Iron-restricted erythropoiesis and risk of red blood cell transfusion in the intensive care unit: a prospective observational study

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Summary

Intravenous (IV) iron can decrease transfusion requirements in selected patients with low, normal and moderately elevated ferritin. Whether the syndrome of iron-restricted erythropoiesis (IRE), diagnosed by iron studies, identifies critically ill patients at risk for subsequent red blood cell (RBC) transfusion, and hence, provides a simple method to determine response to IV iron therapy, is uncertain. We aimed to describe the characteristics of patients with IRE on admission to intensive care and determine the optimal variables to identify patients at risk of RBC transfusion who may benefit from early administration of IV iron. The study included 201 consecutive ICU admissions from a single 23-bed combined medical/surgical ICU. The prevalence of IRE on admission to ICU, defined according to ferritin <300 µg/l and transferrin saturation <20%, was 26.2% (95% CI 19.9 to 32.4). The proportion of patients with IRE subsequently receiving RBC transfusion was significantly lower than the proportion of patients without IRE receiving RBC transfusion (absolute mean difference 18.9% [95% CI 4.7 to 33.1, *P* <0.001]). IRE was not independently associated with risk of transfusion on multivariate analysis, however, a prognostic model with three risk factors (RBC transfusion prior to ICU admission, Hb <100 g/l and ICU length of stay >3 days), had good discrimination and calibration for predicting transfusion (receiver operator curve area under the curve 0.87 [95% CI 0.79 to 0.94, *P*=0.88], Hosmer–Lemeshow 6.21; *P*=0.1). Excluding iron overload and using simple prognostic criteria to identify patients at high risk of RBC transfusion may be a preferable strategy for identifying critically ill patients who may benefit from IV iron.

Key Words: intensive care, red blood cell transfusion, iron

Anaemia is nearly universal in ICU patients and is the most common indication for red blood cell (RBC) transfusion, despite high concordance with restrictive guidelines[1,4]. Both anaemia and RBC transfusion are associated with increased morbidity and mortality in critical illness[1–3]. IV iron therapy increases haemoglobin and decreases transfusion requirement in selected patients[5]. As such, IV iron therapy may plausibly improve outcomes during critical illness, however the optimal criteria for selecting patients who may benefit from this therapy in ICU are uncertain.

IV iron therapy improves haemoglobin by overcoming iron-restricted erythropoiesis (IRE). This syndrome includes absolute iron deficiency, functional iron deficiency (the inability of iron stores to meet elevated erythropoietic demands) and iron sequestration (a reduction in the availability of stored iron in the setting of inflammation)[6,7]. Recent guidelines have promoted ferritin as an essential assay in the diagnosis of IRE and the decision to initiate IV iron therapy[8,9].

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We hypothesised that IRE, diagnosed by iron studies on admission to ICU, would identify a substantial group of patients at high risk for subsequent RBC transfusion, and hence provide a simple method to potentially determine a likely response to IV iron therapy. The aim of this study was, therefore, to describe the characteristics of patients with IRE on admission to ICU and determine the optimal variables to identify the group of patients at risk of subsequent RBC transfusion.

Materials and methods

The study was undertaken in the 23-bed combined medical/surgical ICU at Royal Perth Hospital, a university-affiliated tertiary referral centre in Perth, Western Australia. Data from consecutive ICU admissions was recorded in a pre-specified case report form. Patients were followed from ICU admission until discharge from hospital, censored at 60 days post admission to the ICU. The diagnosis of IRE using a cut-off of ferritin <300 µg/l and transferrin saturation (TSAT) <20% was based on a previously published consensus statement and guidelines for the laboratory diagnosis of functional iron deficiency[8,9,11]. The study was approved by the Clinical Safety Quality Unit (Approval No.: 110623-1).

Statistical analysis

The associations between baseline variables and IRE status

were assessed using chi-square, Student's t-test and Mann–Whitney U tests for categorical, parametric and non-parametric continuous variables, respectively. After excluding patients who received IV iron therapy, univariate logistic analysis was used to assess the association between baseline factors and odds of any subsequent in-hospital RBC transfusion. Baseline factors with a *P*-value <0.25 in the univariate logistic regression analyses were then entered in the initial multivariable logistic regression model and eliminated in backward stepwise fashion with a significance level of *P* <0.05. The utility of the final model of risk factors for predicting RBC transfusion was assessed by receiver operator characteristic curve and the Hosmer-Lemeshow test.

A sensitivity analysis was then conducted, investigating the utility of the predictive model for RBC transfusion in patients eligible for IV iron therapy on the basis of iron study parameters from previously published RCTs of IV iron[5]. Parameters varied between studies, however none included patients with a ferritin >1200 µg/l or TSAT >50%. We therefore limited our sensitivity analysis to patients with a ferritin <1200 µg/l and TSAT ≤50% to exclude patients in whom iron over-saturation may limit the efficacy of IV iron.

Sample size calculation

Compared with a previous estimated prevalence of 35% for functional iron deficiency on admission to ICU, a prevalence of 45% would require a sample size of 184 (*P*=0.05 and power 80%)[12]. Assuming approximately 10% of patients with insufficient baseline results to be included in the analysis, a sample size of 200 patients was planned for inclusion in the study.

Results

Between 5 March and 14 April 2012 there were 201 consecutive ICU admissions. Admission blood results were not available in six cases, therefore, a total of 195 patients were included in the analysis. The median age of the cohort was 53 (IQR 36 to 65); 68% (95% CI 61 to 74) were male and 75% (95% CI 69 to 81) received mechanical ventilation. The participant characteristics are presented in Table 1.

Table 1

Participant characteristics

	n=195
Age	53 (36–65)
Male gender, n (%)	132 (68)
Admission type, n (%)	
Medical	90 (46)
Elective surgical	36 (18)
Emergency surgical	69 (35)
APACHE II admission score	14 (9–18)
SOFA admission score	5 (3–7)
Mechanical ventilation, n (%)	146 (75)
Renal replacement therapy, n (%)	22 (11)

Median (IQR) unless stated otherwise. APACHE=Acute Physiology and Chronic Health Evaluation, SOFA=Sequential Organ Failure Assessment.

Characteristics of patients with iron-restricted erythropoiesis

The prevalence of IRE on admission to ICU, defined according to ferritin <300 µg/l and TSAT <20%, was 26.2% (95% CI 19.9 to 32.4). Age, gender, APACHE II score, sequential organ failure assessment score, haemoglobin and C-reactive protein were similar between those with and without IRE. Compared to patients without IRE, those with IRE had significantly lower mean corpuscular volume and mean corpuscular haemoglobin—mean difference 2.5 fl (95% CI 0.8 to 4.3, *P* <0.001) and 1.3 pg (95% CI 0.6 to 2.0, *P* <0.001), respectively.

The proportion of patients with IRE subsequently receiving RBC transfusion was significantly lower than the proportion of patients without IRE receiving RBC transfusion, as was the proportion of patients with and without IRE discharged from hospital with a haemoglobin <100 g/l—absolute mean difference 18.9% (95% CI 4.7 to 33.1) and 36.6% (95% CI 20.9 to 52.2), respectively. Only four patients received IV iron after admission to ICU, none of whom fulfilled the criteria for IRE on admission to ICU. The characteristics and outcomes of patients according to admission IRE status are presented in Table 2.

Risk factors for RBC transfusion

After excluding four patients who received IV iron therapy, 16 variables were assessed for association with subsequent RBC transfusion on univariate analysis (Table 3). Age, emergency ICU admission, chronic renal impairment, RBC transfusion prior to ICU admission, APACHE II score, sequential organ failure assessment score, renal replacement therapy, ICU length of stay, ICU admission haemoglobin, C-reactive protein, mean corpuscular volume, mean corpuscular haemoglobin and IRE (ferritin <300 µg/l and TSAT <50%) all had a *P*-value <0.25 and were therefore included in the subsequent multivariable logistic regression for stepwise elimination.

In the final multivariable model presented in Table 4, five variables were found to be significantly associated with subsequent risk of RBC transfusion (previous RBC transfusion, sequential organ failure assessment score, ICU length of stay, admission haemoglobin and C-reactive protein). IRE was not independently associated with risk of subsequent RBC transfusion.

The receiver operator characteristic (ROC) area under the curve (AUC) for risk of transfusion using the five-variable multiple regression model was 0.93 (95% CI 0.89 to 0.97). Calibration, as assessed by Hosmer–Lemeshow, was 3.20 (*P*=0.92) (Figure 1).

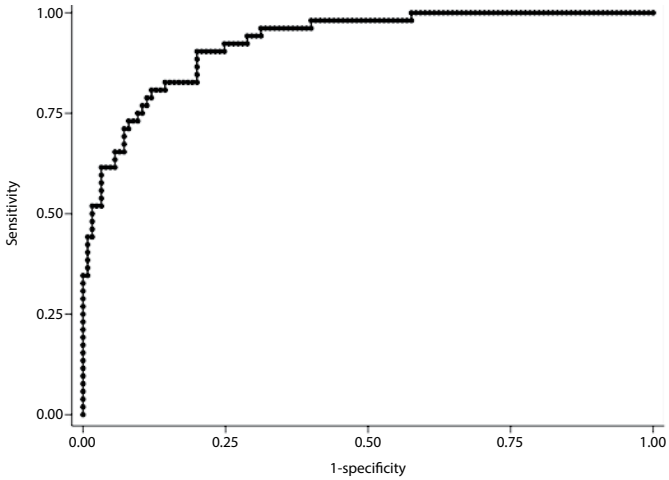

Figure 1: ROC probability of RBC transfusion. n=177, ROC AUC 0.93 (0.89–0.97), Hosmer–Lemeshow 3.20; *P*=0.92. ROC=receiver operator characteristic, RBC=red blood cell, AUC=area under the curve.

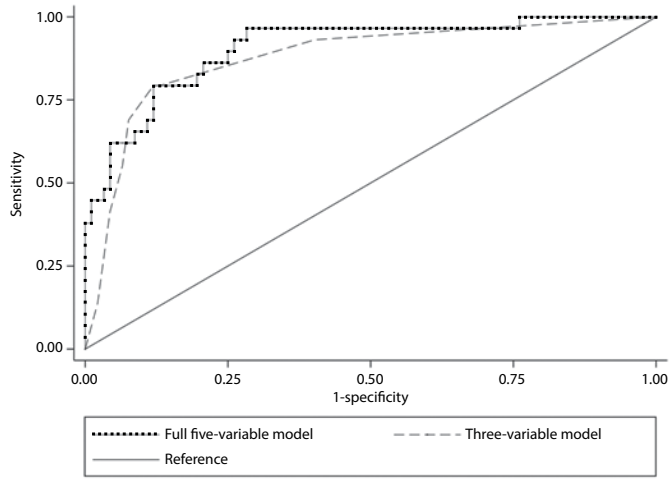

Figure 2: ROC probability of RBC transfusion after excluding patients unlikely to benefit from IV iron (ferritin >1200 µg/l and/or transferrin saturation >50%). Comparison of full model and three risk factor model. ROC AUC 0.91 (95% CI 0.84–0.97) versus 0.88 (95% CI 0.80–0.95), P=0.20; Hosmer–Lemeshow for three-variable model 6.33, P=0.10, n=121. ROC=receiver operator characteristic, RBC=red blood cell, AUC=area under the curve.

Table 2

Characteristics and outcomes of patients with and without iron-restricted erythropoiesis on admission to ICU

	Iron-restricted erythropoiesis, n=51	Not iron-restricted erythropoiesis, n=144	*P*-value
Age	44 (23–59)	54 (42–66)	<0.01
Male gender, n (%)	31 (61)	101 (70)	0.22
APACHE II	14 (10–17)	14 (9–19)	0.39
SOFA score	5 (3–7)	5 (3–7)	0.33
Haemoglobin, g/l, mean (95% CI)	118 (112–124)	115 (111–118)	0.40
Mean corpuscular volume, fl	89 (86–92)	91 (88–93)	<0.01
Mean corpuscular haemoglobin, pg, mean (95% CI)	29.7 (28.9–30.5)	31.0 (30.6–31.3)	<0.001
Fe, µmol/l	5 (3–7)	13 (5–19)	<0.01
Transferrin saturation, %	10 (7–14)	26 (13–50)	<0.01
Ferritin, µg/l	144 (78–215)	448 (227–1165)	0.03
C-reactive protein, mg/l	65 (9–86)	63 (3–90)	0.88
RBC transfusion, n (%)	7 (14)	47 (33)	0.01
RBC units in those transfused, mean (95% CI)	3.4 (1.7–5.2)	5.2 (3.4–7.0)	0.46
ICU LOS	1 (1–4)	2 (1–4)	0.21
ICU mortality, n (%)	6 (12)	9 (6)	0.21
Haemoglobin change from ICU admission to hospital discharge in non-transfused survivors, g/l	2 (-3–6)	-7 (-10 to-4)	<0.01
Discharged from hospital with Hb <100 g/l, n (%)	3 (7)	54 (44)	<0.001
Hospital LOS	6 (2–14)	12 (6–21)	<0.01
Hospital mortality	6 (12)	11 (8)	0.37

Median (IQR) unless otherwise stated. APACHE=Acute Physiology and Chronic Health Evaluation, SOFA=Sequential Organ Failure Assessment, Fe=Iron, RBC=red blood cell, LOS=length of stay.

Table 3

Univariate analysis of association between baseline variable and in-hospital RBC transfusion after admission to ICU (n=191)

	Odds ratio (95% CI)	*P*-value
Age	1.03 (1.01–1.05)	0.004
Gender	1.11 (0.56–2.21)	0.760
Emergency ICU admission	2.02 (0.79–5.20)	0.144
Chronic renal impairment*	3.88 (1.61–9.35)	0.003
Chronic acid suppression use†	1.12 (0.51–2.48)	0.771
RBC units transfused prior to ICU admission	21.32 (8.90–51.08)	<0.001
APACHE II	1.07 (1.02–1.12)	0.006
SOFA score	1.22 (1.08–1.37)	0.001
Mechanical ventilation	0.77 (0.38–1.57)	0.470
Renal replacement therapy	6.95 (2.62–18.44)	<0.001
ICU LOS	1.27 (1.15–1.41)	<0.001
C-reactive protein, mg/l	1.01 (1.00–1.01)	0.001
Haemoglobin, g/l	0.93 (0.90–0.95)	<0.001
Mean corpuscular volume, fl	0.97 (0.91–1.02)	0.264
Mean corpuscular haemoglobin, pg	0.92 (0.81–1.05)	0.236
Iron-restricted erythropoiesis‡	0.34 (0.14–0.80)	0.014

*Chronic renal impairment defined according to creatinine >110 µmol/l. †Chronic acid suppression included all patients receiving proton pump inhibitor or H2 receptor blocker on admission to hospital. ‡Iron-restricted erythropoiesis defined according to ferritin <300 µg/l and transferrin saturation <20%. RBC=red blood cell, APACHE=Acute Physiology and Chronic Health Evaluation, SOFA=Sequential Organ Failure Assessment, LOS=length of stay.

Table 4

Final multivariable model after excluding four patients who received IV iron whilst in ICU, then stepwise elimination of all variables with P >0.05

	Odds ratio (95% CI)	Coefficient*	*P*-value
RBC units transfused prior to ICU admission	11.11 (3.74–33.07)	2.408	<0.001
SOFA score	1.23(1.03–1.48)	0.210	0.02
ICU LOS	1.25 (1.08–1.45)	0.225	0.003
C-reactive protein, mg/l	1.01 (1.00–1.01)	0.007	0.007
Haemoglobin, g/l	0.95 (0.92–0.98)	-0.157	<0.001

*Logistic regression coefficient constant 1.889. RBC=red blood cell, SOFA=Sequential Organ Failure Assessment, LOS=length of stay.

Predicting RBC transfusion in those who may benefit from IV iron

After excluding patients unlikely to benefit from IV iron (ferritin >1200 µg/l and TSAT >50%), the ROC AUC for the five-variable model was 0.91 (95% CI 0.84 to 0.95) (Table 4). Predictive accuracy was also not substantially different when limited to a more clinically useful model comprising only three simple variables categorised according to maximal ROC AUC (RBC transfusion prior to ICU admission, Hb <100 g/l on admission to ICU, and ICU length of stay >3 days), ROC AUC 0.88 (95% CI 0.80 to 0.95), *P*=0.20; Hosmer–Lemeshow for three-variable model 6.33, *P*=0.10 (Table 5). In this subgroup, 30 (22.2% [95% CI 15.1 to 29.3]) and 31 (25.5% [95% CI 17.9 to 33.8]) patients, respectively, were admitted to ICU and discharged from hospital with a haemoglobin <100 g/l.

Discussion

Our study found a diagnosis of IRE, (based on a ferritin <300 µg/l and TSAT <20%) to be moderately prevalent on admission to ICU (26.2% [95% CI 19.9 to 32.4]). However, IRE was not independently associated with risk of subsequent RBC transfusion, despite those with IRE having a significantly lower mean corpuscular volume and mean corpuscular haemoglobin. Rather than identifying a group at high risk of RBC transfusion, IRE appeared to be protective on univariate analysis, possibly due to the competing effect of increased ferritin as a marker of the severity of acute inflammation and illness severity, itself likely to increase the incidence and severity of anaemia.

The optimal criteria for determining the response to IV iron in critically ill patients with IRE remain unknown. A previous study in patients with chronic kidney impairment suggested that iron studies are inadequate in guiding the response to IV iron[14]. Our findings concur and suggest that a diagnosis of IRE on the basis of iron studies alone is likely to have limited clinical utility in determining responses to IV iron in the critical care setting, particularly given the low incidence of RBC transfusion and severe anaemia on hospital discharge in this group.

In contrast, we found that a predictive model based on three simple clinical criteria (RBC transfusion prior to ICU admission, haemoglobin <100 g/l and ICU length of stay >3 days) identified patients at high risk of subsequent in-hospital RBC transfusion and may have greater clinical utility as a way of identifying patients who may benefit from IV iron therapy. This high-risk group was also at high risk of discharge from hospital with severe anaemia, a condition that may then persist long after discharge from hospital and be associated with increased morbidity and mortality[10,15].

Table 5

Model for predicting RBC transfusion, excluding patients with iron oversaturation and comprising only three simple variables categorised according to maximal ROC AUC (RBC transfusion prior to ICU admission, Hb <100 g/l on admission to ICU and ICU LOS >3 days)

	Odds ratio (95% CI)	Coefficient*	*P*-value
RBC units transfused prior to ICU admission	7.44 (2.15–25.78)	2.01	0.002
ICU LOS >3 days	3.59 (1.17–11.02)	1.28	0.025
Haemoglobin <100 g/l	9.50 (2.92–30.87)	2.25	<0.001

*Logistic regression coefficient constant-3.13. RBC=red blood cell, ROC=receiver operator characteristic, AUC=area under the curve, LOS=length of stay.

Free iron associated with RBC transfusion may increase the risk of oxidative stress and infection[16,17]. Whether IV iron therapy is associated with similar free iron release in critical illness is an important additional consideration. A recent RCT of IV iron in trauma patients excluding patients with a ferritin >1000 ng/ml or TSAT >50% found no significant difference in RBC transfusion requirement, infection or mortality but generalisability may be limited by the liberal haemoglobin inclusion threshold, dose and type of IV iron[18,19].

Several limitations of our study bear consideration. First, this was a single-centre observational study. As such, the generalisability of the model for predicting transfusion is uncertain. The cohort of patients and incidence of RBC transfusion however, were generally representative of Australian tertiary ICU admissions. Second, only four patients received IV iron therapy in ICU. We were therefore unable to assess the association between IV iron therapy and subsequent RBC transfusion in patients who fulfilled our high-risk criteria. Further randomised, controlled studies are warranted to determine the role of IV iron in critically ill patients[19]. Finally, we did not assess several potential markers of IRE, including hepcidin, soluble transferrin receptors and zinc protoporphyrin. The role of these markers in critical illness remains uncertain.

Conclusion

Despite moderate prevalence, iron-restricted erythropoiesis, diagnosed on iron studies on admission to ICU, is associated with a low incidence of severe anaemia and subsequent RBC transfusion and is unlikely to be of clinical utility in determining the response to IV iron. Excluding iron over-saturation, plus early identification of patients at high risk of subsequent in-hospital RBC transfusion using a simple three-variable model, may be a preferable strategy for deciding who may benefit from IV iron therapy in ICU.

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