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Original Article

The Effectiveness of Anemia Treatment with Injectable Iron within 48 to 72 Hours before Coronary Artery Bypass Surgery on Cardiac Function and Postoperative Outcome: A Randomized Clinical Trial

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Abstract

Background: Anemia is considered as one of the risk factors affecting the outcomes after cardiac surgery. Accordingly, the improvement of iron deficiency anemia through injection or oral may be associated with the improvement of post-procedure results, especially the improvement of cardiovascular function. This study was aimed at investigating the effectiveness of iron treatment shortly before surgery in reducing the need for blood transfusion and improving myocardial performance parameters (left ventricular ejection fraction) in coronary bypass surgery patients.

Methods: This study was a single-blind randomized clinical trial. In total, 60 candidates for coronary bypass surgery having iron deficiency anemia before the operation were randomly divided into two groups treated with injectable iron supplement (iron sucrose at a dose of 200 *mg*/200 *ml* of normal saline injected in 30 minutes) 48 to 72 hours before surgery or without therapeutic intervention. The patients were examined during and after the operation in terms of surgical outcomes.

Results: Treatment with injectable iron before surgery was associated with improvement in serum hemoglobin level after surgery and a significant reduction in the need for intraoperative and postoperative transfusions. Preoperative treatment of iron deficiency was associated with a reduction in the length of hospitalization of the patients after surgery.

Conclusion: Treatment of iron deficiency anemia within 48 to 72 hours before surgery will improve the condition of patients' anemia and compensate serum hemoglobin, reduce the need for blood transfusion during surgery and the length of hospitalization of the patients after surgery.

Keywords: Anemia, Iron-Deficiency, Ferric oxide, Saccharated, Humans, Iron, Iron deficiencies, Left ventricular function, Saline solution, Single-blind method, Stroke volume, Sucrose

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Introduction

Coronary heart diseases are still associated with high morbidity and mortality in both developed and developing countries (1). Many of these patients require vascularization through various methods such as coronary artery bypass surgery due to the extent of coronary artery involvement, and in this regard and as an intraoperative complication, they experience significant blood loss, therefore the need for blood transfusion is increased (2). On the other hand, the presence and severity of preoperative anemia is an important factor related to the need for intraoperative blood transfusion and is associated with a significant increase in adverse postoperative outcomes such as postoperative hospital morbidity and 30-day mortality (3,4). In many studies, it has been shown that in anemic patients undergoing coronary artery bypass surgery, the amount of intraoperative blood transfusion was 30% higher than in normal non-anemic subjects undergoing this surgery (5). Also, in various studies, the presence of underlying anemia or the lack of optimal management of blood transfusion during coronary artery bypass surgery is closely associated with a significant increase in postoperative complications such as kidney dysfunction, lung damage, the need for long-term hospitalization and even reduced long-term survival of the patients (6-8). This problem has been observed and reported mainly in older population, who are more often faced with underlying comorbidities such as obesity, diabetes and hypertension (9,10). Thus, it seems that normalizing the hemoglobin level before and during coronary bypass surgery, especially through supplying the body with iron or blood transfusion can play an essential role in improving the hospital and even long-term outcomes of these patients. In fact, anemia with various mechanisms is associated with significant tissue damage in the cardiovascular system, especially during surgery. Anemia causes a decrease in tissue oxygen distribution and as a result the occurrence of ischemic tissue damage, the final result of which will be myocardial dysfunction and therefore increase the risk of ventricular dysfunction after surgery (11,12). Hence, it seems that managing anemia and taking advantage of its treatment or blood transfusion can lead to maintaining myocardial function and preventing progression to heart failure. In the literature, the effectiveness of iron treatment has been proven when it is injected a week or more before surgery, but since the hospitalization time of heart surgery patients is usually less before the operation, therefore what we will discuss in the present study is the evaluation of the role of iron treatment shortly before surgery (48 to 72 hours) in reducing the need for blood transfusion and improving myocardial performance parameters (Left Ventricular Ejection Fraction-LVEF) in the patients undergoing coronary bypass surgery.

Methods and Materials

In this single-blinded randomized clinical trial, the patients who were candidates for coronary bypass surgery and had iron deficiency anemia (serum hemoglobin level of less than 12 *g/dL* in men and 13 *g/dL* in women as well as serum ferritin level of less than 30 μg) before the operation were the targeted population. The following criteria were considered as the exclusion criteria: uncontrolled hypertension, blood platelet count above 450,000/mm^3 per cubic millimeter, history of thromboembolism, history of other types of hemoglobinopathies, history of seizures, history of malignancy, liver or kidney function disorders, increased sensitivity to iron, the presence of active bleeding, history of receiving antiplatelet drugs, and warfarin or Novel Oral Anticoagulants (NOAC).

Background information of all the patients including demographic characteristics, clinical and drug records of the patients and the status of coronary involvement in terms of the number and severity of vascular involvement, preoperative blood and laboratory markers including hemoglobin, hematocrit and ferritin levels and other blood biomarkers, as well as cardiac function status before the operation based on echocardiographic findings (including LVEF), were collected in the study checklist. The patients were randomly classified into two groups using a random number table. This study was conducted in a blinded manner so that the patients were completely unaware of the randomization method and treatment protocol

considered. It seemed that the patients' awareness of being treated with injectable iron could affect the patients' clinical performance level. The first group was treated with injectable iron supplement (iron sucrose with a dose of 200 *mg* in 200 *ml* of normal saline injected in 30 minutes) 48 to 72 hours before the operation, and the second group did not receive this treatment. The clinical outcomes evaluated after surgery were as the following: 1) changes in blood hemoglobin levels after surgery, 2) the amount of transfused blood units during surgery, 3) changes in LVEF value based on echocardiographic findings one week after surgery, 4) length of hospitalization, 5) mortality or cardiovascular complications after surgery during hospitalization. All the aforementioned outcomes were compared between the intervention and control groups.

For the statistical analysis, the results were presented as mean ± Standard Deviation (SD) for the quantitative variables and were summarized by frequency (percentage) for the categorical variables. The normality of the data was checked by the Kolmogorov-Smirnov statistical test. The continuous variables were compared using t test or Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. The categorical parameters were compared using the Chi-Square test or the Fisher's exact test if required. p-values of ≤0.05 were considered statistically significant. For the statistical analysis, the statistical software SPSS version 28.0 for windows (IBM, Armonk, New York) was utilized.

Results

In the present study, 60 patients with iron deficiency anemia who were candidates for coronary artery bypass surgery were included, and they were randomly divided into two groups of 30 individuals undergoing intervention with intravenous iron injection before the operation, and 30 patients were not scheduled for this intervention. As shown in table 1, the two groups were similar in baseline variables including gender, mean age, and mean baseline serum hemoglobin level.

In the intervention and control groups, the mean serum hemoglobin level after surgery was 12.40±0.89 *g/dL* and 9.57±0.67 *g/dL*, respectively, which was a significant difference between the two groups (p=0.001). The frequency of cases requiring blood transfusion during surgery was also 36.7% and 73.3%, respectively, which was significantly less in the first group (p=0.004), but the average units of transfused blood had no difference between the two groups (p=0.168).

The mean LVEF before surgery was 33.00±4.07% and 31.50±4.18%, respectively, which showed no significant difference between the two groups (p=0.164). Also, the average LVEF one week after the operation was 37.50±4.50% and 36.50±4.18%, respectively, which demonstrated no significant difference between the two groups (p=0.376).

Regarding the postoperative outcomes (Table 2), the length of hospital stay was significantly shorter in the former group (5.77±0.72 days *vs*. 7.03±1.54 days, p=0.001). In terms of hospital mortality, no deaths were reported in the intervention group, and 1 death

Table 1. Baseline characteristics of study population

Characteristics	Intervention group (n=30)	Control group (n=30)	p-value
Sexual distribution			0.787
Male	19(63.3)	20(66.7)	
Female	11(36.7)	10(33.3)	
Average age, years	68.47±4.77	69.83±5.02	0.285
Average preoperative hemoglobin, *g/dL*	10.24±0.81	10.73±0.90	0.999

Table 2. Postoperative outocme of study population

Characteristics	Intervention group (n=30)	Control group (n=30)	p-value
Average hemoglobin after surgery	12.40±0.89	9.57±0.67	0.001
Cases requiring blood transfusion	11(36.7)	22(73.3)	0.004
Average units of transfused blood	1.18±0.40	1.46±0.58	0.168
Mean LVEF before surgery	33.00±4.07	31.50±4.18	0.164
Average LVEF one week after surgery	37.50±4.50	36.50±4.18	0.376
Average length of hospitalization after surgery	5.77±0.72	7.03±1.54	0.001
Hospital mortality	0(0.0)	1(3.3)	0.999
Frequency of postoperative complications	3(910.0)	5(16.7)	0.760
Postoperative blood transfusion	1(3.3)	8(26.7)	0.011

(3.3%) was reported in the control group, with no difference between the two groups (p=0.999). The frequency of postoperative complications was 3 cases (10.0%) and 5 cases (16.7%), respectively, and there was no difference between the two groups (p=0.760). Complications observed in the intervention group consisted of two cases of atrial fibrillation and one case of pneumonia. In the control group, the complications included three cases of atrial fibrillation, one case of wound infection, and one case of pneumonia. The number of cases requiring blood transfusion after surgery was 1 case (3.3%) and 8 cases (26.7%), which was significantly lower in the first group (p=0.011).

Discussion

Anemia is considered as one of the risk factors affecting the outcomes after major surgeries such as heart surgery. Accordingly, the improvement of iron deficiency anemia through injection or oral may be associated with the improvement of post-procedure results, especially the improvement of cardiovascular function. However, the results of studies regarding the improvement of surgical outcomes following intravenous iron injection have been completely contradictory. What was discussed in this study was to investigate the effectiveness of iron treatment shortly before surgery in reducing the need for blood transfusion and improving myocardial performance parameters (left ventricular ejection fraction) in the coronary bypass surgery patients.

The findings of the present study were: 1) the treatment with intravenous iron before surgery was associated with an improvement in serum hemoglobin level after surgery, 2) treatment of iron deficiency before surgery was associated with a significant reduction in the need for intraoperative transfusion, 3) treatment of preoperative iron deficiency was associated with a reduction in the length of hospitalization of the patients after surgery, 4) administration of preoperative intravenous iron was not associated with changes and improvement in heart function (LVEF), and 5) treatment with injectable iron before surgery had no effect on mortality or postoperative complications. It seems that intravenous iron injection in patients suffering from iron deficiency anemia and candidates for coronary artery bypass surgery improves the anemic condition of the patients, prevents the transfusion during surgery, and as a result, reduces the length of the patients' stay in the hospital, which ultimately reduces treatment costs and the risk of complications after surgery. However, due to the lack of sample size, it was not possible to evaluate the effect of this treatment protocol on mortality and morbidity after the operation, since the frequency of mortality and hospital complications in these patients is significantly low. In general, it seems that such a therapeutic intervention can lead to the improvement of patient outcomes during and

after such major surgeries. Regarding the effect of this therapeutic approach on cardiac function, it seems that more time is required to improve the parameters of cardiovascular function such as LVEF, as the improvement in cardiac function indicators mainly occurs during days and weeks after surgical intervention.

What could be observed in similar studies was the improvement of the anemia condition of the patients and also the reduction of the need for transfusion in them, however, the evidence regarding the improvement of the cardiovascular function of the patients following the treatment of iron deficiency anemia has been limited. In the study by Liu *et al*, in the form of a meta-analysis study, although no difference was observed in the rate of transfusion, hospitalization in the ICU, and the duration of hospitalization, the frequency of hospital mortality in the group under intravenous iron injection was significantly lower than in the placebo group (13). In the study of Corsi *et al*, in the patients with intravenous iron injection, the need for transfusion was significantly less. Also, the duration of hospital stay was significantly shorter and as a result, the hospital cost was significantly lower in the iron injection group (14). In Evans *et al*'s study, cases treated for iron deficiency anemia experienced significantly less blood transfusions after surgery (15). Furthermore, in the study conducted by Hogan *et al*, iron supplementation along with erythropoietin treatment was associated with a reduction in the need for transfusion, a shorter hospital stay, and an increase in patient survival. However, iron treatment had no effect on hemoglobin levels after surgery (16). In Kong *et al*'s study, the amount of blood transfusion in the intravenous treatment group was significantly lower than the oral iron treatment group. Secondly, the increase in the level of hemoglobin in the injection treatment group was much higher than the group treated with oral iron (17). In Tankard *et al*'s study, an increase in hemoglobin was shown following treatment with intravenous iron, and in one study, a reduction was observed in blood transfusion and postoperative morbidity (18). In Elhenawy *et al*'s study, intravenous iron treatment before surgery led to a 16% reduction in the need for blood transfusion. In addition, the level of hemoglobin showed a significant increase after intravenous iron injection during four weeks after the treatment. However, intravenous iron injection did not increase the incidence of side effects after surgery (19). In Jafari *et al*'s study, the amount of intraoperative blood transfusion units in the group treated with iron and erythropoietin was much lower than the control group. The duration of hospitalization of the patients in the hospital and special ward also demonstrated a significant decrease in the group treated with iron and erythropoietin (20). The summary of the studies shows the fact that there is a significant difference in the results of the studies, such as improvement in cardiac function, reduction of postoperative complications and even the need for hospitalization in a special ward, which can be due to the difference in the anemia treatment protocol, the duration of follow-up of the patients, the type of surgical technique, as well as the criteria for entering the patients into the study. However, to achieve more reliable results, long-term follow-up of the patients and comparing different iron deficiency anemia treatment protocols can be very beneficial.

The most important limitation of this study was the small sample size. This problem will enable the evaluation of the differences between the two groups by adjusting for background variables. Also, the investigation of improvement of cardiovascular function in these patients will be provided through long-term follow-up of the patients.

Conclusion

As a final conclusion, the treatment of iron deficiency anemia within 48 to 72 hours before surgery will improve the condition of patients' anemia and compensate for serum hemoglobin, reduce the need for blood transfusion during surgery and reduce the length of hospitalization of the patients after surgery, however this treatment protocol may not have an effect on improving ventricular function indicators or mortality and morbidity.

Conflict of Interest

There was no conflict of interest in this manuscript.

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