Original Article

Effects of Iron Sucrose and Erythropoietin on Transfusion Requirements in Patients with Preoperative Iron Deficiency Anemia Undergoing on-Pump Coronary Artery Bypass Graft

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Abstract

Background: *Preoperative anemia is an independent risk factor for higher rates of blood transfusion in cardiac surgery. This study aimed to evaluate the effects of intravenous iron sucrose and erythropoietin on transfusion requirements in patients with preoperative iron deficiency anemia (IDA) undergoing on-pump coronary artery bypass graft (CABG) surgery.*

Methods: *In this open-label, randomized clinical trial, patients with preoperative IDA who were candidates for on-pump CABG were randomized into intervention (iron plus erythropoietin) or control groups. Iron sucrose was administered as a 200 mg intravenous dose and erythropoietin as a 100 IU/kg bolus 1 to 2 days before surgery. The primary outcome was the amount of blood transfusion during the first 4 postoperative days.*

Results: *The study population consisted of 114 patients. The mean age was 64.11±8.18 years in the intervention group and 63.35±8.70 years in the control group. Twenty-seven patients (47.4%) in the intervention group and 25 (43.9%) in the control group were males. The number of red blood cell units transfused per patient exhibited a significant fall in the intervention group compared with the control group (P<0.001). The ferritin level showed a significant rise in the intervention group on postoperative day 7 (P=0.027). The length of stay in the intensive care unit and the hospital was significantly lower in the intervention arm (P=0.041 and P=0.006, respectively). No adverse events were reported in both groups.*

Conclusion: *The use of erythropoietin and iron sucrose 1 to 2 days before surgery significantly decreased the need for blood transfusion in patients with IDA undergoing CABG without any significant adverse events.*

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Introduction

Each year, more than 800 000 patients undergo coronary artery bypass graft (CABG) surgery.[1] Preoperative anemia, mainly caused by iron deficiency, is a common condition among candidates for CABG.[2] The prevalence of preoperative anemia in cardiac surgery is between 10.0% and 50.0%.[3] Preoperative anemia is a modifiable risk factor that can increase mortality,[4] morbidity, and transfusion requirements.[5-8] Furthermore, cardiac surgeries are at high risk for bleeding and transfusion requirements due to the complexity of the procedures, contact with cardiopulmonary bypass pumps, and the pre- or intraoperative use of antithrombotic agents.[6]

Blood transfusion is associated with adverse outcomes such as acute renal failure, acute lung injury,[7] and infection; additionally, it is an independent risk factor for prolonged lengths of stay in the intensive care unit (ICU) and the hospital as well as increased short- and long-term mortality rates. Thus, using strategies for blood preservation aimed at reducing transfusion requirements is an important step to prevent complications.[8]

According to the international consensus statement on the perioperative management of anemia and iron deficiency, in all surgical procedures with expected blood loss exceeding 500 mL, it is essential to diagnose and treat preoperative anemia. In the time available before most cardiac surgeries, however, effective treatment with oral iron is not feasible. Indeed, preoperative treatment with intravenous iron is more effective and faster than oral iron when the time for surgery is within 6 weeks.[9]

Recently, Spahn et al[10] showed the beneficial efficacy of an ultra-short-term combination treatment of intravenous iron and erythropoietin in lessening blood transfusion requirements in patients with preoperative anemia undergoing elective cardiac surgery. The safety and efficacy of erythropoietin in conjunction with iron have been demonstrated in anemic patients undergoing valvular heart surgery.[11]

In the present study, we sought to evaluate the effects of preoperative intravenous iron and intravenous bolus erythropoietin on transfusion requirements in patients with preoperative iron deficiency anemia (IDA) undergoing on-pump CABG.

Methods

This prospective, randomized, single-center trial was performed in Tehran Heart Center, Tehran, Iran, from May 2019 through March 2020, on patients with IDA undergoing on-pump CABG. The trial protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (approval code: IR.TUMS.tips.REC.1398.027). The trial was registered at the Iranian Registry of Clinical Trials (IRCT20190121042447N1) in November 2019. Written informed consent was obtained from the study participants after they had received verbal explanations about the study.

The study enrolled 114 adult patients with preoperative IDA who were candidates for on-pump CABG. According to the World Health Organization, the criterion for the diagnosis of anemia is a hemoglobin concentration level of less than 12 g/dL in women and less than 13 g/dL in men.[11] In the current investigation, iron deficiency was defined as a ferritin level of less than 30 μg. In addition, if the ferritin level was between 30 μg and 100 μg, the transferrin iron-binding capacity had to be less than 20%, and/or C-reactive protein had to be more than 0.5 mg/dL.[9] Eligible patients were randomized to either the intervention or the control group via permuted block randomization.

The exclusion criteria consisted of preexisting uncontrolled hypertension (systolic blood pressure>180 mmHg), a platelet count of more than 450000/mm^3, a history of thromboembolism, a history of seizure, malignancies, liver dysfunction (liver function test≥3 times the upper limit of normal), renal impairment (serum creatinine≥2 mg/dL), hypersensitivity to iron, and ongoing bleeding.

The intervention group received 200 mg of iron sucrose (Venofer, Vifor Pharma, Ltd, Switzerland) in 200 mL of a normal saline infusion in 30 minutes plus 100 IU/kg of erythropoietin (Pooyesh Darou, Iran) via intravenous bolus administration at 1 to 2 days before surgery. The control group received no additional intervention apart from the standard treatment.

The medications were administered by nurses who were not involved in the study, and the surgery team was blinded to the patients' groups until the end of the study.

The primary outcome was a comparison in terms of the mean number of units of packed red blood cells (RBCs), fresh frozen plasma (FFP), and platelets transfused per patient between the surgical time and the fourth postoperative day. The secondary outcomes were composed of the adverse events associated with injection, the patterns of hemoglobin concentration changes between the surgical time and postoperative day 7, the pattern of changes in the iron profile, and the incidence of postoperative complications.

The transfusion threshold was a hemoglobin concentration of less than 8 mg/dL after CABG and less than 7 mg/dL during surgery. Additionally, liberal transfusions were considered regardless of the hemoglobin concentration in patients with hemodynamic instability.

Preoperative data encompassed demographic characteristics, past medical history (including diabetes mellitus, hypertension, dyslipidemia, chronic renal failure, cerebrovascular accidents, congestive heart failure, chronic obstructive pulmonary disease, and myocardial infarction), and medications. Intraoperative data comprised the duration of aortic cross-clamping and cardiopulmonary

bypass. In addition, the amounts of heparin, protamine, and tranexamic acid administered during surgery were recorded for evaluation. Postoperative data were comprised of the amounts of packed-RBCs, FFP, and platelets transfused until postoperative day 4 and the hemoglobin concentration until postoperative day 7, as well as the iron profile (ie, the serum iron concentration, the total iron-binding capacity, the ferritin concentration, and transferrin saturation) measured preoperatively and on postoperative day 7.

Other parameters evaluated included the incidence of acute kidney injury in the first 48 postoperative hours; atrial fibrillation, infection, liver impairment, and coagulopathy in the first 7 postoperative days; the length of stay in the ICU and the hospital; and the rate of in-hospital mortality.

Acute kidney injury was defined according to The Kidney Disease: Improving Global Outcomes (KDIGO) guideline as an elevation in serum creatinine by at least 0.3 mg/dL or a rise in serum creatinine to at least 1.5 times the baseline value.[12] Surgical mortality was defined as all deaths occurring during the hospital stay. Liver impairment was considered an increase in the liver function test (ALT and AST) exceeding 3 times the upper normal limit. Postoperative infection was defined as any kind of infection occurring within 30 days of surgery, likely related to the operation itself or the postoperative course. Coagulopathy was considered a platelet count below 50000/m^3 or an international normalized ratio above 1.5 or a partial thromboplastin time at least twice the control value.

Continuous variables were presented as the mean with the standard deviation (SD) for normally distributed data. The Student *t* test was used for between-group comparisons. Nonparametric variables were reported as the median with 25th and 75th percentiles. The Mann–Whitney *U* test was employed to compare the intervention and control groups. In addition, the χ^2 test was applied to compare categorical variables, which were expressed as frequencies with percentages. All the statistical analyses were conducted using IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY: IBM Corp).

Results

In this study, 282 patients were assessed for eligibility, and 165 patients were excluded: 127 patients did not have IDA, 20 patients with serum creatinine levels exceeding 2 mg/dL, 3 patients with liver function test values exceeding 3 times the upper normal limit, 5 patients with a history of malignancy, and 10 patients with ongoing bleeding. Of the remaining 117 patients, 59 were allocated to the iron group and 58 were allocated to the control group. One patient from each group was converted to off-pump revascularization. Surgery was canceled for 1 patient in the intervention group (Figure 1).

Of 114 patients, 62 (54.4%) were females. As is shown in Table 1, both groups had similar age, sex, history of diabetes mellitus, hypertension, and dyslipidemia. Laboratory data before surgery were similar in both groups (Table 2). The mean ejection fraction was 42.81±10.44% in the

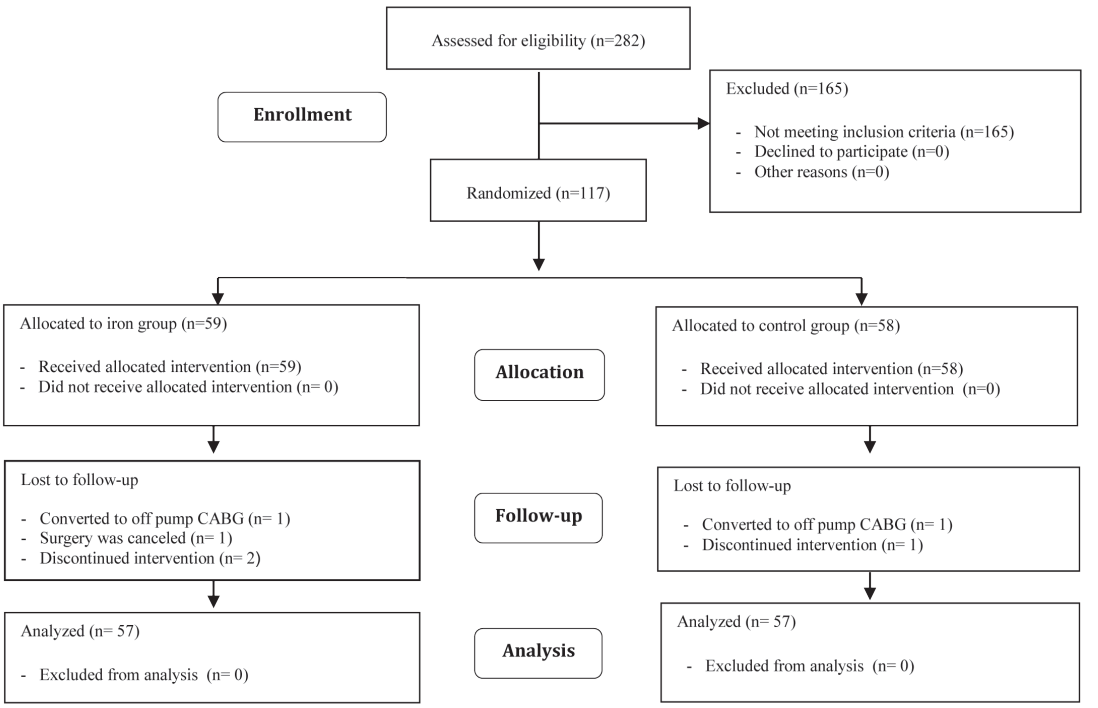

Figure 1. Consort flow chart of patients' enrollment
CABG, Coronary Artery Bypass Graft Surgery

Table 1. Comparison of the baseline characteristics and drug history between the iron and control groups*

	Control Group (n=57)	Iron Group (n=57)	P
Age (y)	64.11±8.18	63.35±8.70	0.634
Sex (male)	27 (47.4)	25 (43.9)	0.707
Dyslipidemia	33 (57.9)	28 (49.1)	0.348
MI	11 (19.3)	5 (8.8)	0.106
Hypertension	35 (61.4)	34 (59.6)	0.848
Diabetes mellitus	36 (63.2)	34 (59.6)	0.700
Heart failure	25 (43.9)	17 (29.8)	0.120
CKD	8 (14.0)	10 (17.5)	0.607
COPD	3 (5.3)	0	0.243
CVA	3 (5.3)	5 (8.8)	0.716
ACEI/ARB	39 (68.4)	38 (66.7)	0.841
β-blocker	49 (86.0)	48 (84.2)	0.793
CCB	9 (15.8)	16 (28.1)	0.113

*Data are presented as mean±SD or n (%).
MI, Myocardial infarction; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; CVA, Cerebrovascular accidents; ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor block; CCB, Calcium channel blocker

Table 2. Comparison of preoperative laboratory and echocardiography data between the iron and control group*

	Control Group (n=57)	Iron Group (n=57)	P
Serum creatinine (mg/dL)	1 (0.9-1.2)	1.08 (0.9-1.3)	0.230
BUN (mg/dL)	40.0 (29.0-48.0)	37.0 (30.0-53.0)	0.616
MCV (fl)	82.73±6.61	81.88±6.15	0.476
Platelet (×1000/cumm)	243.25±67.04	243.95±61.39	0.954
LFT (normal)	55 (96.5)	55 (96.5)	0.999
Hemoglobin (g/dL)	11.64±1.08	11.72±1.03	0.673
Iron (µg/dL)	45.04±17.03	46.96±15.65	0.530
TIBC (µg/dL)	306.11±59.51	300.11±52.26	0.569
TSAT (%)	14.48±4.82	15.24±4.45	0.386
Ferritin (µg/L)	73 (38.0-148.0)	86 (30.0-187.0)	0.762
CRP (mg/dL)	0.8 (0.3-1.4)	0.36 (0.2-2.4)	0.116
Ejection fraction (%)	41.49±8.96	42.81±10.44	0.472

*Data are presented as mean±SD, n (%), or median ($IQR_{25-75\%}$).
BUN, Blood urea nitrogen; fl, Femtoliter; MCV, Mean corpuscular volume; LFT, Liver function test; TIBC, Total iron binding capacity; TSAT, Transferrin saturation; CRP, C-Reactive protein

Table 3. Comparison of intraoperative data between the iron and control group*

	Control Group (n=57)	Iron Group (n=57)	P
CCT (min)	42 (30.0-51.0)	44 (33.0-57.0)	0.200
CPB (min)	70 (55.0-90.0)	70 (57.0-100.0)	0.642
Heparin (number of ampules)	8 (7.0-10.0)	8 (6.0-9.0)	0.135
Protamine (number of ampules)	8 (7.0-8.0)	8 (6.0-8.0)	0.056
Tranexamic Acid (number of ampules)	7.09±3.40	5.81±1.82	0.014

*Data are presented as mean±SD or median ($IQR_{25-75\%}$).
CCT, Cross-clamp time; CPB, Cardiopulmonary bypass

Table 4. Comparison of the postoperative iron profile between the iron and control groups*

	Control Group (n=57)	Iron Group (n=57)	P
Iron (µg /dL)	26 (22.0-40.0)	25 (21.0-43.0)	0.977
TIBC (µg/dL)	231.39±54.60	226.79±55.40	0.656
TSAT (%)	12.7 (10.0-15.7)	12 (9.0-18.2)	0.901
Ferritin (µg/L)	226 (145.0-302.0)	251 (174.0-468.0)	0.027

*Data are presented as mean±SD or median ($IQR_{25-75\%}$).
TIBC, Total iron-binding capacity; TSAT, transferrin saturation

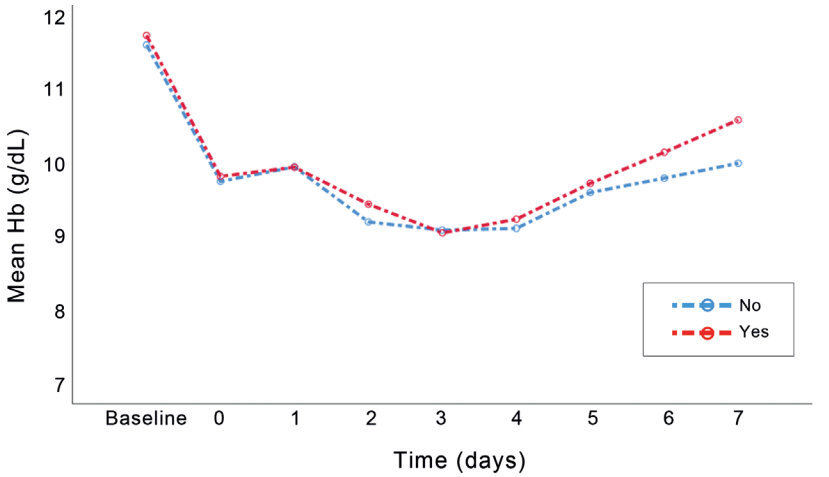

Figure 2. Changes of mean hemoglobin over the time in iron and control groups

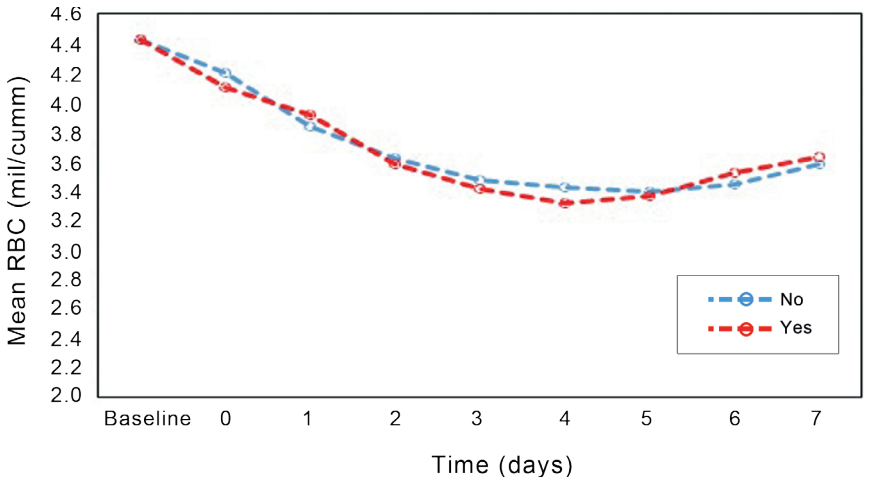

Figure 3. Changes of mean red blood cells over the time in iron and control groups

Table 5. Comparison of changes of mean hemoglobin and red blood cells in post-operative days*

	Control Group (n=57)	Iron Group (n=57)	P
Hemoglobin (g/dL) (base)	11.62±1.08	11.75±1.01	0.673
Hemoglobin (g/dL) (POD0)	9.75±1.39	9.82±1.43	0.435
Hemoglobin (g/dL) (POD1)	9.95±1.23	9.95±1.05	0.852
Hemoglobin (g/dL) (POD2)	9.20±1.08	9.44±1.25	0.276
Hemoglobin (g/dL) (POD3)	9.09±1.08	9.05±1.19	0.744
Hemoglobin (g/dL) (POD4)	9.11±0.89	9.24±1.07	0.273
Hemoglobin (g/dL) (POD5)	9.60±0.92	9.73±0.88	0.467
Hemoglobin (g/dL) (POD6)	9.80±0.93	10.15±1.40	0.323
Hemoglobin (g/dL) (POD7)	10.00±1.00	10.59±1.41	0.008
RBC (mil/cumm) (base)	4.42±0.52	4.42±0.42	0.932
RBC (mil/cumm) (POD0)	4.21±0.51	4.10±0.41	0.715
RBC (mil/cumm) (POD1)	3.83±0.54	3.91±0.38	0.089
RBC (mil/cumm) (POD2)	3.61±0.55	3.57±0.47	0.952
RBC (mil/cumm) (POD3)	3.46±0.47	3.40±0.47	0.519
RBC (mil/cumm) (POD4)	3.42±0.49	3.31±0.52	0.180
RBC (mil/cumm) (POD5)	3.39±0.46	3.36±0.50	0.812
RBC (mil/cumm) (POD6)	3.44±0.36	3.51±0.49	0.407
RBC (mil/cumm) (POD7)	3.57±0.32	3.62±0.42	0.553

*Data are presented as mean±SD.
POD, Postoperative day; RBC, Red blood cell

Table 6. Comparison of the postoperative outcome between the intervention and control groups*

	Control Group (n=57)	Iron Group (n=57)	P
AKI	13 (22.8)	9 (15.8)	0.342
Liver impairment	3 (5.3)	1 (1.8)	0.618
Infection	16 (28.1)	6 (10.5)	0.018
Coagulopathy	11 (19.3)	6 (10.5)	0.189
AF	9 (15.8)	8 (14.0)	0.793
ICU duration	3 (2.0-5.0)	2 (2.0-4.0)	0.041
Hospital	12 (10.0-16.0)	10 (9.0-12.0)	0.006
Death (%)	5 (8.8)	5 (8.8)	0.999

*Data are presented as n (%) or median ($IQR_{25-75\%}$).
AKI, Acute kidney injury; AF, Atrial fibrillation; ICU, Intensive care unit

intervention group and 41.49±8.96% in the control group (P=0.472). Surgical data, including the duration of aortic cross-clamping and cardiopulmonary bypass, were similar in the intervention and control groups (Table 3).

The amounts of heparin and protamine administered during surgery were similar in both groups, but the amount of tranexamic acid administered was significantly lower in the intervention group (P=0.014; 95% CI: 0.51–1.28).

The mean number of units of RBCs transfused per patient showed a significant drop in the intervention group compared with the control group (2.56±1.35 vs 1.53±1.04; P<0.001; 95% CI: 0.58–1.48).

Postoperative serum iron concentrations, total iron-binding capacity, and transferrin saturation were similar in both groups, but the ferritin level was significantly higher in the intervention group (P=0.027; 95% CI, 0.28–0.48) (Table 4).

The effect of time on the increase in the hemoglobin and RBC concentration was significant; still, the average change in the concentration of hemoglobin in the iron group exhibited a slight rise, which was not significantly different (Figures 2 & 3). Changes in hemoglobin concentrations and RBCs were consistent between the groups (Table 5).

The incidence of acute kidney injury, atrial fibrillation, liver impairment, and coagulopathy was not significantly different between the groups; the incidence of postoperative infection was, however, significantly lower in the intervention group (P=0.018; 95% CI: 0.34–0.48) (Table 6).

The median ($IQR_{25–75\%}$) length of hospital stay was 10 ($IQR_{25–75\%}$: 9.00–12.00) days in the intervention group and 12 ($IQR_{25–75\%}$: 10.00–16.00) days in the control group (P=0.006; 95% CI, 0.26–0.45). The median ($IQR_{25–75\%}$) length of stay in the ICU was 2 ($IQR_{25–75\%}$: 2.00–4.00) days in the intervention group and 3 ($IQR_{25–75\%}$: 2.00–5.00) days in the control group (P=0.041, 95% CI: 0.30–0.49). The mortality rate was similar in both groups. There were no reports of hypersensitivity reactions to iron or erythropoietin in the intervention group.

Discussion

Cardiac surgery is associated with blood loss, decreased hematopoiesis, and postoperative anemia. Blood transfusion is recognized as a primary solution for patient blood management. About 20% of transfusions are for cardiac surgery.[13] Nonetheless, not only is blood transfusion associated with adverse outcomes such as acute renal failure, acute lung injury,[7] and infection but also it is an independent risk factor for prolonged lengths of stay in the ICU and the hospital, as well as short- and long-term mortality rates.[8]

Preoperative anemia is common in patients undergoing cardiac surgery.[2] Multiple studies have shown that preoperative anemia is associated with more blood transfusion and adverse clinical outcomes such as increased ICU and hospital lengths of stay and high mortality.[8]

Iron plays an important role in erythropoiesis and hemoglobin synthesis, and erythropoietin requires adequate iron stores for the production of new RBCs.[14] On the other hand, the absorption of iron is decreased by inflammation, and 150 mg of stored iron is required to increase hemoglobin levels by 1 g/dL. Accordingly, in the present study, we used 200 mg of iron intravenously, similar to the study by Yoo et al.[11]

A salient difference between our study and previous investigations is the type of surgery. Several studies have shown that the amount of bleeding after off-pump surgery is low by comparison with on-pump surgery.[6] We excluded both off-pump CABG and CABG with concomitant valve surgery because the amount of bleeding differs based on the type of surgery and we sought a lesser heterogeneity. Thus, to the best of our knowledge, we are the first to evaluate the efficiency of iron and erythropoietin in reducing blood transfusion in on-pump CABG.

In this clinical trial, we observed a statistically significant reduction in the mean number of RBC units transfused per patient between the surgical time and the fourth postoperative day in the intervention group. In line with our study, a meta-analysis of 11 randomized controlled trials showed that the rate of allogeneic blood transfusion was decreased with the administration of erythropoietin before cardiac surgery.[15]

Weltert et al[14] assessed 320 patients undergoing off-pump CABG and compared the effects of a preoperative high-dose erythropoietin treatment protocol (cumulative dose=52000 IU) and a placebo starting 2 days before and ending 2 days after surgery. Postoperative transfusion requirements were

lower in the erythropoietin group than in the placebo group (0.33 vs 0.76 units per patient; P=0.008).

Yoo et al[11] evaluated 74 patients with heart valve replacement and reported that a single administration of 500 IU/kg of erythropoietin and 200 mg of iron sucrose 1 day before surgery reduced the RBC transfusion rate (from 86% to 59%) and the number of transfused RBCs (3±2.2 to 1.0±1.1 RBC units per patient).

Spahn et al[10] demonstrated that ultra-short-term treatment with a combination of iron, erythropoietin, vitamin B12, and folic acid in 505 patients with iron deficiency or anemia undergoing cardiac surgery significantly lessened RBC transfusions and augmented hemoglobin concentrations in the first 7 days.

There are some concerns regarding the safety of erythropoietin. Recent studies have mentioned that the long-term, high dose, and repeated use of erythropoietin leads to thromboembolism events, hypertension, and other complications,[16] which prompted us to prescribe 100 IU/kg of erythropoietin 1 to 2 days before surgery in the current investigation. We also administered erythropoietin via intravenous route due to microcirculation and generalized atherosclerotic condition in cardiac surgery, causing the subcutaneous absorption of erythropoietin.[11]

Chiming in with a previous study,[17] we showed that lower doses of erythropoietin exerted a significant effect on reducing blood transfusion requirements, with no thromboembolic events.

Ferritin levels tend to reach the peak level between 7 and 9 days after iron administration. We also demonstrated a statistically significantly higher elevation in ferritin concentrations on postoperative day 7 in the iron group compared with the control group, suggesting that perioperative intravenous iron supplementation maintains iron stores after cardiac surgery.

In agreement with previous studies,[18] our results showed that cardiac surgery caused changes in iron metabolism, including increased serum ferritin concentrations and decreased serum iron concentrations and transferrin saturation. Indeed, despite intravenous iron and erythropoietin administration 1 to 2 days before surgery, the serum iron concentration and transferrin saturation decreased in both intervention and control groups, which may have been a consequence of the rapid clearance of iron during increased erythropoiesis. Notably, a single RBC unit contains approximately 200 to 250 mg of iron.[19] According to our results, the amount of RBC transfusion was significantly higher in the control group, which is concordant with a previous study reporting that transfusion significantly increased serum iron concentrations.[20]

According to Waltert et al,[13] the administration of erythropoietin in cardiac patients increased hemoglobin concentrations 4 days after surgery. We observed a rise in the concentration of hemoglobin in the treatment group 5 days after surgery, although the change was not significant compared with the control group. The discrepancy in the results could be because of the lower dose of erythropoietin and the type of surgery (on-pump) in our investigation, as well as the fact that the patients in their study had higher baseline hemoglobin concentrations than did our patients.

Tranexamic acid is widely used to reduce bleeding and blood transfusion in cardiac surgery.[21] In our study, intraoperative tranexamic acid administration was significantly lower in the iron group, which may indicate less bleeding in the intervention group.

Earlier studies have reported that erythropoietin has protective properties in the kidney against ischemia/reperfusion injury and, thus, reduces postoperative acute kidney injury.[11-22] We had fewer patients who developed acute kidney injury, but the difference from previous investigations is not statistically significant. A reason for the lower number of patients developing acute kidney injury in the current study could be our use of a low erythropoietin dose by comparison with the aforementioned studies.

Various studies have concluded that preoperative anemia, as well as blood transfusion, is a risk factor for postoperative infection.[5] There is also concern over intravenous iron insofar as it may increase the amount of free iron in the body, which plays a role in the growth of microorganisms and may lead to increased infection.[4] In contrast to a similar study,[14] our results showed that iron therapy not only did not increase the rate of infection but also, by effectively reducing blood transfusion, led to a significant decline in infection compared with the control group.

Similar to a study by Cladellas et al,[14] the length of stay in the hospital and the ICU in our study was significantly shorter in the patients who received iron and erythropoietin than in the control group. This is a valuable finding because although these drugs are expensive, shortening the length of hospital stay may make the combination cost-effective.

The rate of mortality was similar in both of our studied groups. Nonetheless, this rate is higher than that reported by Yoo et al.[11] This dissimilarity is justifiable because whereas Yoo and colleagues evaluated 30-day mortality, we assessed mortality until hospital discharge, which is known to be higher.

Short follow-up periods and the non-measurement of inflammatory factors after surgery could be mentioned as the limitations of our study.

Conclusion

Our result demonstrated that the administration of a single dose of erythropoietin and intravenous iron sucrose 1 to 2 days before surgery significantly decreased the need for blood transfusion and the length of stay in the ICU and the hospital stay in patients with iron deficiency anemia undergoing on-pump CABG. We, therefore, conclude that

this protocol could be a safe and effective intervention for patient blood management in cardiac surgery.

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