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Evaluating Preoperative Intravenous Iron and Erythropoietin Treatment and Outcomes in Cardiac Surgery Patients

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Abstract

Background: Anemia is more common in cardiac surgery patients than in other people. Severe anemia before cardiac surgery strongly predicts blood transfusion.
Objectives: This study aimed to evaluate the outcomes of Intravenous (IV) iron and erythropoietin (EPO) injection preoperatively in anemic patients waiting for coronary artery bypass graft (CABG) surgery.
Methods: This cross-sectional study was performed between May to December 2020 at Masih Daneshvari hospital in Tehran, Iran. Anemia was described according to the WHO definition (Hb < 130 g/L in men). The study was designed in two groups of men CABG patients. Hematocrit level, platelet count, partial thromboplastin time, international normalized ratio, prothrombin time before surgery, red blood cells (RBCs) transfusion, as well as plasma and platelet units' transfusion during surgery and at the time of hospitalization were obtained from patient's files. The length of stay in the hospital and the consequences, including infection, stroke and heart attack, and mortality, were also obtained from the patient's files and recorded in the checklists. Pearson's chi-squared test, Fisher's exact test, independent samples *t*-test, univariate logistic regression, and odds ratio (OR) were used. All statistical analyses were performed by the SPSS software version 21. The significance level in this study was considered 0.05.
Results: In this study, the data of 64 patients were gathered, among whom 16 (25%) were injected with IV iron and EPO, and the remaining 48 (75%) did not receive any medications for stimulating erythropoiesis. The mean age of patients was 64.05 ± 8.21 years, with an age range of 51 - 91 years. Infection (P = 0.258) and mortality rate (P = 0.440) in the two groups of injection and non-injection did not show a statistically significant difference. The duration of the clamp at the time of surgery (r = 0.699, P = 0.001) and the duration of hospitalization (r = 0.399, P = 0.023) had statistically significant positive relationships with the pump duration. Red blood cell consumption in the injection and non-injection groups was 2.50 ± 2.07 and 2.90 ± 1.80 (P = 0.469), respectively.
Conclusions: Infection (P = 0.258), mortality rate (P = 0.440), and RBC utilization (P = 0.469) in the two groups of injection and non-injection were not significantly different.

Keywords: Anemia, Cardiac Surgical Procedures, Patient Outcome Assessment, Blood Transfusion

1. Background

Iron deficiency (ID) is one of the leading causes of anemia. The underlying factors of anemia in surgical patients include an increased iron requirement, limited external supply, and intense blood loss (1). Postoperative anemia may affect up to 90% of patients undergoing major surgery. This anemia is due to postoperative blood loss and may be exacerbated by reduced erythropoiesis following inflammatory responses (2).

One of the critical surgeries that causes bleeding is heart surgery. Anemia is common in cardiac surgery patients (3) and has been reported in half of these patients (4). The severity of anemia before cardiac surgery strongly predicts blood transfusion (5). There is excessive bleeding in cardiac surgery, and various factors affect the amount of this bleeding, such as cardiopulmonary bypass (CPB), which leads to thrombocytopenia and platelet dysfunction, hemodilution during pump time and anticoagulants treatment, hyperfibrinolysis, and residual heparin effect (6). Therefore, bleeding after cardiac surgery is common (6). Bleeding leads to perioperative anemia that requires an allogeneic blood transfusion (6). Allogeneic blood transfusions are a risk factor for higher mortality of patients and increase the length of stay in Intensive Care Units and hospitals (5, 7).

Anemia can raise the risk of death in patients after cardiac surgery (8). The benefits of ID treatment may be fewer blood transfusions and shorter hospitalization (9). Consequently, studies have shown that a single dose of intravenous (IV) iron in patients with iron deficiency anemia before surgery (patient blood management (PBM) programs) can reduce blood transfusion rates by up to 60% and shorten hospital stay by 2.7 days (10, 11).

2. Objectives

Given the importance of anemia in cardiac surgery patients, we considered evaluating the outcomes of patients who received preoperative IV iron and erythropoietin (EPO) versus those who did not. The evaluated outcomes included the amount of blood transfusion, length of stay in the hospital, and some consequences, including infection, stroke and heart attack, and mortality.

3. Methods

The current cross-sectional study was completed from May to December 2020 at Masih Daneshvari hospital in Tehran, Iran. It was conducted on the information and files of heart surgery patients, and all patients who had consented to enter the PBM project were selected. The study was designed as observational, including two groups of anemic male patients waiting for coronary artery bypass graft (CABG) surgery. Anemia was described according to the WHO definition (Hb < 130 g/L in men and < 120 g/L in women). Inclusion criteria included being older than 50 and having undergone elective cardiac surgery. Exclusion criteria included patients on renal dialysis, previous heart surgery, hematologic disorders, respiratory disease, and reluctance to consent to enter the PBM project. Considering lower body mass index (BMI) and the higher probability of blood transfusion and its complications in women, they were excluded from the study. Finally, the data of 64 patients were assessed.

To perform the study, after obtaining the necessary permits (ethical approval code: IR.TMI.REC.1394.1668 from High Institute for Research and Education in Transfusion Medicine, Tehran, Iran), checklists were designed, including demographic information (i.e., age, weight, height, blood type, BMI), ejection fraction, and past histories, such as hyperlipidemia, hypertension, use of anticoagulants and other medications obtained from patients' files.

The Anticoagulant used during CPB was heparin 300 - 400 U/kg. At the end of CPB, the remaining volume in the reservoir and CPB circuit was returned to the patients before removing the aortic cannula. Hematocrit level, platelet count, partial thromboplastin time, international normalized ratio, PT before surgery, red blood cells (RBCs) transfusion, plasma and platelet units' transfusion during surgery and at the time of hospitalization were obtained from patients' files. The length of stay in the hospital and the consequences, including infection, stroke and heart attack, and mortality, were also recorded in the checklists. According to the inclusion and exclusion criteria, all 64 patients for whom cardiac surgery was performed were included in the study by census method.

3.1. Statistical Analysis

Descriptive statistics were reported using numbers and percentages for qualitative variables and mean and standard deviation for quantitative variables. Pearson's chi-Squared and Fisher's exact tests were applied to evaluate the relationship between the qualitative variables. In addition, due to the normal distribution of quantitative variables, independent samples *t*-test and Pearson's correlation test were used. Finally, univariate logistic regression and odds ratio (OR) was used to determine the effect of each variable on injection or non-injection. All statistical calculations were performed by the SPSS software version 21. The significance level in this study was considered 0.05.

4. Results

In this study, 16 (25%) of the patients were treated with IV iron (1000 mg) and EPO (150 - 300 IU/kg body weight) the day before surgery, and then three doses of iron were injected every other day. The remaining 48 (75%) patients did not receive any medications for stimulating erythropoiesis. The mean age of patients was 64.05 ± 8.21 years, with a range of 51 - 91 years. The variables of age, weight, and height were homogeneous in both injection and non-injection groups, and there was no statistically significant difference between the two groups. However, BMI in the injection group was significantly higher than in the non-injection group (P = 0.041). The difference between the blood group of the patients in the two groups was not statistically significant (P = 0.130). Moreover, the underlying diseases of the participants and the medications used in both groups were homogeneous, and there was no statistically significant difference between the two groups in this regard (Table 1).

Infection (P = 0.258) and mortality rate (P = 0.440) in the two groups of injection and non-injection did not show a statistically significant difference. The results also indicated that the ejection fraction index in the injection group was significantly higher than in the non-injection group (P = 0.023) (Table 2).

The results showed that the duration of the clamp at the time of surgery (r = 0.699, P = 0.001) and the duration of

Table 1. Demographic Information, Underlying Diseases, and Medications Used in Coronary Artery Bypass Graft Patients [a]

	Injection (N = 16)	No Injection (N = 48)	P-Value
Age	63.00 ± 8.18	64.40 ± 8.27	0.560 [b]
Weight	77.94 ± 10.83	73.83 ± 13.11	0.263 [b]
Height	163.31 ± 8.85	165.67 ± 7.08	0.284 [b]
BMI	29.30 ± 4.00	26.86 ± 4.07	0.041 [b]
Blood type			0.130 [c]
A+	4 (25.0)	14 (29.2)	
A-	0 (0.0)	2 (4.2)	
B+	6 (37.5)	10 (20.8)	
B-	1 (6.3)	0 (0.0)	
AB+	0 (0.0)	5 (10.4)	
O+	3 (18.8)	16 (33.3)	
O-	2 (12.5)	1 (2.1)	
Hypertension	2 (12.5)	10 (20.8)	0.563 [c]
Hyperlipide	10 (62.5)	29 (60.4)	0.460 [d]
Kidney	0 (0.0)	2 (4.2)	0.750 [c]
DM	8 (50.0)	15 (31.3)	0.176 [d]
Smoking	0 (0.0)	6 (12.5)	0.324 [c]
Opium	0 (0.0)	6 (12.5)	0.321 [c]
ASA	10 (66.7)	39 (81.3)	0.236 [d]
Plavix	4 (26.7)	17 (35.4)	0.755 [c]
Heparin	1 (6.7)	10 (20.8)	0.272 [c]

[a] Values are expressed as Mean ± SD or No. (%).
[b] Independent samples *t*-test.
[c] Fisher's exact test.
[d] Pearson's chi-squared test.

hospitalization (r = 0.399, P = 0.023) had statistically significant positive relationships with the duration of the pump time. Therefore, clamp time and hospitalization time increased significantly with rising pump time. Packed cell, plasma, and platelet utilization were not correlated with pump and clamp time (Table 3).

Furthermore, the increase in ejection fraction in patients who were injected was 1.12 times more than in people who had not been injected. Ejection fraction levels were higher in people who had injections. The BMI variable also had a statistically significant effect on the IV iron injection. The patients with higher BMI needed 1.16 times more injections than people with lower BMI (Table 4).

5. Discussion

The findings of this cross-sectional study presented that the consumption of RBCs in the injection and non-injection groups were 2.50 ± 2.07 and 2.90 ± 1.80 (P = 0.469), respectively. Infection (P = 0.258) and mortality rate (P = 0.440) in the injection and non-injection were not significantly different. Moreover, packed cell, plasma, and platelet utilization had no significant relationships with pump and clamp time. The results also showed that clamp time and hospitalization time rose significantly with increasing pump time.

Comprehensive PBM strategies for minimizing postoperative bleeding and optimal patient care are designed and implemented. One of their principles is diagnosing and treating anemia in patients who need surgery (for example, IV iron in Iron deficiency anemia) (10, 12). Garrido-Martin et al. reported that oral or IV iron treatment did not affect increasing hemoglobin and decreasing blood transfusion consumption. They found that early postoperative treatment with IV iron did not appear to accelerate early recovery from postoperative anemia after cardiac surgery (13). However, Peel et al. recommended preoperative doses of IV iron > 600 mg and epoetin alfa > 80,000 IU. They described that these doses were associated with significant rises in Hb with a lower RBC transfusion in cardiac surgery patients (14).

Sowade et al. revealed that treatment with IV EPO and oral FE2+ 14 days before surgery increased Hb levels in patients undergoing cardiac surgery (15). This was probably because the combined regimen (iron and EPO) was administered long enough before surgery for beneficial effects. Garrido-Martin et al. did not observe an increased infection rate or adverse events in the group that received IV iron supplementation, indicating that this treatment was safe to use in the perioperative period, which is in line with our study (13). We found no difference between the groups in the blood units' consumption, as reported by Bolger et al. (16). However, we observed that in the injection group, the treatment regimen started on the day before surgery.

Garrido-Martin et al. presented that postoperative IV iron administration provided excellent bioavailability, as shown by significantly increased immature reticulocyte fraction and serum ferritin (13). They showed no beneficial effects in the correction of Hb level postoperatively and no reduction in blood transfusion requirements, which is consistent with our study (13). Iron deficiency may occur in major surgeries, including cardiac surgery or perioperatively, due to hemorrhage, phlebotomy losses, hemolysis, and inflammation (7, 17). In great observational studies, perioperative IV iron did not negatively affect the rates of transfusion, infection, and 30-day mortality in surgical patients (7, 18). In cardiac surgery, a decreased Hb level was associated with increased transfusion requirements, mortality, and prolonged hospital stay (19). Subsequently, oral iron was recommended for non-anemic patients who had undergone high-risk surgeries due to developing severe

Table 2. Relationships Between Different Variables and Patient Outcomes with or Without Injection [a]

	Injection (N = 16)	No Injection (N = 48)	P-Value
Infection (after)	2 (12.5)	2 (4.2)	0.258 [b]
Death	1 (6.3)	1 (2.1)	0.440 [b]
Death reason			0.999 [b]
Cardiopulmonary arrest	1 (50.0)	0 (0.0)	
Infection and decreased consciousness	1 (50.0)	0 (0.0)	
Sepsis infection	0 (0.0)	1 (100.0)	
Hematocrit (before surgery)	30.14 ± 2.93	32.20 ± 4.37	0.040 [c]
Platelet (before surgery)	251.50 ± 78.57	214.77 ± 64.88	0.102 [c]
Platelet (after surgery)	208.63 ± 61.38	185.13 ± 75.51	0.265 [c]
Time pump (surgery)	75.79 ± 34.96	69.05 ± 22.57	0.406 [c]
Clamp pump (surgery)	42.50 ± 18.66	42.10 ± 13.69	0.931 [c]
Packed cells transfusion	2.50 ± 2.07	2.90 ± 1.80	0.469 [c]
INR (before surgery)	1.14 ± 0.10	1.15 ± 0.23	0.925 [c]
PTT (before surgery)	31.08 ± 5.34	29.17 ± 6.14	0.273 [c]
PT (before surgery)	12.79 ± 1.20	13.10 ± 2.21	0.601 [c]
EF	52.63 ± 6.55	47.36 ± 8.20	0.023 [c]
Hospitalization time	11.06 ± 10.40	9.83 ± 5.80	0.556 [c]

Abbreviations: PTT, partial thromboplastin time; INR, international normalized ratio.
[a] Values are expressed as No. (%) or Mean ± SD.
[b] Fisher's exact test.
[c] Independent samples *t*-test.

Table 3. Relationships of Plasma, Packed Cell, Platelet Consumption, and Duration of Hospitalization with the Duration of Pump and Clamp Time

	Time Pump (Surgery)		Clamp Pump (Surgery)	
	r	P-Value [a]	r	P-Value [a]
Clamp pump (surgery)	0.699	0.001	-	-
Packed cells transfusion	0.309	0.133	0.166	0.429
Plasma transfusion	-0.107	0.820	-0.119	0.701
Platelet transfusion	0.284	0.134	0.177	0.151
Hospitalization time	0.399	0.023	0.001	0.999

[a] Pearson correlation test.

postoperative anemia. If surgery was to be performed in less than 4 weeks or the patient could not tolerate oral iron, prescribing IV iron (e.g., 500 mg) was considered (9).

In comparison with blood transfusion and alternative therapies, such as oral iron, IV iron has been shown to be net savings in direct (attainment and administrative treatment costs) and indirect costs (hospitalization costs) (7, 20). Various national and international guidelines have recommended the treatment of iron deficiency anemia in anticipation of cardiac surgery patients (21). There is evidence for more effectiveness of preoperative IV iron in comparison with postoperative. This might be related to the time required for iron to be metabolized and the subsequent maturation of reticulocytes. The primary cause of iron deficiency may also affect the time needed for iron deficiency anemia treatment (9). The peak effect of erythropoiesis in IV iron therapy was observed for roughly 3 weeks (22). However, some studies have reported the beneficial effects of IV iron prescription for less than 2 weeks. Johansson et al. revealed that the IV administration of iron one day before or on the day of the surgery could decrease the incidence of postoperative anemia to one month (22). We evaluated the patients during hospitalization, which might explain the difference between the two groups.

Table 4. Summary of Univariate Logistic Regression for the Effects of Demographic and Medical Variables[a]

	OR (Injection/No Injection)	95% CI for OR		P-Value [b]
		Lower	Upper	
Age	0.98	0.91	1.05	0.554
Weight	1.03	0.98	1.07	0.263
Height	0.96	0.89	1.04	0.281
BMI	1.16	1.01	1.34	0.045
Hemoglobin (after surgery)	0.70	0.44	1.10	0.117
Hematocrit (before surgery)	1.14	0.99	1.31	0.077
Hematocrit (after surgery)	0.87	0.74	1.12	0.091
Platelet (before surgery)	1.01	0.99	1.02	0.109
Platelet (after surgery)	1.00	0.99	1.01	0.263
Time pump (surgery)	1.01	0.99	1.05	0.404
Clamp pump (surgery)	1.02	0.96	1.04	0.629
Packed cells (surgery)	0.88	0.51	1.50	0.634
INR (before surgery)	0.87	0.051	8.74	0.824
PTT (before surgery)	1.06	0.96	1.16	0.276
PT (before surgery)	0.92	0.66	1.27	0.598
EF	1.12	1.01	1.42	0.031
Hospitalization time	1.02	0.95	1.10	0.552

Abbreviations: OR, odds ratio; CI, confidence interval; INR, international normalized ratio; PTT, partial thromboplastin time.
[a] N = 64.
[b] Univariate logistic regression.

Spahn et al. demonstrated that combination treatment with IV iron, EPO alpha, vitamin B12, and oral folic acid the day before the operation reduced RBC and total allogeneic blood product transfusions in cardiac surgery patients (23). Jafari et al. showed that EPO and iron sucrose 1 - 2 days before CABG surgery diminished the need for blood transfusion (24). Munoz et al. showed that preoperative IV iron therapy, very shortly before or after surgery, diminished the incidence of allogeneic blood transfusion, postoperative infection, 30-day mortality, and length of hospital stay (25). In our study, there was no difference between the two groups, which may be due to the nature of our research, the small sample size, and the use of other pillars of PBM. In the best case, Iron might be administrated in a single dose and at least 3 - 5 weeks before the surgery, which had the best effect in diminishing the risk of infection (26). Munoz et al. indicated that the highest effect of IV iron therapy on erythropoiesis was roughly 3 weeks (9).

The limitations of the present study included the small number of patients, descriptive design, use of different PBM methods in two groups of patients, and lack of laboratory test results to confirm the kind of anemia.

5.1. Conclusions

Infection (P = 0.258) and mortality rate (P = 0.440) in the two groups of injection and non-injection did not show a statistically significant difference. Our results showed that the duration of the clamp at surgery (r = 0.699, P = 0.001) and the duration of hospitalization (r = 0.399, P = 0.023) had statistically significant positive relationships with the duration of the pump. With increasing pump time, clamp time and hospitalization time increased significantly. Moreover, no significant relationship was found between PRBCs, plasma, and platelet consumption.

Footnotes

Authors' Contribution: Study concept and design: Azita Chegini and Alireza Jahangirifard; data collecting: Alireza Jahangirifard; analysis and interpretation of data: Amirhossein Maghari and Azita Chegini; manuscript preparation: Azita Chegini, Alireza Jahangirifard, and Amirhossein Maghari; critical revision: Azita Chegini and Alireza Jahangirifard.

Conflict of Interests: There was no conflict of interest to declare.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: This study was approved by High Institute for Research and Education in Transfusion Medicine, Tehran, Iran (IR.TMI.REC.1394.1668).

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Informed Consent: Written informed consent was obtained from the patients.

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