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RESEARCH ARTICLE

Red blood cell transfusion and the use of intravenous iron in iron-deficient patients presenting to the emergency department

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Abstract

Background and aims: Red blood cell transfusions are often used to treat iron-deficient patients in the emergency department (ED), while treatment with intravenous (IV) iron is preferred, as it increases hemoglobin concentration rapidly and durably. We aim to evaluate the incidence of iron deficiency anemia, frequency of blood transfusion and iron supplementation, and factors associated with blood transfusion in the ED.

Methods: We conducted a retrospective cohort study of adult patients presenting to the St. Boniface Hospital (Winnipeg, Canada) ED from 2014 to 2018. Electronic data obtained from the Emergency Department Information System and Laboratory Information Services databases identified patients presenting with iron deficiency anemia, defined as microcytic (mean corpuscular volume < 75 fL) anemia (hemoglobin < 120 g/L) with either a transferrin saturation <20% or ferritin < 30 µmol/L. Ferritin > 100 µmol excluded iron deficiency anemia. The use of blood transfusions or iron supplementation was determined for each patient. Factors associated with blood transfusion were determined using logistic regression analyses.

Results: Of 39,222 patients, 17,945 (45%) were anemic. In anemic patients, iron parameters were ordered in 1848 (10.3%) and iron deficiency anemia was diagnosed in 910 (5.1%). Ninety-five patients (10.4%) received one red blood cell unit, and 197 patients (21.6%) received ≥2 units. Oral iron and IV iron were prescribed for 64 (7.0%) and 14 (1.5%) patients, respectively. Hemoglobin concentration was the main determinant for treatment with blood transfusion.

Conclusions: Iron deficiency is underinvestigated among anemic patients presenting to the ED. The only clinical factor associated with red blood cell transfusion in the ED was hemoglobin level, irrespective of symptoms or clinical stability.

Ryan Zarychanski and Brett L. Houston are contributed equally.

KEYWORDS
anemia, blood transfusion, iron deficiency, iron replacement

1 | INTRODUCTION

Iron deficiency anemia is common, with a prevalence of approximately 3% in the Canadian adult population [1]. Iron replacement is the treatment of choice for hemodynamically stable patients with iron deficiency anemia, [2] yet red blood cell transfusion is often used to treat these individuals in the emergency department (ED). Blood is a scarce and expensive donor resource, [3] and its use is associated with potential adverse reactions including allergic reactions, infection, and alloimmunization. [4–6] Intravenous (IV) iron is an effective, safe, and cost-efficient alternative to red blood cell transfusion, which increases hemoglobin concentration, reduces or avoids the need for blood transfusion, and reduces recurrent ED visits [7–11]. To target interventions designed to improve the quality of care and conserve blood products, our objective is to evaluate the incidence of iron deficiency anemia, the frequency of iron supplementation and red blood cell transfusion, and clinical factors associated with red blood cell transfusion.

2 | METHODS

2.1 | Study design

We performed a retrospective cohort study of all adult patients presenting to the St Boniface Hospital (Winnipeg, CAN) ED with iron deficiency anemia from 2014 to 2018. This is one of two tertiary care centers in Winnipeg, CAN that provide health services to approximately 1.4 million people. Ethics for the study was approved by the Health Research Ethics Board at the University of Manitoba.

2.2 | Data sources

We obtained patient demographics and clinical data from the Emergency Department Information System. Laboratory data was obtained from the hospital's Laboratory Information System. Blood transfusion data was obtained from the Canadian Blood Services Traceline database.

2.3 | Study population

We included all adult patients who presented to the ED with iron deficiency anemia. To target a clinically stable patient population, we excluded patients presenting with acute hemorrhage, in whom red blood cell transfusion may be most appropriate regardless of other hemodynamic parameters. We included new patient encounters only; subsequent visits to ED by the same patient were disregarded. We defined iron deficiency anemia based on hemoglobin, iron parameters, mean corpuscular volume, and red blood cell count. Patients were initially included if their hemoglobin was below 120 g/L. In these patients, ferritin less than 30 μg/L confirmed iron deficiency anemia, and greater than 100 μg/L ruled out iron deficiency anemia. In patients without ferritin values, or in patients with ferritin values between 30 and 100 μg/L, patients were considered to have probable iron deficiency anemia if their mean corpuscular volume was less than 75 fL, and red blood cell count less than 4.0 [12]. The red blood cell count criteria was used to exclude thalassemia patients, as they also have microcytosis but rarely have red blood cell counts less than 4.0 in the absence of concurrent iron deficiency anemia [12]. When available, a transferrin saturation of less than 20% was also taken to confirm iron deficiency anemia, if ferritin was not greater than 100.

2.4 | Study variables

We obtained patient demographics including patient age and sex. Triage vital signs and the Canadian Triage and Acuity Scale (CTAS) were used to assess clinical acuity [13]. The CTAS score is a clinical acuity score assigned by the triaging nurse for patients presenting to ED. The electronic patient record was reviewed to ascertain the patient's presenting complaint as well as symptoms of anemia, including chest pain, dyspnea, pre-syncope, and fatigue. Laboratory data included hemoglobin, mean corpuscular volume, red blood cell count, ferritin, and transferrin saturation.

2.5 | Outcomes

We characterized the incidence of iron deficiency anemia in all adult patients presenting to the ED. We also evaluated the proportion of anemic patients who had iron indices (ferritin, transferrin saturation) performed and the proportion of patients who met the criteria for iron deficiency anemia. We characterized the percentage of patients exposed to red blood cell transfusions, as well as the number of red blood cell units transfused. We also evaluated the proportion of patients with iron deficiency anemia who received IV and oral iron.

2.6 | Statistical analysis

We described baseline characteristics using means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous variables, and frequencies and proportions for categorical

TABLE 1 Baseline characteristics of iron deficiency anemia population by therapeutic intervention received in the emergency department (ED).

	All patients with iron deficiency anemia	No red blood cell transfusion	1-unit red blood cells transfused	2+ units of red blood cells transfused	Oral iron prescribed	IV iron prescribed
Total	910	618	95	197	64	14
Age (IQR)	66 (47,80)	65 (43,80)	68 (56,81)	69 (53,79)	63 (47,82)	47 (28,58)
Male (%)	334 (36.7)	217 (35.1)	34 (35.8)	83 (42.1)	25 (39.1)	3 (21.4)
CTAS score 1 or 2 (%)	302 (33.2)	224 (36.2)	22 (23.2)	56 (28.4)	17 (26.6)	3 (21.4)
Triage Heart Rate (IQR)	92 (78, 106)	90 (77, 106)	93 (83,107)	94 (81,106)	93 (79,109)	91 (86,109)
Triage systolic BP (IQR)	129 (113,146)	129 (113, 146)	130 (113,143)	130 (114,146)	133 (115,148)	130 (120,144)
Triage diastolic BP (IQR)	67 (60, 77)	69.5 (64, 77)	65.5 (57,71)	65 (57,71)	71 (67,83)	74 (62,84)
Cardiac Symptoms* (%)	346 (38.0)	243 (39.3)	33 (34.7)	70 (35.5)	20 (31.2)	4 (28.6)
Hemoglobin (IQR)	84 (67,101)	95 (82,108)	65 (58,73)	62 (54,70)	83 (74,98)	77 (59,84)

Abbreviations: BP, blood pressure; CTAS, Canadian Triage and Acuity Scale; ED, emergency department; IQR, interquartile range; IV, intravenous.
*Cardiac Symptoms defined as any of Dyspnea, Chest Pain, Palpitations, or Syncope in the documented presenting complaint.

data. Analyses were conducted using Statistical Analysis Software (SAS version 9.4 for Windows; SAS Institute Inc.). We used univariate and multivariate logistic regression analyses to determine factors associated with red blood cell transfusion, which we presented as odds ratios and their 95% confidence intervals. In our multivariable model, we included variables that could potentially impact the decision to transfuse red blood cells including patient age > 65 years, sex, CTAS score of 1 or 2, triage heart rate of greater than 110 bpm, systolic blood pressure less than 90 mmHg, symptoms of chest pain, dyspnea, pre-syncope, and baseline hemoglobin concentration. The impact of hemoglobin concentration was evaluated using a priori hemoglobin subgroups: hemoglobin >90, 81–90, 71–80, 61–70, or ≤60 g/L.

3 | RESULTS

3.1 | Baseline characteristics

We identified 39,222 unique patients who presented to an ED between 2014 and 2018. Of these, 17,945 patients had a hemoglobin of less than 120 g/L. 1110 patients were excluded as their documented presenting complaint included acute hemorrhage. Of the anemic patients, 1848 (10.3%) had ferritin ordered in the ED. 910 patients met the criteria for iron deficiency anemia, representing 2.3% of all patients, and 5.1% of anemic patients. The baseline characteristics for the patients with iron deficiency anemia are summarized in Table 1.

3.2 | Frequency of red blood cell transfusion and iron supplementation

Of the patients with iron deficiency anemia, 67.8% (618/910) patients did not receive a red blood cell transfusion, 10.4% (95/910) of patients received one unit of red blood cells, and 21.6% (197/910) of patients received two or more red blood cell units. Patient characteristics including age, triage heart rate and blood pressure, triage CTAS score, and cardiac symptoms were similar between transfused and non-transfused groups (Table 1). The hemoglobin concentration varied significantly by transfusion status. The hemoglobin concentration (median and IQR) in patients who received 0, 1, and 2 or more red blood cell units was 95 g/L (82–108), 65 g/L (58–73), and 62 g/L (54–70), respectively. Oral iron and IV iron were prescribed in the ED for 64 (7%) and 14 (1.5%) patients, respectively.

3.3 | Predictors of red blood cell transfusion

On univariate analysis, a CTAS score of 1 or 2, indicating higher acuity, was associated with lower odds of red blood cell transfusion (odds ratio [OR] 0.6; $p = 0.0045$). Both univariate and multivariate logistic regression analyses demonstrated that a hemoglobin of greater than 90 g/L was associated with significantly lower odds of receiving transfusion (OR 0.02, $p < 0.0001$).

In multivariate analysis, male sex showed a slight trend towards increased transfusions (OR 1.6, $p = 0.0116$), as did age over 65 years (OR 1.6, $p = 0.00676$). Vital signs, CTAS score, and cardiac symptoms were not associated with transfusion (Table 2).

3.4 | Sub-group analyses

In pre-specified subgroup analyses by hemoglobin concentration and by hemodynamic compromise (defined as either triage heart rate >110 bpm or systolic blood pressure less than 90 mmHg), we found that hemoglobin concentration, but not hemodynamic compromise, was associated with red blood cell transfusion (Table 3).

TABLE 2 Results of logistic regression models assessing factors associated with red blood cell transfusion in the emergency department (ED).

	Odds ratio (univariate logistic regression)	*p*-value	Adjusted odds ratio (multivariate logistic regression)	*p*-value
Hemoglobin > 90 mmHg	0.02	<0.0001	0.01	<0.0001
Age > 65 years	1.3	0.0504	1.6	0.00676
Male	1.2	0.148	1.6	0.0116
CTAS score 1 or 2	0.6	0.0045	0.8	0.217
Heart rate > 110 bpm	0.9	0.725	1.1	0.815
Systolic BP < 90 mmHg	2.1	0.0563	2.2	0.128
Cardiac Symptoms	0.8	0.241	1.3	0.281

Abbreviations: bpm, beats per minute; CTAS, Canadian Triage and Acuity Scale; ED, emergency department.

TABLE 3 Comparison of transfusion practices among patients based on anemia severity and the presence or absence of hemodynamic compromise.

	No transfusion, *n* = 618 (%)	One unit transfused, *n* = 95 (%)	Two or more units transfused, *n* = 197 (%)
Hemoglobin(g/L)			
<60	19 (3.1)	34 (35.8)	90 (45.7)
60–70	25 (4.0)	34 (35.8)	62 (31.5)
70–80	88 (14.2)	16 (16.8)	32 (16.2)
80–90	123 (19.9)	8 (8.4)	9 (4.6)
>90	363 (58.7)	3 (3.2)	4 (2.0)
Hemodynamic compromise			
Present*	309 (50.7)	39 (41.1)	83 (42.8)

*Defined as having either a CTAS score of 1 or 2 or heart rate <110 or systolic BP less than 90.

Twenty-four (4.7%) patients with hemoglobin greater than 80 g/L received a blood transfusion, whereas only 19 (13%) patients with hemoglobin less than 60 g/L did not receive a transfusion. Evidence of hemodynamic compromise was present in 50.7%, 41.1%, and 42.8% of patients receiving zero, one unit, or two or more units of blood, respectively.

4 | DISCUSSION

4.1 | Interpretation of findings

In this retrospective cohort study, we observed that approximately 2% of all patients presenting to an ED had evidence of iron deficiency anemia, although this may be an under-representation as iron parameters were infrequently checked. The incidence of iron deficiency anemia in our study population is slightly higher than in a recent study in Toronto, Ontario, which identified an incidence of 0.3%. The increased incidence of iron deficiency in our study may be explained by using more sensitive inclusion criteria, accounting for patients with ferritin between 30 and 100 μg/L, with red blood cell counts less than 4.0 [14]. We described the use of blood transfusion and iron replacement therapy and found that blood transfusion is used more frequently than IV iron. Hemoglobin concentration appears to be the primary factor that influences the decision to transfuse. Other patient variables, including age, symptoms of anemia, or vital sign abnormalities, did not appear to influence the decision to transfuse, nor the decision to transfuse 1 unit versus 2 or more red blood cell units. This was consistent across preplanned subgroup analyses and is consistent with a prior study from Toronto, Ontario [15].

4.2 | Clinical implications

Our study highlights an opportunity to improve the care of patients with iron deficiency anemia who present to the ED. Possible areas of improvement include more routine evaluation of iron parameters among anemic patients and increased prescription of oral and IV iron. The preferential use of iron supplementation directly addresses the underlying problem (i.e., iron deficiency), and is more efficient, less costly, and safer for patients [16]. For example, ferric derisomaltose can administer 1 g of iron in approximately a quarter of the time that it takes for a blood transfusion. This is less costly and prevents risks related to transfusion including allergic reactions, alloimmunization, and transfusion-associated circulatory overload [17, 18]. Minimizing risks of alloimmunization among women of childbearing potential, a population frequently affected by iron deficiency anemia, is of particular importance, to prevent future risk of hemolytic disease of the fetus and newborn [19, 20]. Furthermore, recent literature demonstrates that iron-deficient patients who receive IV iron may be more likely to be discharged directly from the ED [21].

Another opportunity to improve care delivery includes the judicious use of blood transfusions, with use guided by hemodynamic instability and symptomatic anemia. Choosing Wisely Canada recommends a case-by-case consideration of red blood cell transfusion, rather than transfusions triggered by hemoglobin concentration alone [22, 23]. Red blood cell transfusion at a hemoglobin threshold of less than 70 g/L is appropriate for patients with symptomatic anemia, hemodynamic

instability, or active bleeding. However, patients with asymptomatic, chronic, iron-deficient anemia could be managed with alternative therapies such as iron supplementation [18, 19]. If a red blood cell transfusion is felt to be indicated, a single red blood cell unit is likely sufficient among non-bleeding patients with chronic anemia [23]. In our study, 21.6% of patients were treated with 2 or more units of red blood cells, with a median (IQR) pre-transfusion hemoglobin of 62 g/L (54–70). This further represents another opportunity to minimize the use of unnecessary red blood cell transfusions and their associated risks.

4.3 | Research implications

We have identified an under investigation of iron parameters among patients with anemia presenting to the ED. A possible explanation for reduced iron indices testing could include stresses on the Canadian Health Care System, whereby critical bed shortages require the discharge of stable patients and expedient admission of patients requiring inpatient management. Therefore, the ED priority may be on patient stability, rather than investigation of stable anemia. Future research could investigate the impact of healthcare provider education and protocolized blood work implementation to identify patients at risk and increase the detection of iron deficiency anemia.

We have also identified limited use of iron supplementation among patients with iron deficiency anemia in the ED. Future studies could include qualitative interviews and/or a survey of emergency room physicians to identify perceived barriers and facilitators to iron administration, which would aid in the development of guidelines and processes to increase iron replacement, and ultimately reduce the use of inappropriate red blood cell transfusions. Recent studies have demonstrated that the use of a clinical decision tool when treating stable iron deficiency anemia in the ED resulted in the increased use of IV iron and a reduction in the rate of inappropriate blood transfusions [24].

A multi-center, prospective evaluation of iron parameter testing and the use of iron supplementation in the ED would be beneficial to overcome the inherent limitations of a retrospective design and increase the generalizability of study findings.

4.4 | Strengths and limitations

Strengths of our study include the use of a comprehensive, high-fidelity dataset that allows the evaluation of iron deficiency anemia in the context of clinical stability, by including patient symptoms and CTAS score. Additionally, our study characterizes the frequency of blood transfusions used in the treatment of iron deficiency anemia and the associated patient demographics and clinical factors related to the use of transfusion. Limitations of this study include the likely underestimation of the true incidence of iron deficiency anemia due to limited ferritin testing in our cohort. We tried to mitigate this by using mean corpuscular volume-based criteria, although this may have inadvertently included a subset of patients with anemia or inflammation. The prescribing of oral iron in the ED is not accurately captured, as oral iron does not require a prescription, and physicians may recommend oral iron to patients without issuing a discharge prescription that would be recorded in the Emergency Department Information System. Further, missing data and the reliance on accurate documentation in the Emergency Department Information System could introduce bias into the analysis, due to the retrospective nature of this study. Additionally, this is a single-center study, and while this center serves a broad referral base, this may limit generalizability to other health care settings, with varying guidelines, patient populations, or resource availability.

Lastly, our data was collected on patients presenting to the ED between 2014 and 2018, although there have been no major changes to guidelines or clinical practice recommendations since the conclusion of this study [22, 23, 25].

5 | CONCLUSION

Iron deficiency is underinvestigated among anemic patients presenting to the ED. The only clinical factor associated with red blood cell transfusion in the ED was hemoglobin level, irrespective of symptoms or clinical stability.

AUTHOR CONTRIBUTIONS

Kevin Thomas: Writer and editor of the manuscript. **Arvand Barghi**: Writer and editor of manuscript; data collection and statistical analysis. **Robert Balshaw**: Editor of the manuscript. **Emily Rimmer**: Editor of the manuscript. **Murdoch Leeies**: Editor of the manuscript. **Donald Houston**: Editor of the manuscript. **Allan Garland**: Editor of the manuscript. **Ryan Zarychanski**: Editor of the manuscript. **Brett Houston**: Writer and editor of manuscript; data collection; and statistical analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING INFORMATION

None to declare.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

This research was conducted within Wiley's ethics and integrity policies. This study was conducted in compliance with all ethical guidelines within the Human Research Ethics Board at the University of Manitoba.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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