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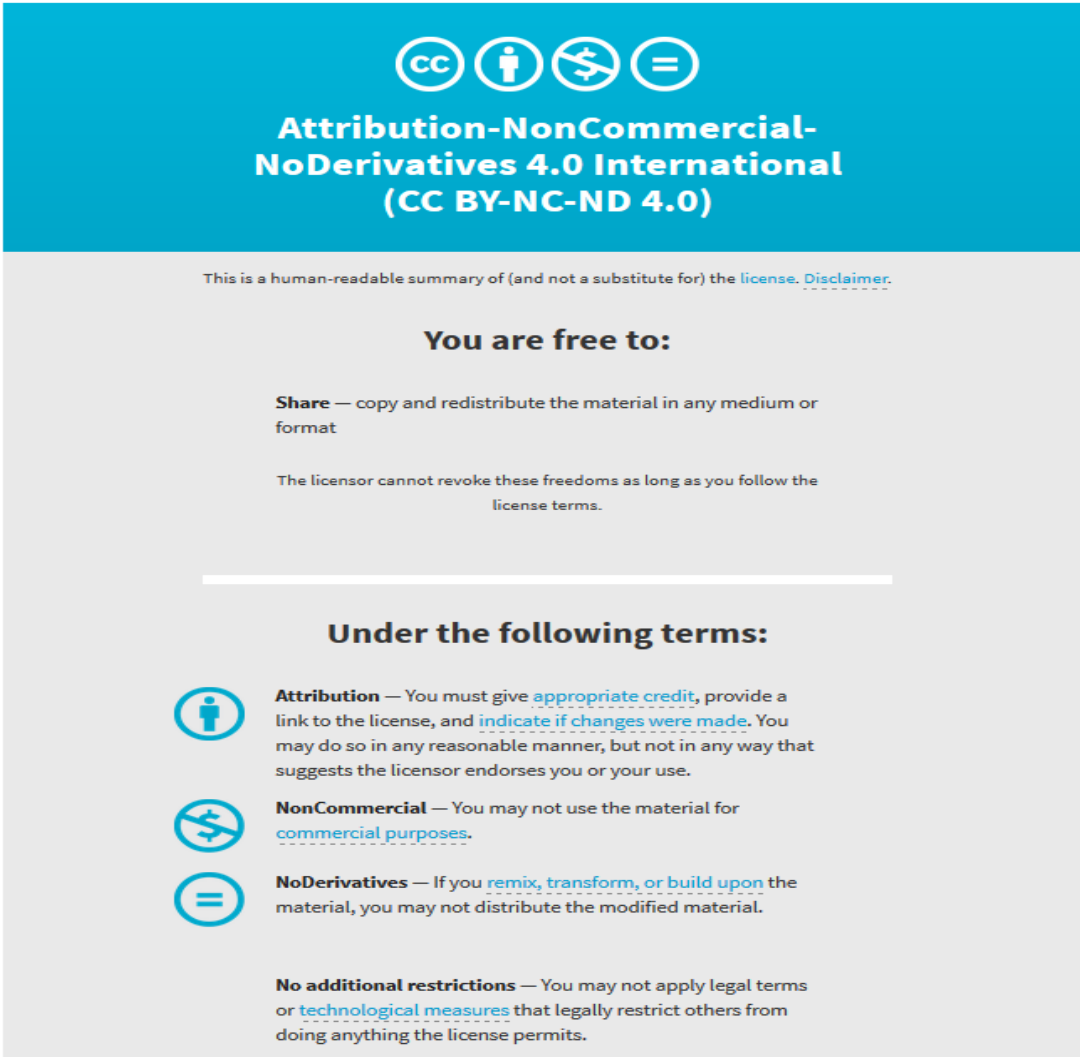
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# The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery

## A Randomized Controlled Trial

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**Objective:** To determine if preoperative intravenous (IV) iron improves outcomes in abdominal surgery patients.

**Summary Background Data:** Preoperative iron deficiency anemia (IDA) occurs frequently; however if left untreated, increases the risk of blood transfusion allogeneic blood transfusion (ABT). Limited evidence supports IDA treatment with preoperative IV iron. This randomized controlled trial aimed to determine whether perioperative IV iron reduced the need for ABT.

**Methods:** Between August 2011 and November 2014, 72 patients with IDA were assigned to receive either IV iron or usual care. The primary endpoint was incidence of ABT. Secondary endpoints were various hemoglobin (Hb) levels, change in Hb between time points, length of stay, iron status, morbidity, mortality, and quality of life 4 weeks postsurgery.

**Results:** A 60% reduction in ABT was observed in the IV iron group compared with the usual care group (31.25% vs 12.5%). Hb values, although similar at randomization, improved by 0.8 g/dL with IV iron compared with 0.1 g/dL with usual care ( $P = 0.01$ ) by the day of admission. The IV iron group had higher Hb 4 weeks after discharge compared with the usual care group (1.9 vs 0.9 g/dL,  $P = 0.01$ ), and a shorter length of stay (7.0 vs 9.7 d,  $P = 0.026$ ). There was no difference in discharge Hb levels, morbidity, mortality, or quality of life.

**Conclusions:** Administration of perioperative IV iron reduces the need for blood transfusion, and is associated with a shorter hospital stay, enhanced restoration of iron stores, and a higher mean Hb concentration 4 weeks after surgery.

**Keywords:** intravenous iron, iron deficiency anemia, outcomes, red blood cell transfusion, surgery

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Iron deficiency (ID) and iron deficiency anemia (IDA) are common conditions affecting a quarter of the world's population.<sup>1</sup> Aside from age, socioeconomic circumstances, poor nutrition, and pregnancy, many pathological states frequently lead to iron depletion. In patients presenting for noncardiac surgery, ID with or without anemia is found in up to 39% of patients.<sup>2</sup> In certain subgroups, like colorectal cancer or patients with heavy menstrual bleeding, the occurrence of preoperative anemia has been found to be as high as 57%.<sup>3,4</sup> The cause of the ID is either disease related, for which the patient is being treated, or therapy related, as for many individuals on nonsteroidal anti-inflammatory drugs.<sup>5</sup>

Anemia, ABT, and perioperative significant blood loss have all been established as adversely impacting clinical outcomes.<sup>6</sup> Perioperatively, anemic patients frequently are exposed to allogeneic transfusion events, increased rates of infections, increased numbers of cardiac complications, an increased number of days in hospital, and more deaths.<sup>2,7–9</sup> Anemia is often corrected by ABT, despite the evidence that even small amounts of transfused allogeneic red cells have a significant negative effect on morbidity, mortality,<sup>10</sup> and reduces cancer-related survival and overall survival in colorectal cancer patients.<sup>9</sup> Transfusion-associated hazards and the noninferiority of restrictive transfusion approaches have been demonstrated, challenging traditional transfusion practice.<sup>11–13</sup>

Comprehensive patient blood management (PBM) programs offering effective approaches for minimizing perioperative blood loss and optimized patient care have been designed and implemented in some countries.<sup>14,15</sup> However, due to evidence gaps, translational delays for existing evidence, and ongoing skepticism, transfusion practices continue to vary considerably among clinicians.<sup>16</sup> Preoperative optimization of anemia seems to be a key aspect of PBM.<sup>6,16,17</sup> In particular, patients scheduled for major surgery and with medical conditions often associated with ID should be assessed at least 4 weeks before surgery to allow clinicians to interpret blood results with a window of opportunity to act and correct reversible hemopoietic deficiencies.<sup>17–19</sup>

Both oral and IV iron have been shown to correct ID and IDA,<sup>20,21</sup> but neither has become standard practice,<sup>22</sup> nor has the ideal timing of preoperative intervention for IV iron been determined.<sup>20,23</sup> Oral iron replacement is in many instances poorly tolerated, ineffective, or even detrimental.<sup>24,25,26</sup> There is increasing evidence that in select patient groups presenting for elective surgery and in urgent cases, treatment with IV iron might benefit the patient and should result in a reduction of RBC transfusion and transfusion-related adverse events.<sup>17,27</sup> Should an increased use of IV iron for at-risk patients have the predicted effect of improved hematological parameters and restored iron levels, the impact would translate to significant benefits for the individual in the immediate postoperative period and the weeks after hospital discharge.

## METHODS

This was a randomized controlled trial. The protocol was approved by the study hospital's human research ethics committee and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000387921).

We randomly allocated participants (1:1) to either perioperative intravenous (IV) iron administration (intervention) or usual care. Randomization followed a computer-generated number sequence and allocation was conducted by telephone. The surgeon performing the operation was informed of patient participation in the study but group allocation was not revealed.

We screened 626 patients scheduled for abdominal surgery for the presence of IDA between August 2011 and November 2014. After informed written consent, patients eligible for inclusion (>18 yrs with IDA, ferritin <300 mcg/L, transferrin saturation <25%, Hb <12.0 g/dL for women, Hb <13.0 g/dL for men) were randomized between 4 and 21 days before surgery into 2 groups. Owing to this wide range in the preoperative period between patients, a standard approach was used to assess transfusion events in the preoperative period, including any transfusion administered in the 21 days before surgery. Patients in the intervention group received IV ferric carboxymaltose, given as a single dose over 15 minutes, before surgery (simplified dosing protocol; 15 mg/kg bodyweight to a maximum dose of 1000 mg). Postoperatively, within 2 days of surgery, intervention group participants received 0.5 mg of ferric carboxymaltose per recorded 1 mL of blood loss, if blood loss was at least 100 mL. Blood loss was measured as accurately as possible by recording suction bottle volume and weighing packs at the end of the operation. Patients in the usual care group received perioperative care, including anemia management, provided by the primary care physician or surgical home team. Usual care provided included no treatment, continued observations, oral iron recommendations, and ABT. At the time of initiation of the study, IV iron was not considered usual care; however, prescription and administration was not disallowed.

In the institution, the prescription and administration of the intervention was facilitated by the anesthetic team. Baseline testing of the Short Form Health Survey (SF36) was conducted at study entry.<sup>28</sup>

Follow-up of participants was scheduled for 4 weeks after surgery. The SF36 and screening bloods were repeated at this time. Patients found to have noteworthy ID or IDA at follow-up, irrespective of group allocation, were referred to their General Practitioner for ongoing management.

## Quality Control Procedure

A trial information session was given to the departmental members involved before commencing the study. Regular refreshers were scheduled to assure protocol knowledge and adherence. The multidisciplinary composition of the research team facilitated this process. Follow-up and data entry were meticulously conducted by a research assistant, and primary care physician follow-up and care initiated when necessary to assure patient safety.

## Outcomes

The primary endpoint was incidence of ABT. Secondary endpoints included hemoglobin (Hb) on admission, Hb difference from randomization to admission, ICU admission, perioperative morbidity (defined as new onset infection, respiratory failure, renal impairment, deep venous thrombosis), discharge Hb, length of stay, Hb at follow-up, Hb difference from discharge to follow-up, iron status, 30-day mortality, and quality of life (QoL). QoL score was scaled from 36 to 160, with lower scores reflecting poorer well-being.

## Statistical Analysis

The sample size of this study was calculated for the primary outcome parameter (perioperative allogeneic transfusion event). To reduce the risk of a perioperative allogeneic transfusion event from 30% to 15% (a 50% risk reduction) with a power of  $\beta = 0.8$  and a significance level of  $\alpha = 0.05$ , it was determined that a total of 121 patients in each group would be needed. To account for possible dropouts, we intended to include 134 patients per group. The power calculation was performed using nQuery Advisor Version 7.0 (Statistical Solutions, Saugus, MA). Parametric data were tested with one-way ANOVA, and are presented as mean and standard error of the mean or as mean and 95% confidence intervals. Nonparametric data were tested with Mann-Whitney *U* tests, and are reported as either median (IQR) or median (minimum–maximum), as indicated. Categorical data were analyzed with the 2-tailed Pearson  $\chi^2$  test, and are presented accordingly as number and percent of total. Statistical analysis was performed using SPSS software version 17.0 (SPSS Inc, Chicago, IL).

## RESULTS

An early interim data analysis was requested following concerns raised by the clinical investigator team after high rates of RBC transfusion, considered to be an independent risk factor for adverse clinical outcomes, noted after the 4-week follow-up in a subset of patients. This was performed by an independent statistician on the interim data-monitoring committee with the data blinded (intervention group *n* = 32, usual care group *n* = 26). The results of the interim analysis were forwarded to 2 independent experts in the field to assess safety concerns. Enrolment continued while waiting for a response. There was disagreement among the assessors, and a third independent expert opinion was sought. Based on advice from 2 of the 3 independent experts, the study was terminated early due to higher than expected rates of poor outcome in the usual care group.

At the time of study termination, 72 eligible patients were enrolled and randomized (intervention group *n* = 40, usual care group *n* = 32) (see Supplemental Digital Content eFigure 1). Group characteristics are shown in Table 1, and the type of surgery for the patient groups is shown in Supplementary Table 1, <http://links.lww.com/SLA/A967>. Cancer was the underlying condition in 73% of group 1 patients and 85% of patients in the usual care group. The overall transfusion rate in the study was 20.8%. Ten patients in

TABLE 1. Group Characteristics

	Intervention <i>n</i> = 40	Usual Care <i>n</i> = 32
Demographics		
Age	64 ± 15	68 ± 15
Height, cm	166 ± 10	167 ± 10
Weight, kg	86 ± 27	88 ± 20
BMI, kg/m <sup>2</sup>	30 ± 8	31 ± 7
ASA 2	17 (42.5)	17 (53.1)
ASA 3	22 (55)	15 (46.9)
ASA 4	1 (2.5)	0
Sex (male/female)	19/21	17/15
Surgery		
Days before surgery*	8 (6–13)	10 (5–15)
Estimated blood loss during surgery*	360 (200–700)	300 (100–512)

\*Data are median (IQR).

BMI indicates body mass index; ASA, physical status classification system; IQR, interquartile range.

**TABLE 2.** Primary Outcome; Perioperative Red Blood Cell Transfusions

Transfusion Events Occurring in Each Period	Intervention n = 40	Usual Care n = 32	P
Preoperative	0	2 (6%)	0.190
Units transfused	0	7	
Intraoperative	0	5 (16%)	0.014
Units transfused	n.a.	7	
Postoperative	5 (12%)	10 (31%)	0.079
Units transfused	8	18	
Total number of Patients transfused	5 (12.5%)	10 (31.25%)	0.079
Units transfused	8	32	
Total number of transfusion events	5	17	<0.001
Total units/patient (median, minimum–maximum)	0 (0–2)	0 (0–5)	0.021
Total units/transfused patient (median, minimum–maximum)	2 (1–2)	3 (2–5)	0.016

Transfusion events presented in the table are differentiated into time of transfusion and total events experienced in the perioperative period. The preoperative period was defined as the 3 weeks before surgery; data are n (%) unless otherwise stated.

the usual care group (10/32 = 31.25%) were transfused vs 5 in the intervention group (5/40 = 12.5%), equating to a 60% relative reduction in transfusions between the 2 groups shown in Table 2. There were no intraoperative RBC transfusions in the intervention group compared with 5 in the usual care group ( $P = 0.014$ ) and a significant reduction in the number of total perioperative ABT events in group 1 (5/40, 12.5%) compared with group 2 (17/32, 53%),  $P < 0.0003$ . The median number of units per transfused patient was also decreased in the intervention group (2 compared with 3 in the usual care group;  $P = 0.016$ ; Table 2). There was no difference in the rationale for transfusion between the 2 groups with the majority being performed due to low hemoglobin (Supplementary Table 2, <http://links.lww.com/SLA/A967>). The median IV iron dose administered to participants in the intervention group was 1200 mg (IQR 1088–1363). Five participants in the usual care group were given a median IV iron dose of 1800 mg (IQR 1467–2000). Any participant receiving IV iron had a maximum of 2 infusions. No serious adverse event resulted from the iron infusion. Three participants suffered the following mild adverse events: headache, light-headedness, and back pain. The latter settled with simple analgesics. Hb levels across study period and other important secondary outcome parameters are shown in Tables 3 and 4. Hb values were not different at randomization and improved by 0.8 g/dL in group 1 and by 0.1 g/dL in the usual care

group ( $P = 0.01$ ) by the day of admission. Despite higher transfusion rate in the usual care group, there were no differences between groups in discharge Hb (10.3 vs 10.2 g/dL for the intervention group and usual care group, respectively). However, Hb increased by 1.9 g/dL in the intervention group and 0.9 g/dL in the usual care group ( $P = 0.01$ ) from the time of discharge to follow-up and was significantly higher at 4 weeks postsurgery (12.2 g/dL compared with 11.1 g/dL in the usual care group,  $P < 0.001$ ). Length of stay was shortened by 3 days in the intervention group compared with the usual care group (6 vs 9 d,  $P = 0.05$ ). There was no significant difference in morbidity or mortality (Table 4). QoL scores were higher at baseline for the intervention group; however, score reduction was equal between the groups.

## DISCUSSION

This first RCT on managing preoperative anemia in abdominal surgery, involving only patients with confirmed IDA, demonstrates the important role for IV iron in perioperative PBM. The results also highlight the ongoing mismanagement of a treatable condition despite the well-known negative impact of IDA.<sup>29,30</sup> In addition, it also confirms the ongoing overuse of ABT as a default treatment approach<sup>31–33</sup> regardless of the well-described transfusion-related risks<sup>34</sup> and the safety of restrictive transfusion practices.<sup>10,12,13</sup> We

**TABLE 3.** Secondary Outcomes; Hematological Indices Across Study Period

	Intervention n = 40	Usual Care n = 32	P
Hemoglobin values, g/dL*			
Randomization	10.7 ± 1.3, n = 40	10.6 ± 1.4, n = 32	0.76
Admission	11.5 ± 1.3, n = 36	10.7 ± 1.7, n = 29	0.12
Difference between randomization and admission	0.8 ± 0.8, n = 36	0.1 ± 1.3, n = 29	0.01
Discharge	10.3 ± 1.3, n = 37	10.2 ± 0.9, n = 31	0.31
4 wk	12.2 ± 1.2, n = 36	11.1 ± 1.2, n = 28	<0.001
Postdischarge change (4 wk minus discharge value)	1.9 ± 1.4, n = 36	0.9 ± 1.4, n = 28	0.01
Iron status†			
Ferritin at randomization, µg/L	19 (6–48), n = 40	37 (11–82), n = 32	0.06
Ferritin at 4 wk, µg/L	248 (137–546), n = 36	99 (35–228), n = 27	0.002
Transferrin saturation at randomization, %	6 (3–10), n = 40	9 (7–15), n = 32	0.03
Transferrin saturation at 4 wk, %	21 (16–26), n = 36	14 (7–18), n = 27	0.003
CRP‡			
CRP at randomization, mg/L	7.2 (2.9–19.3), n = 40	7.7 (2.6–16.8), n = 32	0.99
CRP at 4 wk, mg/L	5.8 (2.3–12.6), n = 36	11 (3.1–23), n = 27	0.18

Sample size varies due to missing values at each time point.

\*Data presented as mean ± SD.

†Data are expressed as median (IQR).

**TABLE 4.** Other Secondary Outcomes of Interest

	Intervention n = 40	Usual Care n = 32	P
Length of stay, d*	6 (1–19)	9 (1–23)	0.05
Infection†	4 (10%)	5 (16%)	0.5
Respiratory failure‡	3 (7.5%)	3 (9%)	0.99
Renal impairment‡	1 (2.5%)	1 (3%)	0.99
DVT‡	0	1 (3%)	0.45
Readmission‡	6 (15%)	3 (9%)	0.72
Discharged on oral iron‡	5 (12.5%)	1 (3%)	0.22
Death‡	1 (2.5%)	0	0.99
QoL (presurgery/intervention)‡	104 ± 15	96 ± 18	0.02
QoL (4 wk postsurgery)‡	96 ± 14	90 ± 26	0.24
Difference in QoL (pre–post)‡	8 ± 18	6 ± 17	0.70

QoL score scale; 36–160, lower scores reflecting poorer well-being.

\*Median (minimum–maximum).

†Data are n (%).

‡Data are expressed as mean ± SD unless otherwise stated.

also report that although Hb levels were equivalent in the 2 groups at discharge, they were 1 g/dL higher in the treatment group compared with the usual care group at 4 weeks after surgery. This demonstrates that perioperative iron repletion has substantial benefit in the postoperative recovery period, potentially due to the iron repletion allowing bone marrow to increase erythropoiesis, compared with transfused RBCs which are rapidly cleared from the circulation and have a shorter lifespan than normal RBCs.<sup>35</sup> The superiority of IV iron over oral or no iron in reducing ABT was previously demonstrated in other clinical setting and extensively discussed in a recent review by Muñoz.<sup>36</sup>

Transfusion triggers and the appropriateness of ABT administration were the focus of perioperative transfusion management at the time when we designed this study. Our aim was to determine whether perioperative IV iron, administered within 4 to 21 days before substantial abdominal surgery, would lead to a significant reduction in transfusion events. We anticipated that we would demonstrate that this intervention would not only obviate ABT, but also correct underlying iron deficits, facilitating better recovery and outcomes. Since the commencement of our study, the importance of correcting preoperative ID has been more widely accepted as an appropriate standard of care, strengthening our hypothesis.<sup>6,17,18,21,37</sup> The value of preoperative correction of IDA has thus become a cornerstone of PBM guidelines around the world.<sup>14,15,38</sup>

However, data monitoring of our participants indicated that a large proportion of enrolled subjects in the usual care group were transfused with RBC to correct anemia but received no treatment for their ID. RBC transfusion is considered to be an independent risk factor for adverse clinical outcomes.<sup>10,31,39</sup> Recognition of this situation and the ethical responsibility to our participants prompted an interim analysis, and the seeking of advice from impartial experts to assess whether early termination of the study was recommended scientifically and ethically. Enrolment in the study continued during the assessment and decision-making process. After definitive analysis of the expert opinion, it was deemed that the study should be terminated in the interest of the patients.

As early as 1985, influenced by the AIDS epidemic, strategies for avoiding or minimizing ABT were published.<sup>40</sup> Compelling evidence on the importance of anemia and blood management from the last 15 years<sup>13,37,41</sup> put PBM on the agenda and illustrated how PBM should be carried out. Logically, one would expect that “standard care” had moved on. However, our results show that the translational gap is huge and that anemia management has some way to go in clinical practice.<sup>19,33,34,42–45</sup>

The assessment of adequate iron stores can be difficult. With ferritin levels influenced by chronic disease and/or inflammation, ID may be masked. Therefore, screened subjects were included with ferritin levels of less than 300 mcg/L in our study, as recommended in a consensus statement on the role of IV iron in perioperative anemia management.<sup>46</sup> The distribution of ferritin levels was essentially the same in the 2 groups of participants; 48% (intervention) and 40% (usual care) presented with profound ID, demonstrated by ferritin levels less than 30 mcg/L. Despite sometimes longstanding and previously diagnosed IDA, only 3 patients in our entire cohort had been prescribed oral iron replacement therapy within the 6 weeks before surgery. Only 1 patient in the usual care group was treated with IV iron pre- and postoperatively, and 4 received IV iron while in hospital. IV iron was not considered usual care, at the time of study commencement, nonetheless was not prohibited. Patients were randomized in our study between 8 and 10 days before admission. Although it is desirable for ID to be corrected in a timely manner, the study establishes that a successful “rescue” intervention is available and effective at a later stage, even for those with profound IDA. Our results support a proposed “opportunity” approach, discussed in a recent review article by Muñoz et al, and suggested earlier based on results from pooled data by the same author.<sup>17,47</sup>

In addition to risk minimization and outcome improvement, our findings might have significant economic implications. According to the Australian Institute of Health and Welfare, 15,840 patients were diagnosed with bowel cancer in Australia in 2012 and many had to undergo abdominal surgery. Cancer patients made up the majority of our cohort. The patients randomized to receive pre- and postoperative IV iron left hospital 3 days earlier. We suggest that this earlier discharge was due to treatment of ID with IV iron, thus minimizing the associated risks of this exposure. Although a cost analysis was beyond the scope of this research, we propose that this would result in a significant cost savings, offsetting the initial expenditure of screening.

### Limitations

Early termination is the main limitation of our study. However, ethical concerns were paramount, and we made the necessary decision in the interest of our patients. Although more cases would strengthen the statistics, it was not anticipated that the conclusions would change. In our view it would have been unethical to have iron-deficient patients in a control group at increased risk of receiving a blood transfusion. A serious hazard from an ABT resulting in morbidity or mortality in a control patient would be difficult to defend. Another limitation is that we performed simple randomization instead of block randomization.

This was apparent at the time of the interim analysis and the final analysis after stopping the study. Block randomization would have achieved a more equal balance in the allocation of participants. In this study, 5 participants randomized to the usual care group received IV iron as part of their standard care. Although this may have influenced the results, the final analysis between groups would then represent a more conservative analysis of the effects of IV iron. This change in standard care of iron deficient patients further adds clarity to the decision for early termination.

## CONCLUSIONS

In conclusion, the administration of IV iron in the perioperative setting resulted in a significant reduction of RBC transfusion, significant Hb improvement from the time of randomization to admission, shorter hospital stays, and enhanced restoration of iron stores and Hb at 4 weeks after surgery. Usual care failed the majority of participating patients, leaving them untreated with a treatable condition.

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