morbidity and mortality in the peri-operative period. While we found no difference in in-hospital mortality when patients were treated with i.v. iron before surgery compared with the non-anaemic population, with such heterogeneity, it is unclear if this represents a direct benefit of treatment or is a consequence of the differing underlying pathology of the two groups.

The administration of i.v. iron is not without risk. Historically, i.v. iron products were associated with a high incidence of anaphylaxis. Newer agents have a significantly lower rate of anaphylaxis, secondary to a carbohydrate shell slowing release of elemental iron. Despite this, all i.v. iron preparations should be administered in a setting with resuscitation equipment and trained personnel. Minor infusion reactions may occur and include flushing and mild arthralgia, the so called Fishbane reaction. The majority resolve without therapy and the iron infusion can be completed[24]. Concerns also exist regarding the risk of i.v. iron in the setting of infection. Patients with iron overload disorders have been found to be at significantly higher risk of infection with some siderophilic organisms that would usually pose a lower risk to the wider population [25]. This cohort of patients is more likely to develop more severe, more rapidly progressive and more lethal infection. Given that, in chronic inflammation, the rise in hepcidin is deemed somewhat protective to reduce the availability of iron to pathogens, there is a fear that administration of i.v. iron may be associated with an increased risk of infection. Studies conducted within the dialysis population where there is more experience of the use of i.v. iron with erythropoiesis-stimulating agents, there are no prospective studies showing an increased risk of infection, while others suggest the opposite [25], and current data are conflicting. Finally, the use of ferric carboxymaltose (Ferinject, Vifor Pharma, Glattbrug, Switzerland) has been associated with varying degrees of hypophosphataemia secondary to increased renal losses [26]. While, in the majority of patients, this is transient and asymptomatic, patients with pre-existing hypocalcaemia, hypophosphataemia, low vitamin D levels or elevated parathyroid hormone levels may be at increased risk. Hypophosphataemia may persist for up to 6 months in this patient group and is associated with non-specific symptoms of fatigue, muscle cramps, dizziness and nausea. This is a rare side-effect and is not seen with all iron preparations; nonetheless, prescribers should be aware of it. Iron infusions must also be given via a reliable cannula and the site of insertion should be monitored closely during and after the infusion. Extravasation of i.v. iron can be associated with skin irritation and permanent skin staining. Our experience of administration of i.v. iron has been largely uneventful to date.
One patient experienced an episode of marked flushing and arthralgia (Fishbane reaction), and there have been occasional reports of mild facial flushing that resolved with slowing of the infusion.

The role of iron is more than just in the formation of haemoglobin; iron has significant involvement in mitochondrial function; oxygen transport; DNA metabolism; host defence; and apoptosis [19]. Rossler et al. [27] recently demonstrated that iron deficiency, even in the absence of anaemia, is associated with higher mortality in patients undergoing cardiac surgery. With iron deficiency alone, mortality increased from 2% to 5%. Where anaemia was also present, mortality increased from 4% to 14% and there was an increase in serious adverse events, major cardiac and cerebrovascular events, transfusion and duration of hospital stay. The extended role of iron and the benefits of treatment in other populations demonstrates the effectiveness of replacement therapy in the absence of anaemia. In the heart failure population, the treatment of iron deficiency with or without anaemia is associated with an improvement in exercise tolerance and quality of life, and reduction in hospital admissions. Anecdotally, in our experience, this is within a time frame unrelated to the production of new red cells. The use of quality of life questionnaires allows measurement of this improvement [28]. In the cardiac surgical population, the measurement of this is more difficult, because the surgery performed is likely to lead to a significant improvement in quality of life, and identifying improvement solely related to iron replacement is therefore more challenging.

The delivery of a successful patient blood management programme requires education of clinicians, and our experience represents a ‘real-world’ setting where clinical autonomy regarding prescribing exists outside of a prescriptive study framework, particularly in terms of triggers to transfusion. The impact of intervention on one pillar of blood management is unlikely to produce a benefit without intervention on the other two. Where programmes collectively address all three pillars, there is evidence of a reduction in transfusion of red cells, and a lower complication and mortality rate [14]. We endeavour to educate staff according to recent consensus guidance, including the Frankfurt Patient Blood Management consensus document [29] and 2017 EACTA/ESCTS guidance [30], but ultimately decisions are made by the individual clinician.

Our experience raises several questions that future research may answer. To confer benefit in terms of reduction in requirement for transfusion and morbidity, do we need to achieve Hb > 130 g.l⁻¹ before surgery or should we seek out a more individualised target Hb? Is anaemia alone an appropriate identifier of the ‘at-risk’ patient or are we looking at the wrong trigger for treatment? Should we be considering ferritin levels and/or TSAT as a trigger to treatment, rather than Hb alone? Development of anaemia occurs at a relatively advanced stage of iron deficiency, and it is not our practice to screen all patients for the presence of iron deficiency. As many patients demonstrate a fall in Hb during the peri-operative period, the presence of undiagnosed iron deficiency may hinder their ability to return to pre-operative levels as swiftly, potentially influencing their overall recovery. Should we screen and treat all patients with iron deficiency, regardless of their pre-operative Hb?

The potential benefits of iron replacement in the cardiac and wider surgical population have been described as significant in terms of the impact on patient outcomes, duration of hospital stay and overall costs of patient care. There is increasing experience that treatment is more complex than solely replacing iron, and simply setting up a service for administration may not be sufficient. Identifying patients who will benefit most, those who require concomitant treatment with other agents, and the optimum time frames in research populations, will hopefully help to create protocols that will transfer this potential benefit into the real-world setting.

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**Supporting Information**

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**Figure S1.** Flow diagram representing the preoperative anaemia service pathway.