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Correcting pre-operative iron deficiency as part of patient blood management in the "real world": Results of an audit on an Australian cohort

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Short title: preoperative iron therapy in elective surgery

Abstract

Background: The Peri-operative module of the Australian Patient Blood Management guidelines recommended pre-operative iron therapy for surgical patients with, or at risk of, iron deficiency anaemia. After implementing a pre-operative haemoglobin optimisation programme in our institution, an audit was undertaken to evaluate the benefit of pre-operative iron therapy in "real world" clinical practice.

Methods: Elective major surgery patients assessed in surgical pre-admission clinics from 1 July 2013 to 30 June 2014 were screened for iron deficiency and anaemia. Those who were iron deficient (ferritin <30 µg/L), regardless of haemoglobin level, received either daily oral iron supplementation until day of surgery or intravenous iron polymaltose 1 gram pre-operatively (intervention group). Controls patients who were not iron deficient were matched to the intervention group using propensity scores based on age, sex and surgical unit. The primary end point was the proportion of patients requiring peri-operative red cell transfusion in intervention and control groups.

Results: One hundred and fourteen patients (8.75%) had iron deficiency. Ninety-three patients received pre-operative iron therapy, 17 (18.3%) of whom required red cell transfusions post-operatively. Of the 332 control patients 71 (21.4%) required red cell transfusion. After adjusting for pre-operative haemoglobin and time from screening to surgery, the odds of red cell transfusion were significantly lower in the intervention group compared to controls (odds ratio: 0.512, 95% confidence interval: 0.268-0.977; $p = 0.04$).

Conclusion: Pre-operative iron therapy was associated with reduced need for post-operative red blood cell transfusion in elective major surgery patients who were initially iron deficient.

Key words: Transfusion - surgery, patient blood management, red cells, iron deficiency

Introduction

Pre-operative anaemia is associated with increased length of stay (LoS) in hospital, post-operative complications and mortality [1-3]. It is also a strong predictor of post-operative red blood cell transfusion (RBCT) requirement [4-6].

Post-operative RBCT is associated with potentially deleterious effects on surgical patients such as increased mortality [6-11], greater risk of infection [6-9,12,13] (including wound infections, sepsis and pneumonia) and significantly longer LoS in hospital and Intensive Care [7,8,14,15]. Moreover, RBCT has been implicated in reduced overall survival and disease recurrence-free survival among cancer patients undergoing surgery [16-18].

Because of the significant clinical and economic costs, more focus is being placed on patient blood management (PBM) to reduce the risk and number of RBCT required post-operatively. PBM is not just about appropriate transfusion practice; it encompasses strategies to conserve blood, manage haemostasis and optimise pre-operative haemoglobin. Since 2011, the National Blood Authority in Australia has released a number of PBM guidelines including the Peri-operative module in 2012 [19].

The Peri-operative guidelines recommended establishing a multidisciplinary, multimodal peri-operative blood management programme to optimise pre-operative red blood cell mass, minimise peri-operative blood loss and tolerate post-operative anaemia. In particular, it recommended identifying pre-operative anaemia and for those with, or at risk of, iron deficiency anaemia, to receive pre-operative iron therapy (PIT). When the guideline was released, it was noted that there were no published studies that assessed the efficacy of non-transfusion interventions such as iron therapy in pre-operative patients. Since then, however, some controlled trials assessing the efficacy of PIT with or without concomitant erythropoietin administration have been reported [20-22].

In light of the recommendations of the National Blood Authority in Australia, our institution implemented a multidisciplinary pre-operative haemoglobin optimisation programme in 2013. As there is lack of data on the effectiveness of PIT on post-operative RBCT requirements outside the controlled clinical trial setting with its attendant pre-defined RBCT triggers and/or other strictly

mandated management pathways, we conducted an audit on our practice. This audit would provide "real world" information on whether PIT influences RBCT requirement during the first post-operative week in iron deficient elective major surgery patients. We hypothesised that PIT was associated with reduced post-operative RBCT with or without correction of pre-operative haemoglobin.

Methods

The audit was approved by the Human Research Ethics Committee (Project number H2013/05052) at our institution.

Participants

Patients aged 18 years or over who went through the pre-operative haemoglobin optimisation programme during the period 1 July 2013 to 30 June 2014, and who underwent elective major surgery in our institution before 31 December 2014 were included. Elective major operations included cardiothoracic surgery, colorectal surgery, major joint replacements and vascular surgery. These patients had full blood examination and iron studies ordered during initial assessment at the surgical pre-admission clinics to screen for anaemia and iron deficiency.

Patients were divided into intervention and control groups. The intervention group comprised patients who received PIT for iron deficiency. Controls were patients whose ferritin was ≥ 30 μg/L and who did not receive PIT. Controls were matched to the intervention group using a propensity score based on age, sex and surgical unit (orthopaedic, cardiac, thoracic, colorectal, upper gastrointestinal, hepatobiliary, vascular, urology and head and neck).

Patient demographic and laboratory data were collected. RBCT during and for seven days after the operation were obtained using the hospital blood bank information system, or through review of patients' medical records.

Intervention

Patients with absolute iron deficiency (ferritin < 30 μg/L) received either oral or intravenous PIT. If surgery was scheduled within the next 30 days, patients were given a one-off dose of 1 gram intravenous iron polymaltose pre-operatively. Otherwise, patients were instructed to take one Ferrograd C tablet daily (elemental iron 105mg) until the day of surgery (DoS). Patients who received PIT (oral or intravenous) had repeat full blood examination and iron studies before induction of anaesthesia on DoS to determine response to the intervention whereas controls did not have repeat blood tests pre-operatively.

Statistical analyses

Patient characteristics were summarised and reported as medians (interquartile ranges) for continuous variables and as proportions for categorical variables. Due to the non-randomised nature of the study, to ensure broad equivalence between groups with respect to sex, age and surgical unit, a propensity score matching was performed where every patient in the intervention group was matched with up to five patients from the control group. Matching by surgical units minimises the influence of vastly different surgical procedures on post-operative RBCT requirement.

The association between PIT and post-operative RBCT requirement was investigated using a logistic regression model. Adjustments were made for: (1) pre-operative haemoglobin at screening since it is a strong predictor of post-operative RBCT; and (2) length of time from screening to surgery as it was variable among patients and could potentially confound the results. The effect sizes were reported as Odds Ratios (ORs) with corresponding 95% confidence intervals (95% CI) and p-values. P-values below 0.05 were regarded as statistically significant. Statistical analyses were performed using Stata v13 IC (StataCorp LP, College Station, Texas, USA).

Results

One hundred and fourteen of 1303 (8.75%) elective major surgery patients were iron deficient, including one patient who was already receiving oral iron therapy at time of screening. Colorectal

surgery patients had the highest prevalence of iron deficiency at 14.7% (15/102), while 8 – 10% of patients were iron deficient in other large surgical units such as orthopaedic, cardiac and thoracic units. Only 93 iron deficient patients received PIT (intervention group). Twenty-nine of these patients had haemoglobin <120 g/L. Fifty-four patients received oral iron only and 39 patients were administered intravenous iron (including eight patients who had received oral iron initially and then intravenous iron). Due to this study being an audit, it was not possible to determine if all patients on oral PIT were compliant.

Twenty patients with iron deficiency did not receive PIT due to various reasons, including very short lead time (1-2 days) from screening to surgery, when it was not possible to arrange iron infusion pre-operatively, or the treating unit decided not to give PIT when ferritin was only marginally <30 μg/L and the patient is not anaemic. Only two of these patients had haemoglobin <120 g/L. Six out of the 20 patients (30%) received RBCT.

Propensity scores based on age, sex and surgical unit were used to match 332 controls to the intervention group (Table 1).

Of the 93 patients constituting the intervention group, 17 (18.3%) received RBCT post-operatively whereas among controls, the proportion was 71/332 (21.4%) (p = 0.514). After adjusting for pre-operative haemoglobin and the time from screening to surgery, the odds of RBCT were significantly lower in the intervention group compared to controls (OR = 0.512, 95% CI: 0.268 – 0.977; p = 0.042). Based on the same regression model, assuming other characteristics being similar, each 1 g/L increase in pre-operative haemoglobin in both intervention and control groups was associated with 4% reduction in the odds of needing RBCT peri-operatively.

There was no significant difference in hospital LoS between the two groups (p = 0.24). The median LoS was 6 days for both the intervention (IQR: 4 – 9 days) and control groups (IQR: 4 – 8 days).

Most PIT was started or given within 3 – 4 weeks of surgery (median: 23 days; IQR: 8 – 68.5 days). Haemoglobin on DoS was available for 75 patients (39 of whom received intravenous iron and 36 oral iron only). The change in haemoglobin on DoS following PIT was highly variable, ranging from -26 g/L to +31 g/L, with a median of -2 g/L (IQR: -7 – +7 g/L). Twenty seven of these 75 patients had Hb <120 g/L on screening, and 22 of them remained anaemic (Hb <120 g/L) on DoS, although haemoglobin had improved in five patients. In seven patients, haemoglobin fell below 120 g/L while awaiting surgery, despite PIT.

Ferritin on DoS was available for 76 patients. Sixty-two of them were iron replete on DoS based on ferritin being ≥30 mcg/L; they included all patients who received intravenous PIT, while 14 remained iron deficient. This did not appear to impact on the need for RBCT, as 16 out of 62 iron replete patients received transfusion while one out of 14 iron deficient patients received transfusion (26% and 7% respectively, 95% CI 0.04-1.92%). However, overall numbers are relatively small.

Discussion

Pre-operative iron deficiency is associated with higher peri-operative transfusion rates [23,24]. Controlled clinical trials have demonstrated that correction of iron deficiency with or without improvement in pre-operative anaemia resulted in lower rates of RBCT [20,25]. These controlled studies had protocols governing patient management which might include carefully defined timelines between screening for, and correction of, iron deficiency in relation to elective surgery, pre-defined RBCT triggers and other aspects of PBM. In contrast, our study reports on the "real world" experience in a cohort of patients undergoing elective major surgery.

Our results indicate PIT negated the effect of iron deficiency on post-operative RBCT, leading to lower odds of peri-operative RBCT. While this is consistent with the findings in controlled clinical trials [20, 21,25,26], our study differs in that our cohort were transfused at the discretion of the treating surgeons/anaesthetists, rather than following pre-defined trial criteria for post-operative RBCT. Due to the nature of the study, it was not possible to determine the trigger(s) for RBCT in every case. Whilst it could be argued that PIT influenced the decision for RBCT or otherwise, it is more likely that decisions on RBCT were based on patients' clinical status as first post-operative

haemoglobin levels were similar (Table 1). We also observed that hospital LoS in the intervention group was comparable to the controls, whereas we would have expected hospital LoS to be longer in patients with untreated iron deficiency than among the controls [14,15].

Ideally, PIT should be instituted as soon as iron deficiency is detected to allow time for haemoglobin to improve prior to surgery. Once iron replete, haemoglobin can be expected to rise by about 20 g/L every 3 weeks, provided there are no ongoing losses [27]. In elective surgery patients, especially those undergoing colorectal operations, there may be ongoing bleeding (due to the underlying disease) while they await surgery, which may explain the observed inconsistent haemoglobin response after PIT. One drawback of our programme is that PIT was often given within a short time before planned surgery, as screening for iron deficiency occurred relatively close to the date of elective surgery. This might not have allowed the full benefit of PIT to be realised prior to surgery. Although surgery was elective, in some instances, delaying the procedure merely because of uncorrected anaemia was not desirable.

Nevertheless, the reduction in RBCT among our patients who received PIT might not be due to increased pre-operative haemoglobin alone, since we did not find a consistent increase in pre-operative haemoglobin in the intervention group. It is possible that PIT reduced RBCT by replenishing iron stores, thus hastening recovery from peri-operative blood loss [22]. This is supported by the finding that although intravenous iron was more efficacious in improving pre-operative haemoglobin than oral iron supplementation among patients undergoing surgery for colorectal cancer, there was no difference between the groups in terms of patients requiring RBCT or the amounts of red blood cells administered [28].

Unlike some controlled trials that mandated the administration of erythropoiesis-stimulating agents to correct anaemia [29], our institution did not use erythropoietin routinely, the principal reason being this drug is not available for this indication in the Australian public health care system.

Our study has its limitations. As it is a single centre study, our patient population may not be comparable to other health care services. Only a small number of patients (93 patients) received PIT, so there is insufficient power to detect small differences between the intervention group and controls. Compliance with oral PIT is also unknown due to the retrospective nature of the study. As this is a study evaluating the effectiveness of PIT in iron deficiency, ideally, the control group should comprise iron deficient patients who did not receive PIT, this could possibly then demonstrate the effect of PIT more clearly, but it is ethically inappropriate to not treat known iron deficiency. The comparison between the intervention and control groups would be strengthened by using DoS haemoglobin for the control group. However, FBE was not routinely performed in our institution on the DoS for elective operations. Other potential confounders are peri-operative bleeding (e.g. from surgical complications), which was not evaluated as part of the study and would likely to impact RBCT, and post-operative transfusion triggers which mightc vary between surgical units or even among surgeons/anaesthetists within the same surgical unit.

In conclusion, our "real world" data confirm that PIT, either oral or intravenous, does reduce peri-operative RBCT in elective major surgery patients who are iron deficient. This is despite PIT being given only a short time before surgery and not consistently increasing haemoglobin on DoS. Whilst this effect may be modest, we nevertheless recommend that health care services consider targeted PIT among their patients identified as likely to require peri-operative RBCT.

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Author's contributions

Study design/planning: F.S.H., N.S., C.P., W.K.H., C.S.

Study conduct and data acquisition: F.S.H., N.S., C.P., F.N., A.M., A.W., W.K.H., C.S.

Data analysis: F.S.H., L.C., W.K.H.

Writing paper: F.S.H., L.C., W.K.H.

Revising paper: all authors

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Tables

Table 1. Intervention and control groups.

	Intervention group (n = 93)	**Matched controls (n = 332)**	***p*-value**
Male:Female (n:n)	36:57	131:201	>0.99
Age (years)[a]	68 (55 – 73)	66 (56 – 74)	0.96
Haemoglobin at screening (g/L) [a]	126 (116 – 134)	137 (127 – 145)	<0.001
Ferritin at screening (mcg/L)[a]	19 (14-24)	121 (73-228)	
Ferritin on day of surgery (mcg/L)[ab]	144 (35-332)	N/A	
Orthopaedic surgery	38 (40.9%)	131 (39.5%)	
Cardiac surgery	15 (16.1%)	57 (17.2%)	
General surgery (including colorectal)	23 (24.7%)	72 (21.7%)	
First post-operative haemoglobin (g/L)[a]	108 (96-115)	109 (96-122)[c]	0.47
Length of time to surgery (days) [a]	13 (2 – 30)	8 (1 – 27)	0.03
Number of patients transfused	17 (18.3%)	71 (21.4%)	0.514
Red blood cells transfused (units) [a]	2 (2 – 4)	2 (2 – 4)	0.532
Length of stay in hospital (days) [a]	6 (4 – 9)	6 (4 – 8)	0.24

[a]Values are median (IQR)

[b]17 patients did not have ferritin measured on day of surgery

[c]7 patients did not have haemoglobin checked after surgery