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Impact of Intravenous Iron Supplementation Before Coronary Artery Bypass Grafting

Koroner Arter Bypass Greftleme Öncesinde İntravenöz Demir Desteğinin Etkisi

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ABSTRACT

Objective: Current studies, link preoperative anemia to problematic perioperative period, including higher rates of red blood cell transfusion need, longer hospital stay time, higher rates of acute kidney injury, myocardial infarction, stroke and increased mortality. The aim of this retrospective study was to analyze the impact of preoperative intravenous supplementation of iron on postoperative adverse events in patients undergoing elective coronary artery bypass grafting (CABG).

Methods: This single center, retrospective, observational study investigated patients who underwent CABG surgery between 2016-2019. The patients, who were above 18 years old, had iron deficiency anemia (IDA) and underwent elective isolated CABG surgery were included in this study.

Results: Population of this study was consisted of 84 (51.2%) men and the median age of the whole population was 66 (39-80) years old. Preoperative iron supplementation was statistically associated with shorter length of hospital stay and lower in-hospital mortality. More patients in IDA group without iron supplementation needed red blood cell transfusion postoperatively. Preoperative iron supplementation was independently associated with lower risk for in-hospital mortality in patients with IDA who underwent isolated CABG. In addition, 1 unit decrease in preoperative hemoglobin level was found to be related with a 1.8-fold higher risk of mortality.

Conclusion: This study showed that preoperative intravenous infusion of iron is related with a shorter length of hospital stay and reduced perioperative red blood cell transfusion requirement. In-hospital mortality was significantly lower in pretreated patients with iron.

Keywords: Iron deficiency, anemia, iron supplementation, coronary artery bypass grafting

ÖZ

Amaç: Mevcut çalışmalarda, preoperatif anemi varlığı yüksek eritrosit süspansiyonu transfüzyonu, uzamış hastanede kalış süresi, akut böbrek hasarı, miyokard infarktüsü, inme ve artmış mortaliteyi içeren sorunlu perioperatif dönemle ilişkili bulunmuştur. Bu retrospektif çalışmanın amacı elektif koroner arter bypass greft (KABG) cerrahisi uygulanan hastalarda preoperatif intravenöz demir desteğininin postoperatif olumsuz olaylar üzerine etkisini incelemektir.

Yöntem: Tek merkezli, retrospektif, gözlemsel bu çalışmada, 2016-2019 yılları arasında KABG yapılan hastalar araştırılmıştır. On sekiz yaş üzeri, demir eksikliği anemisi olan (DEA) ve elektif KABG yapılmış hastalar bu çalışmaya dahil edilmiştir.

Bulgular: Bu çalışma popülasyonunun ortanca yaşı 66 (39-80) olup, 84 (%51.2)'ü erkeklerden oluşmaktadır. Preoperatif demir desteği alanlar istatistiksel olarak daha kısa hastanede kalış süresi ve daha düşük hastane mortalitesi ile ilişkili bulunmuştur. Demir desteği almayan DEA olan hastalarda ameliyat sonrası daha fazla eritrosit süspansiyonu transfüzyonu gerekmiştir. İzole KABG yapılan DEA olan hastalarda demir desteği bağımsız olarak hastane mortalitesi riskinin azalması ile ilişkili bulunmuştur. Ayrıca preoperatif hemoglobin düzeyindeki 1 birim azalmanın, mortalite riskini 1,8 kat artırdığı görülmüştür.

Sonuç: Bu çalışmada, ameliyat öncesi intravenöz demir desteğinin, daha kısa hastanede kalış süresi ve perioperatif dönemde kırmızı kan hücresi transfüzyonu gereksinimlerinin azalması ile ilişkili olduğu bulundu. Demir ile önceden tedavi edilmiş hastalarda hastane içi mortalite anlamlı derecede düşüktü.

Anahtar sözcükler: Demir eksikliği, anemi, demir desteği, koroner arter bypass grefti

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INTRODUCTION

Anemia is a most frequently accompanying comorbidity with an incidence of up to 50% among cardiac surgery patients (1). Approximately 80% of all causes of anemia in these patients are due to iron deficiency (2). Current studies link preoperative anemia to problematic perioperative period, including higher rates of red blood cell (RBC) transfusion need, longer hospital stay time, higher rates of acute kidney injury, myocardial infarction, stroke and increased mortality (3,4). Therefore, it is mandatory to diagnose and treat iron deficiency anemia (IDA) preoperatively. Taking preclusive measures with a multidisciplinary approach as the first step in anemia treatment will help to diminish the need for blood transfusion. In this way, faster recovery and improved outcomes can be provided postoperatively (5).

In particular, patients with anemia, undergoing coronary artery bypass grafting surgery (CABG), has been associated with short-term outcomes such as myocardial dysfunction and acute renal impairment by several investigators (6,7). Another study found that higher preoperative hemoglobin (Hb)levels had served for better long-term survival (8). According to a recent, retrospective, observational blood transfusion was detected as an independent factor of postoperative mortality in isolated CABG surgery (9). Thus preoperative administration of intravenous (IV) iron seems to be crucial.

The aim of this retrospective study was to analyze the impact of preoperative intravenous supplementation of iron on postoperative adverse events in patients with IDA undergoing elective CABG.

MATERIAL and METHODS

This single center, retrospective, observational study investigated 164 patients who underwent CABG surgery between January 2016 and December 2019 at The Department of Cardiovascular Surgery in Ankara University School of Medicine. The data was collected by screening of local medical database. The patients who were above 18 years old, had IDA and underwent elective isolated CABG surgery were included in this study. Exclusion criteria were:

- The patients whose clinical data could not be accessed
- < 18 years old patients
- Emergency cases
- The patients underwent off-pump CABG surgery
- The patients underwent concomitant cardiac surgery

A written informed consent was obtained from each patient. The study protocol was approved by Ankara University School of Medicine Ethics Committee (2023/496). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All demographical, clinical and laboratory data were obtained through review of original hospital and physician records. Demographics and clinical data included age, gender, body mass index, presence of diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease and cerebrovascular events. Laboratory data included perioperative Hb (g dL^{-1}), serum iron (µg dL^{-1}), ferritin (ng mL^{-1}), transferrin saturation (%) and serum creatinine (mg dL^{-1}) levels.

Surgical Procedure

Cardiac function assessment of the patients were achieved routinely by laboratory (Hb, biochemical parameters, coagulation factors and serum iron panel) and imaging (echocardiography, coronary angiography) tests. Full monitorization with central venous access and invasive arterial blood pressure measurements were established. All of the operations were performed under general anesthesia. In order to minimize the blood loss, 10 mg kg^{-1} of tranexamic acid was administered and autotransfusion was considered if patient had a coagulopathy. Decision of RBC transfusion was made according to cardiac index, near infrared spectroscopy, lactate levels, central venous oxygen saturation, carbon dioxide gradient between mix venous and arterial blood gas measurements.

Anemia and iron deficiency anemia criteria

All patients were screened before elective CABG surgery, including a full blood count. Anemia was diagnosed as Hb level <13 g dL^{-1} for women and men depending on the recent studies (10,11). Iron deficiency anemia was defined as a serum ferritin level of less than 100 ng mL^{-1}, or between 100-300 ng mL^{-1} accompanied by transferrin saturation <20%.

Iron supplementation

In the group of patients who was administered iron, patients received a single intravenous dose of ferric carboxymaltose (1000 mg in 250 mL saline) infused within 15-30 minutes, at least 3 weeks prior to surgery.

Outcomes

The primary outcome of this study was to evaluate the impact of preoperative iron supplementation on in-hospital mortality. The secondary outcomes of interest were blood transfusion rates, amount of postoperative mediastinal drainage, need for re-operation for bleeding control, rate of renal injury, length of intensive care unit stay and hospital stay.

Statistical Analysis

Data were presented as median (min-max) or mean ± SD, as appropriate. The study cohort was separated into two groups according to whether they received iron supplementation or not. The univariate analysis was processed using Fisher exact, the Mann-Whitney U-test, Student's T and Chi-Square test, where appropriate. For multivariate logistic regression analysis, the possible risk factors identified by univariate analyses were further entered into the logistic regression analysis to determine independent predictors of patient outcome. Homer-Lemeshow goodness of fit statistics were used to assess model fit. A p-value of less than 0.05 was considered to show a statistically significant result. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 23.

RESULTS

One hundred sixty four patients with IDA, who underwent isolated coronary artery bypass grafting between January 2016 and December 2019, were included in this study. Population of this study was consisted of 84 (51.2%) men and the median age of the whole population was 66 (39-80) years old. The most common comorbidities were diabetes mellitus 136 (82.9%), hypertension 108 (65.9) and hyperlipidemia 28 (17.1%). Median levels of Hb and serum iron were 12 (8.9-12.9) g dL^{-1} and 47 (15-306) µg dL^{-1}, respectively (Table I).

Patients were divided into two groups according to whether they received preoperative iron supplementation or not. Ninety two patients had received iron supplementation and 72 had not received. These two groups showed no significant differences in demographics except presence of cerebrovascular events. Hemoglobin levels at the preoperative and postoperative period were higher in the group of patients who had received iron supplementation (p=0.002, 0.04 respectively) (Table II). The difference in Hb levels did not persist at discharge, probably because the patients, in the group of patients not received iron supplementation, required more unites of blood transfusions postoperatively. Patients with IDA had higher preoperative EuroScore outcomes (5 vs 4), but there was no statistically significant difference between patients with and without IDA (p=0.232).

Preoperative iron supplementation was statistically associated with shorter length of hospital stay and lower in-hospital mortality (Table III). More patients in group of IDA without iron supplementation needed RBC transfusion postoperatively (51% vs 45%, p=0.038). There was no statistically significant difference between two groups in terms of mediastinal drainage, re-operation for bleeding, acute kidney injury and length of intensive care unit stay.

The risk factors associated with mortality were analyzed by multivariate logistic regression analysis. Preoperative iron supplementation was independently associated with lower risk for in-hospital mortality in patients with IDA, who un-

Table I: Demographics and Preoperative Laboratory Parameters of Patients with Iron Deficiency Anemia, who Underwent Isolated Coronary Artery Bypass Grafting (n=164)

Demographics	
Age, years, median (min-max)	66 (39-80)
Male gender, n (%)	84 (51.2)
Body mass index, median (min-max)	28 (19-42)
EuroScore II, median (min-max)	4 (0-9)
Diabetes mellitus, n (%)	136 (82.9)
Hypertension, n (%)	108 (65.9)
Hyperlipidemia, n (%)	28 (17.1)
Cerebrovascular event, n (%)	8 (4.9)
Chronic obstructive pulmonary disease, n (%)	4 (2.4)
Preoperative laboratory parameters, median (min-max)	
Hemoglobin, g dL^{-1}	12 (8.9-12.9)
Iron in serum, µg dL^{-1}	47 (15-306)
Transferrin saturation, %	16 (3-84)
Ferritin, ng mL^{-1}	68 (10-406)
Vitamin B12, pg mL^{-1}	340 (157-1247)
Folic acid, ng mL^{-1}	6.7 (2.1-14.8)
Creatinine, mg dL^{-1}	1.1 (0.4-3.2)

Table II: Comparision of Demographics and Hemoglobin Levels of Patients with Iron Deficiency Anemia, with or without Intravenous Iron Supplementation (n=164).

	Patients without iron supplementation (n=72)	Patients with iron supplementation (n=92)	p value
Age, years, median (min-max)	63 (39-66)	63.5 (47-75)	0.062
Male sex, n (%)	36 (50)	48 (52.2)	0.782
Body mass index, median (min-max)	26 (20-29)	28 (21-42)	0.055
EuroScore II, median (min-max)	5 (1-8)	4 (0-9)	0.232
Diabetes mellitus, n (%)	64 (47.1)	72 (52.9)	0.073
Hypertension, n (%)	52 (48.1)	56 (51.9)	0.128
Hyperlipidemia, n (%)	12 (16.7)	16 (17.4)	0.903
Chronic obstructive pulmonary disease, n (%)	0 (0)	4 (4.3)	0.073
Cerebrovascular event, n (%)	0 (0)	8 (8.7)	**0.01**
Preoperative hemoglobin, g dL^{-1}, median (min-max)	10.2 (9.2-12.3)	12.2 (9.5-12.8)	**0.002**
Postoperative hemoglobin, g dL^{-1}, median (min-max)	9.2 (9.1-9.3)	10 (7.7-11.5)	**0.04**
Hemoglobin at discharge, g dL^{-1}, median (min-max)	10.1 (7.8-11.5)	10.1 (8-12.8)	0.642

Table III: Cinical Outcomes of the Study Population (n=164)

	Patients without iron supplementation (n=72)	Patients with iron supplementation (n=92)	p
Red blood cell transfused patients postoperatively, n (%)	51 (70.8)	45 (48.9)	**0.038**
Mediastinal drainage 24 h postoperatively, mean ± SD, mL	440 ± 197	427 ± 234	0.278
Re-operation for bleeding	4 (5.5)	3 (3.3)	0.162
Renal injury	5 (6.9)	4 (4.3)	0.234
Length of intensive care unit stay, days, median (min-max)	1 (1-8)	1 (1-6)	0.512
Length of hospital stay, days, median (min-max)	8 (7-16)	6 (4-30)	**0.001**
In-hospital mortality, n (%)	18 (25)	12 (13)	**0.049**

derwent isolated CABG [p=0.029, OR 2.757 (CI95%:1.111-6.846)]. In addition, 1 unit decrease in preoperative Hb level was found to be related with a 1.8-fold higher risk of mortality [p=0.002, OR 1.808 (CI95%:1.237-2.641)].

DISCUSSION

The effect of IDA on patients undergoing elective isolated CABG was investigated in this study. As known, IDA was associated with decreased preoperative Hb levels and an increased incidence of anemia. Preoperative IDA worsen the survival of patients compared to healthy population (8). This can be explained by the limitation in establishing the optimum cardiac output due to impaired compensatory mechanisms of patients with IDA (12). Also morbidity rates were negatively affected by IDA during postoperative period (8). An increment of 15% for non-cardiac adverse events were found due to each decrease of 1 g dL^{-1} below 14 g dL^{-1} of Hb concentration (13).

Kim and associates reported that 30% of the patients scheduled for CABG surgery, had preoperative anemia and 16.9% of them had IDA (14). Preoperative low Hb levels have a negative impact on morbidity and mortality (15). This commonly seen disorder and salvage with intraoperative RBC transfusion were reported as independent but additive risk factors for adverse outcomes (13). Large database reviews reported that even a single unit of blood transfusion is associated with increased morbidity and mortality (16). All these emphasize the need to treat IDA preoperatively.

Better biochemical outcomes and hematopoietic response to severe anemia were achieved by intravenous iron administration, also providing long-term normalization of Hb levels in 4 weeks (14,17). Guidelines recommend treating anemia preoperatively to avoid blood transfusion, for patients who are scheduled for cardiac surgery (18). However, there is lack of evidence for these recommendations in cardiac surgery area. The aim of this study was to analyze the effect of preoper-

ative intravenous supplementation of iron on postoperative adverse events in patients undergoing elective CABG.

The randomized controlled trials could not demonstrate an impact on mortality depending on IV iron supplementation (19-22). However, observational studies reported benefits of intravenous iron supplementation on mortality, with respect to patients who didn't received IV iron prior to surgery (RR 0.39, 95% CI 0.23–0.65; p<0.001) (23). Also, in this study, we showed that preoperative iron supplementation was independently associated with lower risk for in-hospital mortality in patients with IDA, who underwent isolated CABG. Larger, multicentre, placebo-controlled, double-blinded, trials are needed to explain the impact of IV iron in CABG patients.

Quarterman C et al. reported that preoperative IV iron supplementation did not improve outcomes, such as transfusion rates or the need of re-operation for bleeding control, compared to patients who did not receive iron supplementation (24). Although, the re-operation need for bleeding control rate was similar between the groups with or without iron supplementation. Patients who did not receive IV iron supplementation required more blood transfusions postoperatively in this study (25). Several blood conservation strategies are needed for blood transfusion in cardiac surgery. This study demonstrated the increased requirement of postoperative blood transfusion in patients with IDA, who did not received iron preoperatively. Thus it can be concluded that not administrating IV iron preoperatively, would adversely affect the clinical outcomes in patients with IDA who are scheduled for isolated CABG.

There were limitations in this study. First of all, this is a retrospective and single center study. The sample size had to be larger to interpret the efficacy of preoperative IDA management with intravenous iron supplementation. Although there was a significant difference in hemoglobin levels between patients who received and did not receive IV iron supplementation preoperatively, in patients without IV iron infusion, preoperative hemoglobin levels were already lower than the other group, so requirement of more RBC transfusion was expected and might be a bias.

CONCLUSION

Management of preoperative IDA with intravenous iron supplementation is a feasible alternative to provide a safer perioperative period for patients undergoing CABG surgery. This study found that preoperative intravenous infusion of iron is related with a shorter length of hospital stay and reduced perioperative RBC transfusion requirements. In-hospital mortality was significantly lower in pretreated patients with iron, however, there was no significant difference in terms of postoperative adverse events.

Currently, there are several studies with contrary results and outcomes, concerning the preoperative administration of intravenous iron in patients with IDA, underwent elective CABG. Therefore, more randomized, controlled trials are needed to obtain sufficient evidence to recommend treatment.

AUTHOR CONTRIBUTIONS

Conception or design of the work: MCS, OB
Data collection: MCS, OB
Data analysis and interpretation: MCS
Drafting the article: MCS, OB
Critical revision of the article: OB
The author (MCS, OB) reviewed the results and approved the final version of the manuscript.

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