General Anesthesia

Intravenous iron and recombinant erythropoietin for the treatment of postoperative anemia

[L'administration intraveineuse de fer et d'érythropoïétine recombinante pour le traitement de l'anémie postopératoire]

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Purpose: To determine if early recovery from severe postoperative anemia is accelerated by *iv* iron therapy alone or in combination with recombinant erythropoietin (EPO).

Methods: In this double-blinded, placebo-controlled randomized study, consenting adult patients without preoperative anemia whose hemoglobin concentration (Hb) was 70 to 90 $g \cdot L^{-1}$ on the first day after cardiac or orthopedic surgery (POD 1) were assigned to one of three groups: control, *iv* iron alone (200 mg of iron sucrose on POD 1, 2, and 3) or in combination with EPO (600 $U \cdot kg^{-1}$ on POD 1 and 3). The primary outcome was increase in Hb (adjusted for red blood cell transfusions) from POD 1 to 7. Analysis was by intention-to-treat in patients for whom the primary outcome was available. Group effect was analyzed by the ANOVA test, and between-group differences were specified with a Duncan multiple-range test.

Results: The primary outcome was available in 31 of 38 randomized patients. The average POD 1 Hb was 84 ± 4 $g \cdot L^{-1}$. There were no between-group differences in outcomes except for higher reticulocyte counts on POD-7 in the combination group. The average adjusted one-week increases in Hb were 7 ± 8 $g \cdot L^{-1}$ in the control group ($n = 10$), 9 ± 9 $g \cdot L^{-1}$ in the *iv* iron group ($n = 11$), and 10 ± 14 $g \cdot L^{-1}$ in the combination group ($n = 10$). The average adjusted six-week increases in Hb were 37 ± 14 $g \cdot L^{-1}$ in the control group, 40 ± 7 $g \cdot L^{-1}$ in the *iv* iron group, and 45 ± 12 $g \cdot L^{-1}$ in the combination group.

Conclusion: Early postoperative treatment with *iv* iron alone or in combination with EPO does not appear to accelerate early recovery from postoperative anemia.

***Objectif** : Vérifier si la récupération précoce d'une sévère anémie postopératoire est accélérée par le fer iv seul ou en combinaison avec de l'érythropoïétine recombinante (EPO).*

***Méthode** : Pour l'étude à double insu, randomisée et contrôlée contre placebo, des adultes sans anémie préopératoire, chez qui la concentration d'hémoglobine (Hb) était de 70 à 90 $g \cdot L^{-1}$ au premier jour post-opération cardiaque ou orthopédique (JPO 1), ont été assignés à l'un des trois groupes : témoin, fer iv seul (200 mg de sucrose ferreux aux JPO 1, 2 et 3) ou en combinaison avec de l'EPO (600 $U \cdot kg^{-1}$ aux JPO POD 1 et 3). Le résultat principal était une hausse de l'Hb (ajustée pour les transfusions de culots globulaires) des JPO 1 à 7. L'évaluation, pour les patients ayant atteint ce résultat, utilisait l'analyse par intention de traiter. L'effet de groupe a été analysé par le test ANOVA test et les différences intergroupes ont été précisées avec le test à gamme multiple de Duncan.*

***Résultats** : Le résultat principal était atteint chez 31 des 38 patients randomisés. La moyenne de l'Hb au JPO 1 a été de 84 ± 4 $g \cdot L^{-1}$. Il n'y a pas eu de différence de résultat intergroupe sauf pour une numération plus élevée des réticulocytes au JPO 7 dans le groupe d'EPO. Les hausses moyennes d'Hb ajustées sur une semaine ont été de 7 ± 8 $g \cdot L^{-1}$ dans le groupe témoin ($n = 10$), 9 ± 9 $g \cdot L^{-1}$ avec le fer iv ($n = 11$) et 10 ± 14 $g \cdot L^{-1}$ avec l'EPO ($n = 10$). Les hausses moyennes d'Hb ajustées sur six semaines ont été de 37 ± 14 $g \cdot L^{-1}$ chez les témoins, 40 ± 7 $g \cdot L^{-1}$ avec le fer iv et 45 ± 12 $g \cdot L^{-1}$ avec l'EPO.*

***Conclusion** : Le traitement postopératoire précoce avec du fer iv seul ou en combinaison avec l'EPO ne semble pas hâter la récupération de l'anémie postopératoire.*

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UNTIL recently, surgical patients were routinely transfused red blood cells (RBCs) if their hemoglobin concentration (Hb) decreased below 100 $g \cdot L^{-1}$.[1] Owing to the risks of RBC transfusion (most notably viral transmission), and the realization that patients can tolerate markedly lower Hb concentrations without increased risk of major morbidity or mortality,[2] a "transfusion trigger" of 100 $g \cdot L^{-1}$ is no longer considered acceptable, and transfusion guidelines now recommend that patients not be routinely transfused RBCs unless their Hb decreases below 70 $g \cdot L^{-1}$.[1]

Consequent to this change in practice, many postoperative patients who were not anemic before surgery may be left severely anemic (defined here as Hb = 70–90 $g \cdot L^{-1}$) after major surgery. Although in these patients acute anemia may not necessarily lead to overt organ dysfunction, it may lead to debilitating symptoms of anemia that include reduced exercise capacity, fatigue, dizziness, disorientation, indigestion, and loss of appetite.[3–6] Moreover, owing to the slow recovery from postoperative anemia,[7–9] these patients may have longer hospital stays and delayed postoperative recovery. Treatment modalities that accelerate recovery from severe postoperative anemia may therefore hasten patient recovery, improve quality of life, and decrease duration and cost of hospitalization.

Other than RBC transfusion, there are three clinically available therapies for postoperative anemia. One is dietary iron supplementation; however, its effectiveness for this indication is, at best, minimal.[7,8,10,11] Two other therapies are *iv* iron therapy and recombinant erythropoietin therapy, both of which are effective in treating other types of anemia that have similar pathophysiological features to postoperative anemia, such as anemia of chronic diseases. The efficacy of these therapies in treating postoperative anemia, however, has not been appropriately assessed through randomized controlled clinical trials. The objective of this clinical trial was to determine if recovery from postoperative anemia is accelerated in patients randomized to receive early postoperative *iv* iron therapy alone or in combination with recombinant erythropoietin.

Methods

Design

This was a single-centre, randomized, double-blinded, placebo-controlled clinical trial with three arms. Patients were enrolled from October 2001 to September 2003. Approval was obtained from the University Health Network Research Ethics Board, and informed consent was obtained from all patients before surgery.

Participants

Adult patients (> 18 yr-old) undergoing open-heart surgery, total hip arthroplasty, or spinal fusion with Hb between 70 to 90 $g \cdot L^{-1}$ on the morning of the first postoperative day (POD-1) were eligible for inclusion in the trial. Preoperative exclusion criteria were: preoperative anemia (Hb < 120 $g \cdot L^{-1}$ in women and < 140 $g \cdot L^{-1}$ in men); preoperative autologous blood donation, *iv* iron or erythropoietin therapy; active infection; pregnancy or lactation; major comorbidities (previous history of stroke, transient ischemic attacks, or seizures; significant respiratory disease [FEV_1 < 50% predicted], renal disease [creatinine > 200 $\mu mol \cdot L^{-1}$], or liver disease [hepatitis, cirrhosis]; uncontrolled hypertension [systolic > 180, diastolic > 100 mmHg]); and any hematological diseases (e.g., thromboembolic events, hemoglobinopathy, coagulopathy, or hemolytic disease). In addition, patients with ongoing hemorrhage or evidence of organ dysfunction on POD-1 were excluded.

The study was performed at the University Health Network, a tertiary/quaternary care adult hospital affiliated with the University of Toronto.

Interventions

Patients were randomly assigned to one of three study groups: placebo (Control group), *iv* iron (Iron group), and *iv* iron plus erythropoietin (Combination group). All three groups were prescribed dietary iron supplementation (150 $mg \cdot day^{-1}$) polysaccharide-iron complex (Niferex; Landmark Medical Systems, Unionville, ON, Canada) as soon as they were able to tolerate oral intake after surgery. Both treatment groups received iron sucrose 200 mg *iv* (Venofer, Genpharm Inc., Etobicoke, ON, Canada) on POD-1, POD-2, and POD-3, for a total of 600 mg. The iron preparation was diluted in 200 mL of normal saline and given over one hour and the Control group received 200 mL of normal saline. For all three groups the *iv* solution was draped with an opaque cover and the *iv* tubing was covered with a translucent tape. In addition to *iv* iron, patients in the Combination group received erythropoietin (Eprex , Ortho Biotech, Toronto, ON, Canada) as follows: 300 $U \cdot kg^{-1}$ *iv* plus 300 $U \cdot kg^{-1}$ *sc* on POD-1 and 600 $U \cdot kg^{-1}$ *sc* on POD-3, for a total of 1200 $U \cdot kg^{-1}$. Patients in the Control group and the Iron group received *sc* and *iv* injections of normal saline. Transfusion guidelines for all study participants recommended that patients not be transfused RBCs unless their Hb concentration was below 70 $g \cdot L^{-1}$ or there was a clinical indication for transfusion.

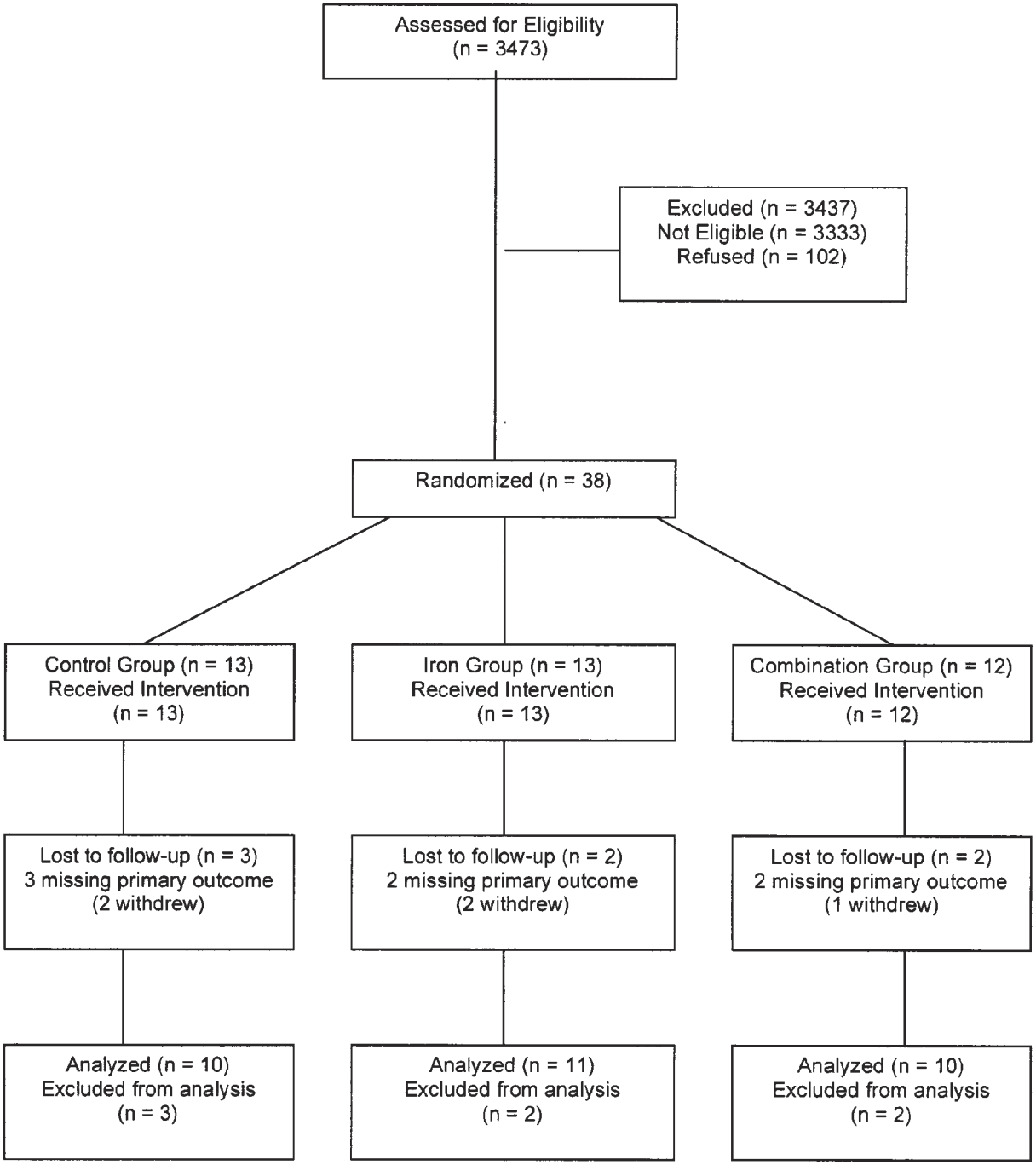

FIGURE 1 Participant flow.

TABLE I Baseline demographics and clinical characteristics*

	Control group (n = 10)	*Iron group (n = 11)*	*Combination group (n = 10)*
Female	2 (20%)	3 (27%)	3 (30%)
Age	62 ± 5	62 ± 11	56 ± 15
Weight	81 ± 19	83 ± 18	77 ± 16
Preoperative anti-platelet therapy	4 (40%)	6 (54%)	3 (30%)
ASA class III or IV	6 (60%)	8 (73%)	4 (40%)
Cardiac surgery	4 (40%)	5 (45%)	4 (40%)
Creatinine – preoperative ($\mu mol \cdot L^{-1}$)	73 ± 13	91 ± 16	81 ± 16
Creatinine – POD1 ($\mu mol \cdot L^{-1}$)	73 ± 17	90 ± 23	85 ± 17
INR – POD1	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.1
PTT – POD1	43 ± 6	42 ± 9	41 ± 9
Erythropoietin – POD1 ($U \cdot L^{-1}$)	90 ± 51	94 ± 65	108 ± 71

ASA = American Society of Anesthesiologists; POD = postoperative day; INR = international normalization ratio; PTT = partial thromboplastin time; *All values are reported as mean ± standard deviation or *n* (%).

Outcomes and follow-up

The primary efficacy outcome was the increase in Hb concentration from POD-1 to POD-7, adjusted for postrandomization RBC transfusions. For this adjustment, the POD-7 Hb was revised downward based on the amount of RBCs transfused relative to the patients' RBC mass (calculated using standard formulas based on patients' gender, body weight, and [POD-1] Hb;[12] each unit of RBC was assumed to contain 165 mL of red cells). Secondary outcomes were: six-week increase in Hb concentration (adjusting for postrandomization RBC transfusions) and one-week increase in reticulocyte counts. Other outcomes were incidence and volume of RBC transfusion up to six weeks after surgery, iron indices on POD-7, duration of hospitalization, and postoperative quality of life (measured at two and six weeks after surgery using the SF-36 and the 'Fatigue Inventory Scale'). Patients were followed for six weeks after surgery and all adverse events during this period were documented. Study procedures are outlined in the Appendix (available as Additional Material at www.cja-jca.org).

Sample size

It was estimated *a priori* that 20 patients in each group would be sufficient to detect an incremental increase in Hb of 8 ± 9 $g \cdot L^{-1}$ (this was based on the average in-hospital increase observed in untreated severely anemic patients)[13] from POD-1 to POD-7 in the Combination group *vs* the Control group ($\alpha = 0.05$ [two-tailed], power = 0.8). Because of slowing enrollment, it was decided to conduct an interim analysis in a blinded fashion once ten patients in each group had fully completed the trial. Using stochastic curtailment methods for the primary outcome, the conditional power of the study were it to be completed was estimated using ExpDesign™ Studio (CTriSoft International, MA, USA). Based on the results of the interim analysis, it was elected to terminate the study.

Randomization and blinding

A restricted stratified randomization scheme was used to allocate the patients to the three arms of the study. Patients were stratified according to open-heart surgery *vs* hip/spine surgery. In each stratum, patients were randomized in randomly permuted blocks of three patients according to a computer-generated table of random numbers. The assignments were placed into opaque sequentially numbered envelopes with pharmacy. An unblinded pharmacist prepared all medications according to the randomization schedule, taking steps to ensure blinding of other study personnel. Placing the solution in a locked opaque box and covering the *iv* tubing by translucent coloured tape masked iron sucrose.

Statistical methods

The baseline comparability of the groups was assessed using summary statistics: mean and standard deviation for continuous variables; frequency and percentage for categorical variables. Group comparisons were based on the intention-to-treat principle in patients for whom the primary outcome was available. Analysis of group effects was carried out by one-way ANOVA. When the ANOVA F statistic was significant ($P < 0.05$), between-group differences were specified with a Duncan's multiple-range test. Analysis of covariance was performed to adjust for within-group POD-1 Hb.

TABLE II Red blood cell transfusions and hemoglobin, reticulocyte, and iron indices*

	Baseline	*POD-1*	*POD-7*	*POD-42*
Control group (four patients received a total of 5 U of RBCs)				
Hb ($g \cdot L^{-1}$)	142 ± 10	83 ± 4	96 ± 8	120 ± 13
Adjusted Hb ($g \cdot L^{-1}$)	142 ± 10	83 ± 4	90 ± 9	115 ± 15
Reticulocyte ($\times 10^9 \cdot L^{-1}$)		55 ± 40	180 ± 55	
Iron ($\mu mol \cdot L^{-1}$)		3.6 ± 3.5	5.4 ± 1.0	
Transferrin ($g \cdot L^{-1}$)		1.6 ± 0.3	2.2 ± 0.3	
Ferritin ($\mu g \cdot L^{-1}$)		259 ± 174	311 ± 286	
Untransfused patients				
Hb ($g \cdot L^{-1}$)	143 ± 8	84 ± 4	94 ± 9	119 ± 15
Reticulocyte ($\times 10^9 \cdot L^{-1}$)		43 ± 14	175 ± 52	
Iron ($\mu mol \cdot L^{-1}$)		5.0 ± 3.9	5.0 ± 1.4	
Transferrin ($g \cdot L^{-1}$)		1.7 ± 0.3	2.3 ± 0.3	
Ferritin ($\mu g \cdot L^{-1}$)		190 ± 101	132 ± 79	
Iron group (two patients received a total of 3 U of RBCs)				
Hb ($g \cdot L^{-1}$)	141 ± 11	85 ± 5	97 ± 7	127 ± 6
Adjusted Hb ($g \cdot L^{-1}$)	141 ± 11	85 ± 5	94 ± 11	124 ± 7
Reticulocyte ($\times 10^9 \cdot L^{-1}$)		70 ± 50	197 ± 84	
Iron ($\mu mol \cdot L^{-1}$)		3.5 ± 4.8	6.9 ± 2.4	
Transferrin ($g \cdot L^{-1}$)		1.8 ± 0.3	2.3 ± 0.5	
Ferritin ($\mu g \cdot L^{-1}$)		258 ± 224	513 ± 221	
Untransfused patients				
Hb ($g \cdot L^{-1}$)	140 ± 12	86 ± 4	98 ± 8	126 ± 5
Reticulocyte ($\times 10^9 \cdot L^{-1}$)		76 ± 53	198 ± 89	
Iron ($\mu mol \cdot L^{-1}$)		3.7 ± 5.2	7.1 ± 2.4	
Transferrin ($g \cdot L^{-1}$)		1.9 ± 0.3	2.3 ± 0.5	
Ferritin ($\mu g \cdot L^{-1}$)		251 ± 249	507 ± 238	
Combination group (two patients received a total of 3 U of RBCs)				
Hb ($g \cdot L^{-1}$)	140 ± 9	83 ± 5	98 ± 9	128 ± 11
Adjusted Hb ($g \cdot L^{-1}$)	141 ± 11	85 ± 5	94 ± 15	126 ± 13
Reticulocyte ($\times 10^9 \cdot L^{-1}$)		62 ± 34	263 ± 98	
Iron ($\mu mol \cdot L^{-1}$)		4.0 ± 2.7	6.1 ± 1.4	
Transferrin ($g \cdot L^{-1}$)		1.8 ± 0.2	2.4 ± 0.3	
Ferritin ($\mu g \cdot L^{-1}$)		163 ± 119	435 ± 289	
Untransfused patients				
Hb ($g \cdot L^{-1}$)	143 ± 8	84 ± 5	98 ± 10	129 ± 12
Reticulocyte ($\times 10^9 \cdot L^{-1}$)		62 ± 37	279 ± 105	
Iron ($\mu mol \cdot L^{-1}$)		4.3 ± 2.9	6.0 ± 1.6	
Transferrin ($g \cdot L^{-1}$)		1.8 ± 0.2	2.5 ± 0.3	
Ferritin ($\mu g \cdot L^{-1}$)		172 ± 128	444 ± 332	

POD = postoperative day; RBCs = red blood cells; Hb = hemoglobin. *All values are reported as mean ± standard deviation.

Primary and secondary outcomes were also compared in the subgroup of patients who did not receive any RBC transfusions after randomization. Changes in iron indices were only compared in the untransfused subgroup. P values of < 0.05 were considered significant. SAS™ version 8.2 (SAS Institute, Inc., Cary, NC, USA) was used for the statistical analyses.

Results

Figure 1 details the flow of participants screened for the trial. A total of 3,473 patients were screened. While 854 (25%) had a Hb concentration between 70 to 90 $g \cdot L^{-1}$ after surgery, only 140 patients met all of the inclusion criteria. The primary reasons for ineligibility were preoperative anemia and postoperative organ dysfunction. Of the 140 eligible patients, 102 refused to participate and 38 were randomized. Of the 38 randomized patients, the primary outcome was available in 31 (Control group = 10, Iron group = 11, Combination group = 10) and these patients were analyzed. Three patients in the Control group, two in the Iron group, and two in the Combination group were lost to follow-up or withdrew from the study. Except for two patients in the Iron group who missed

TABLE III Calculated differences in laboratory values*

	Control group (n = 10)	*Iron group (n = 11)*	*Combination group (n = 10)*
Fall in Hb ($g \cdot L^{-1}$) from baseline to POD-1	59 ± 11	55 ± 13	57 ± 11
1-week Hb ($g \cdot L^{-1}$) rise, adjusted for RBC transfusion	7 ± 8	9 ±9	10 ± 14
1-week recovery of Hb (%)	12 ± 15	17 ± 16	16 ± 25
6-week Hb ($g \cdot L^{-1}$) rise, adjusted for RBC transfusion	37 ± 14	40 ± 7	45 ± 12
6-week recovery of Hb (%)	65 ± 24	76 ± 10	80 ± 15
1-week reticulocyte count ($\times 10^9 \cdot L^{-1}$) rise	125 ± 50	121 ± 83	211 ± 84†
Subgroup analysis in untransfused patients			
	Control group (n = 6)	*Iron group (n = 9)*	*Combination group (n = 8)*
1-week Hb ($g \cdot L^{-1}$) rise	10 ± 9	12 ± 6	14 ± 10
6-week Hb ($g \cdot L^{-1}$) rise	35 ± 14	38 ± 6	46 ± 14
1-week reticulocyte count ($\times 10^9 \cdot L^{-1}$) rise	133 ± 58	121 ± 88	217 ± 90
1-week iron ($\mu mol \cdot L^{-1}$) rise	0.5 ± 5.0	2.7 ± 5.4	1.3 ± 2.8
1-week transferrin ($g \cdot L^{-1}$) rise	0.7 ± 0.1	0.4 ± 0.5	0.7 ± 0.3
1-week ferritin ($\mu g \cdot L^{-1}$) rise	-38 ± 33‡	221 ± 165	232 ± 209

Hb = hemoglobin; POD = postoperative day; RBC = red blood cell; *All values are reported as mean ± standard deviation. †$P < 0.05$ *vs* control; ‡$P < 0.05$ *vs* each of the treatment groups.

one of their iron injections, all analyzed patients completed their course of therapy.

As can be seen in Table I, the groups were comparable on baseline demographics and clinical characteristics. On POD-1, all three groups had similarly elevated erythropoietin concentrations (Table I). The Hb, reticulocyte counts, and iron levels were also similar between the three groups on POD-1 (Table II). The average drop in Hb from before surgery to POD-1 was 59 ± 11 $g \cdot L^{-1}$ in the Control group, 55 ± 13 $g \cdot L^{-1}$ in the Iron group, and 57 ± 11 $g \cdot L^{-1}$ in the Combination group (Table III).

Patient outcomes are shown in Tables II and III. The Hb and reticulocyte outcomes are also shown graphically in Figures 2 and 3, respectively. Four patients in the Control group, two patients in the Iron group, and two patients in the Combination group received RBCs after randomization. In the intention-to-treat analysis, the Combination group had a significantly higher reticulocyte count at POD-7 than the other two groups. There were, however, no statistically or clinically significant differences among the three groups for any of the other measured outcomes, including one-week or four-week increases in Hb ($P = 0.7$ and 0.2, respectively) or measures of quality of life ($P > 0.4$). The results were similar in the subgroup analyses that included only those patients who did not receive RBC transfusions. None of the study patients had serious adverse events after randomization.

The conditional power at the interim analysis was 0.29. That is, the chance of rejecting the null hypothesis that there was no difference in the primary outcome between the Combination group and Control group had the trial gone to completion was 29%. Given this low chance of finding a between-group difference if the study were completed, it was elected to stop the study for futility after the interim analysis.

Discussion

Consistent with recent changes in perioperative transfusion practice, namely the lowering of the "transfusion trigger" for RBCs, this study found that severe anemia after major surgery is now a common occurrence: in consecutive patients who had undergone major surgery and were screened for this study, 25% were found to be severely anemic on the morning after surgery with a Hb concentration between 70 and 90 $g \cdot L^{-1}$.

Little is known about the time it takes to recover from this degree of postoperative anemia and what effects it has on patients' postoperative course. Studies on less severe degrees of postoperative anemia have found that correction of the anemia is slow, owing to the inflammatory effects of surgery on iron metabolism and erythropoietin response to anemia.[7,8] In the observational study by Biesma *et al.*, which included orthopedic surgery patients without preexisting anemia (average Hb = 141 ± 11 $g \cdot L^{-1}$) who developed postoperative anemia with an average Hb of 111 ± 13 $g \cdot L^{-1}$, there was no correction of anemia by one-week

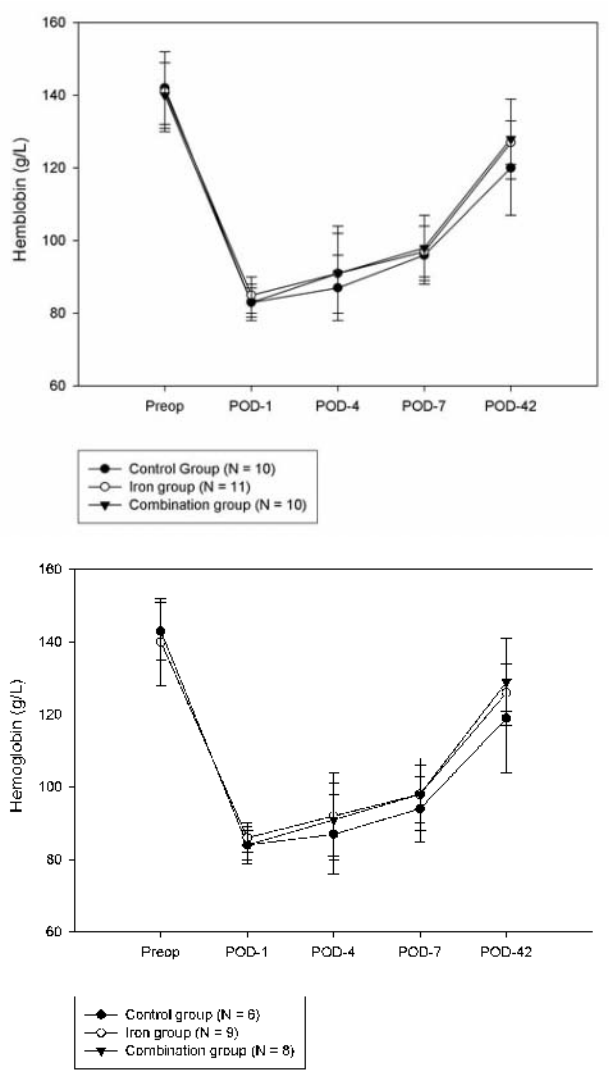

FIGURE 2 Hemoglobin concentrations in all patients and in untransfused patients. (A) All patients; (B) untransfused patients.

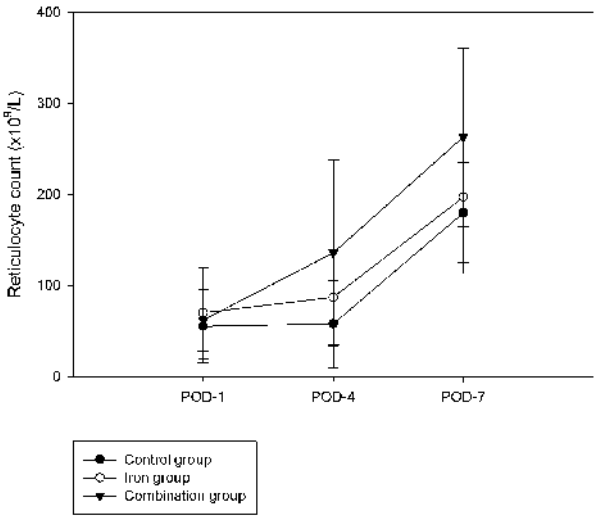

FIGURE 3 Reticulocyte counts in all patients.

after surgery, while by two and six weeks after surgery there was a one-third and two-thirds correction of anemia, respectively.[8] A similar study by van Iperen *et al.* had similar findings.[7] In a randomized controlled study examining treatments for postoperative anemia (see below for details of this study), Madi-Jebara *et al.* found that, in their control group in whom the average postoperative Hb was 108 ± 13 g·L^{-1}, there was no correction of anemia by two-weeks after surgery, and there was only a one-third correction of anemia at four-weeks after surgery.[14] In the current study, which included patients who were markedly more anemic than those in previous studies (average postoperative Hb was 84 ± 4 g·L^{-1} in this study), in the Control group there was a 12% recovery of anemia after one-week and 65% correction after six-weeks.

The realization that the inflammatory effects of surgery create a relative iron and erythropoietin deficient state that may delay recovery from postoperative anemia has led to the hypothesis that the speed of recovery may be accelerated by *iv* iron alone or in combination with recombinant erythropoietin therapy.[9] At the time of initiation of this current study, the effectiveness of *iv* iron for accelerating recovery from postoperative anemia had been assessed by only three small observational studies, all of which found it to be highly effective in treating postoperative anemia.[15–17] These studies, however, were limited by their lack of concurrent controls and therefore could not comment on the effects of *iv* iron on the speed of recovery.[15–17] As well, several studies had found that recombinant erythropoietin was effective in accelerating recovery from postoperative anemia. These studies, however, were preliminary in nature and were limited to preclinical studies on animals,[18–21] case reports,[22–27] and one small cohort study with historical controls.[28]

Unlike these preliminary studies, the current study – which was a randomized, double-blinded, placebo controlled clinical trial that included patients without

preexisting anemia who developed severe postoperative anemia – found that early postoperative treatment with *iv* iron alone or in combination with recombinant erythropoietin does not appear to sufficiently accelerate recovery from anemia within the first postoperative week, to have a clinical impact.

The results of our study are consistent with those of a recently published randomized controlled trial that also assessed the efficacy of treating postoperative anemia with *iv* iron alone or in combination with recombinant erythropoietin.[14] In that study, which included cardiac surgery patients with postoperative anemia (Hb concentration between 70 and 100 $g \cdot L^{-1}$), treatment with *iv* iron (iron sucrose 200 $mg \cdot day^{-1}$ starting on POD-1; average dose given = 438 ± 148 mg) alone or in combination with recombinant erythropoietin (300 $U \cdot kg^{-1}$ given on POD–1) did not accelerate recovery from anemia within one month of surgery. This finding was despite the fact that, as in our study, there was accelerated erythropoiesis (as measured by reticulocyte counts) in the group receiving both *iv* iron and recombinant erythropoietin. There were several important differences between this study and ours. In our study, subjects were not limited to those undergoing cardiac surgery (to enhance generalizability), patients were more anemic upon presentation (average POD-1 Hb was 84 ± 4 $g \cdot L^{-1}$ in our study while it was greater than 100 $g \cdot L^{-1}$ in the other study), and we used higher doses of *iv* iron (iron sucrose 600 mg *vs* 438 ± 148 mg) and recombinant erythropoietin (1200 $U \cdot kg^{-1}$ *vs* 300 $U \cdot kg^{-1}$). While the optimal dose of iron sucrose is not known, the dose used in this study would provide enough iron to replace 40 $g \cdot L^{-1}$ of Hb (i.e., 150 mg of stored iron is required to replace 10 $g \cdot L^{-1}$ of Hb). The erythropoietin dose selected for this study is known to be effective in the treatment of preoperative anemia and is used clinically in our blood conservation program.[29,30] Thus, it is unlikely that lack of drug efficacy was due to inadequate dosing.

Our study has several limitations. First, the sample population was small. Originally the study was powered to detect an 8 ± 9 $g \cdot L^{-1}$ difference in the Hb concentration one week after surgery between the Combination group and the Control group, which we considered to be a clinically important difference. The one-week time point was selected as the primary outcome because any clinical benefits of accelerated recovery from postoperative anemia, such as reduced RBC transfusion or duration of hospitalization would most likely be limited to that time period. The study, however, was terminated early due to slow recruitment, and the results of the interim analysis that the likelihood of detecting a significant increase in Hb one week after surgery in the Combination group relative to the Control group was small (29%). The small sample size means that the study was underpowered for detecting between-group differences in secondary outcomes such as six-week increase in Hb (in which there was a trend in favour of the combination therapy) or quality of life measures.

A second weakness of the study is the small number of patients recruited relative to the number of patients screened, which limits the generalizability of the results. Although the incidence of severe postoperative anemia was high, only 4% of patients were found to be eligible for the study, with the primary reasons for exclusion being presence of preoperative anemia (these patients were excluded to eliminate the confounding effects of chronic anemia on recovery from acute postoperative anemia) and postoperative organ dysfunction (these patients were excluded to minimize the incidence of RBC transfusion after randomization). The study's restrictive inclusion criteria were designed to limit the study population to those who would be most likely to respond to the study interventions. Another limitation is that Hb was measured only at POD-4, POD-7, and POD-42. Given that erythropoiesis was higher in the Combination group on POD-7, it is possible that a difference in Hb may have existed between one and six weeks after surgery, which this study would not have been able to detect. In addition, this study cannot exclude the possibility that higher doses or different timing of postoperative *iv* iron and recombinant erythropoietin may be effective in accelerating correction of postoperative anemia.

In summary, this study indicates that, in previously non-anemic patients who develop severe postoperative anemia, early postoperative treatment with *iv* iron alone or in combination with recombinant erythropoietin does not appear to accelerate recovery from anemia within the first postoperative week to an extent that would have a clinical impact.

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