DOI: 10.4274/TJAR.2023.22856

Original Article
Cardiovascular and Thoracic Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):324-330

Preoperative Anemia and Female Gender are Risk Factors for Transfusion in Patients Undergoing Coronary Artery Bypass Grafting with a Restrictive Transfusion Strategy

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Cite this article as: Koçyiğit ÖI, Koçyiğit M, Güllü AÜ, Şenay Ş, Toraman F, Alhan C. Preoperative Anemia and Female Gender are Risk Factors for Transfusion in Patients Undergoing Coronary Artery Bypass Grafting with a Restrictive Transfusion Strategy. *Turk J Anaesthesiol Reanim.* 2023;51(4):324-330.

Abstract

Objective: Red blood cell (RBC) transfusion in cardiac surgery is associated with increased morbidity and mortality. Even when using patient blood management methods, blood transfusions may still be needed in cardiac surgery. This study examined the risk factors for blood transfusion in isolated coronary artery bypass graft (CABG) surgery with a restrictive transfusion strategy, along with individualized patient blood management.

Methods: We enrolled 198 patients (age, 61.8 ± 9.9 years; 28 females and 170 males) who underwent isolated CABG surgery in a single private hospital using a restrictive transfusion strategy between April 2015 and October 2020. Pre-, intra-, and postoperative parameters were compared between patients with and without RBC transfusions. The risk factors for transfusion and transfusion probability were analyzed.

Results: Patients who received RBC transfusions had higher European System for Cardiac Operative Risk Evaluation values (13.60 ± 18.27%). Preoperative hematocrit (Hct) [odds ratio (OR)=0.752; 95% confidence interval (CI) 0.639-0.884; *P*=0.001] and female gender (OR=7.874; 95% CI 1.678-36.950; *P*=0.009) were significant independent risk factors for RBC transfusion in logistic regression analysis. When the preoperative Hct was 30%, the RBC transfusion probability was 61.08% in females and 16.6% in males. Patients who received RBC transfusions had longer intensive care unit (31.40 ± 25.42 hours) and hospital (11.18 ± 6.75 days) stays.

Conclusion: Risk factors for RBC transfusion in isolated CABG surgery with a restrictive blood transfusion strategy were preoperative anemia and female gender.

Keywords: Anemia, blood transfusion, coronary artery bypass, patient blood management, restrictive blood transfusion

Main Points

- Red blood cell transfusion during cardiac surgery is associated with increased morbidity and mortality.
- Cell saving is one of the main ways to conserve blood during cardiac surgery.
- Preoperative anemia and female gender were the only significant independent risk factors for blood transfusion during isolated coronary artery bypass graft surgery with a standardized operating technique and restrictive transfusion protocol.

Introduction

Red blood cell (RBC) transfusion during cardiac surgery is associated with increased morbidity and mortality.[1] Population aging is leading to an increase in the consumption of blood products and a decrease in donations, which poses a challenge for blood services globally.[2,3] Various studies have compared restrictive and liberal blood

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Received: March 31, 2022 Accepted: February 23, 2023

transfusions in cardiac surgery,[4,5] and guidelines have been created to limit the use of RBC transfusion.[6,7] However, despite such efforts, blood transfusion is not completely avoidable.

Patient blood management, which is the major method for reducing RBC transfusion, proceeds via three stages: detecting/treating preoperative anemia; reducing perioperative blood loss; and managing anemia.[8] Cell saving is one of the main ways to conserve blood during cardiac surgery.[9] Although cell salvage systems can decrease the odds of blood transfusion by recovering blood, blood transfusion may still be required.

This study identified independent risk factors for RBC transfusion in patients undergoing isolated coronary artery bypass graft (CABG) surgery using a restrictive transfusion strategy, along with individualized patient blood management.

Methods

After receiving Institutional Review Board of Acıbadem University Ethical Approval (ATADEK; 2022-07/30), patient data were retrieved from the electronic medical records of our institution's database. Informed consent was obtained from all patients and the study was conducted in accordance with the principles of the Declaration of Helsinki.

This study enrolled 198 patients (age, 61.8 ± 9.9 years; 28 females and 170 males) who underwent isolated CABG surgery using a restrictive transfusion strategy between April 2015 and October 2020. Patients who had off-pump or concomitant surgery were excluded.

All operations were performed by the same surgical team and anaesthesiologist. Where possible, enoxaparin sodium, rivaroxaban, apixaban, and antiplatelet drugs (clopidogrel and ticagrelor) were discontinued for 24 hours to 7 days preoperatively.

Patients were monitored perioperatively (five-lead electrocardiogram, pulse oximetry, invasive blood pressure, central venous pressure, bispectral index, and cerebral oximetry). Transesophageal echocardiography was used routinely for hemodynamic monitoring. All patients underwent balanced anaesthesia using clinical protocols. The initial dose of heparin was 300 U kg^{-1}. After achieving an activated clotting time of >400 s, aortic and caval cannulation were performed and cardiopulmonary bypass (CPB) was initiated. Ringer's lactate solution was used for CPB priming. The pump flow rate was set at 2.2-2.4 L $min\ m^{-2}$ (30-32°C). Cold blood cardioplegia was used for myocardial protection. Heparin activity was reversed with a 1:1 dose of protamine sulfate.

Postoperatively, all patients were transferred to the intensive care unit (ICU) and extubated once the weaning criteria were met.

The patients' demographic characteristics, European System for Cardiac Operative Risk Evaluation (EuroSCORE), ejection fraction, hematocrit (Hct) and creatinine levels, use of medication, and comorbidities were analyzed. Cross-clamp and CPB of distal anastomoses were also analyzed (times and numbers). The durations of endotracheal intubation and ICU and hospital stays, and the morbidity and hospital mortality rates, were evaluated. Patients with and without RBC transfusion were compared.

Restrictive Transfusion Strategy

All patients were infused with tranexamic acid (25 mg kg^{-1}, IV) after inducing anaesthesia within 10 minutes. Meticulous hemostasis and careful tissue handling were of paramount importance in all steps of the operation. The bypass circuit volume used to reduce hemodilution was 1.150 mL of crystalloid in all operations. We do not use retrograde autologous priming, venous autologous priming, or acute normovolemic hemodilution. An autotransfusion device was used in all cases (Sorin XTRA; LivaNova, Arvada, CO, USA). Throughout the cardiac procedure, blood was collected from the pericardial and pleural spaces into the collection reservoir of the cell salvage device. The bloody sponges were squeezed and blood was suctioned into the cell saver system. All remaining pump contents were added to the cell saver reservoir and washed before being returned to the patient. After closing the sternum, chest drainage tubes were connected to the autotransfusion circuit. Autotransfusion continued in the ICU for the first 6 hours postoperatively; a new device was used after 6 hours. If the bleeding amount was >200 mL h (over >2 hours) in the absence of a coagulation disorder, re-exploration for bleeding was carried out (Figure 1).

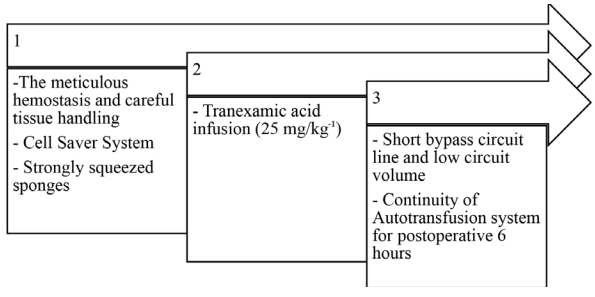


Figure 1. Blood conservation strategy.

If the Hct was <17% during the hypothermic period of CPB, <20% after CPB, or <21% during the postoperative period, RBC transfusion was considered. However, blood transfusion was not based on a numerical value alone; rather, a restrictive RBC transfusion policy was implemented according to the Hct level and hemodynamic and clinical parameters.

Hct was measured before, during, and after CPB, on arrival in the ICU, and on days 1, 2, 4, and 7 (while the patient was still hospitalized) at a minimum. If the Hct fell below the threshold at any time, red cells were administered (1 unit at a time) and the Hct was reassessed.

Statistical Analysis

The statistical analyses were performed using SPSS software (version 23, IBM Corp., Armonk, NY, USA). The normality distribution of variables was checked with the Shapiro-Wilk test. Normally distributed data were presented using mean ± standard deviation. Categorical variables were compared with the chi-square test or Fisher's exact test and expressed as numbers and frequency (%). Continuous variables were compared with Student's t-test or the Mann-Whitney U test. Variables significant at $P < 0.05$ were included in the binary logistic regression model. The Hosmer and Lemeshow goodness-of-fit test was also performed. Binary logistic backward regression analysis was used to investigate the impact of several pre- and perioperative factors on the likelihood of receiving at least RBC transfusion. A P value < 0.05 indicated statistical significance in all tests. Regression analysis as odds ratio (OR) with 95% confidence intervals (CIs) are reported. The probability of blood transfusion was calculated using a probability formula.

The power analysis was performed using G*Power version 3.1.9.7 (Heinrich Heine Universität Düsseldorf, Germany) software. The sample size was calculated based on a study by Kim et al.[10] who compared the patients with blood transfusion or without blood transfusion and preoperative hemoglobin (Hb) levels. It was determined that the effect size was 85% at the power 86% and 5% alfa error significance level in our study.

Results

The baseline demographic and clinical characteristics of the patients were compared (Table 1). Of the 198 patients who underwent CABG using a restrictive transfusion strategy, only 11 (5.6%) had RBC transfusions. The patients who received transfusions were significantly older and had higher logistic EuroSCOREs than those who did not receive RBCs (P=0.007 and P=0.026, respectively); the former patients were also more likely to be females undergoing reoperations (Table 1). The preoperative Hct was significantly lower ($P < 0.001$), and the total fluid balance was higher (P=0.001), in the transfusion group (Table 1).

Table 1. Patients' Demographics and Clinical Data

	RBC transfusion (n = 11)	No-RBC transfusion (n = 187)	*P* value
Age (years)	69.70 ± 6.06	61.38 ± 9.96	0.007
BMI (kg m^{-2})	27.79 ± 4.08	28.76 ± 4.25	0.483
Sex (female:male)	8:3	20:167	<0.001
Logistic EuroSCORE	13.60 ± 18.27	5.71 ± 10.84	0.026
NYHA class 3 and 4	18.2% (n = 2)	8.0% (n = 15)	0.242
Left ventricle EF (%)	52.36 ± 9.83	55.76 ± 10.03	0.276
Previous cardiac operations	18.2% (n = 2)	2.1% (n = 4)	0.003
Hypertension	63.6% (n = 7)	64.7% (n = 121)	0.960
Diabetes mellitus	54.5% (n = 6)	42.7% (n = 80)	0.758
Hypercholesterolemia	45.5% (n = 5)	56.1% (n = 105)	0.575
COPD	0.0% (n = 0)	6.4% (n = 12)	0.386
Cerebrovascular attack	18.2% (n = 2)	5.3% (n = 10)	0.083
Preoperative AF	0.0% (n = 0)	2.1% (n = 4)	0.624
Smoking			
Smokers	20.0% (n = 2)	36.1% (n = 66)	0.140
Former smokers	20.0% (n = 2)	33.9% (n = 62)	
Never smoked	60.0% (n = 6)	30.1% (n = 55)	

Table 1. Continued			
	RBC transfusion (n = 11)	**No-RBC transfusion (n = 187)**	***P* value**
Preoperative medications			
Beta blockers	36.4% (n = 4)	50.8% (n = 95)	0.352
ACE inhibitors	45.5% (n = 5)	33.2% (n = 62)	0.402
Aspirin	45.5% (n = 5)	32.1% (n = 60)	0.359
Clopidogrel	18.2% (n = 2)	7.5% (n = 14)	0.206
Non-elective surgery	18.2% (n = 2)	26.2% (n = 49)	0.554
Pre-operative hematocrit level (%)	32.82 ± 3.63	41.03 ± 4.11	<0.001
Hct level - Female (%)	32.67 ± 1.52	36.87 ± 4.89	0.169
Hct level - Male (%)	33.3 ± 4.16	41.76 ± 3.41	<0.001
Pre-operative creatinine level (mg dL^{-1})	1.10 ± 0.29	0.96 ± 0.28	0.108
CC time (min)	57.44 ± 20.43	55.64 ± 16.97	0.759
CPB time (min)	91.60 ± 23.18	87.40 ± 23.34	0.580
Number of distal anastomosis (mean)	3 (min 2 - max 4)	4 (min 1 - max 7)	0.263
Total fluid balance after CPB (mL)	1560 ± 603.6	998.37 ± 529.94	0.001

BMI, body mass index; NYHA, New York Heart Association; EF, ejection fraction; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; ACE, angiotensin-converting enzyme; CC, cross clamp; CPB, cardiopulmonary bypass.

The intubation time and ICU and hospital stays were significantly longer in the blood transfusion than non-transfusion group, and there were more ICU readmissions in the former group (Table 2). There were no cases of new-onset dialysis or stroke, no hospital readmissions within 4 weeks after discharge, and no deaths during the hospital stay or first postoperative month (Table 2).

RBCs were transfused in three patients during, and three patients after, CPB because of low Hct (<17% and <20%, respectively). Three patients had RBC transfusions on the second and fourth postoperative days because of low Hct (<21%). One patient had an RBC transfusion because of hemodynamic instability during revision for bleeding on the day of surgery. One patient had an RBC transfusion because of gastrointestinal bleeding on postoperative day 4.

Table 2. Patients' Postoperative Data			
	RBC transfusion (n = 11)	**No-RBC transfusion (n = 187)**	***P* value**
Total recycled RBC volume (mL)	519 ± 238	581 ± 302	0.545
Intubation time (hr)	11.57 ± 10.61	5.93 ± 2.04	<0.001
Chest tube output (mL)	239.09 ± 100.84	282.73 ± 160.31	0.374
ICU duration (hr)	31.40 ± 25.42	19.24 ± 4.19	<0.001
Post-operative hematocrit level	27.01 ± 3.53	33.93 ± 4.92	<0.001
Hct level - Female	28.73 ± 2.55	29.02 ± 4.66	0.888
Hct level - Male	27.40 ± 2.10	34.76 ± 4.70	0.008
Postoperative AF	18.2% (n = 2)	6.4% (n = 12)	0.139
Platelet use	9.1% (n = 1)	0.5% (n = 1)	0.108
Platelet use (U/patient)	0.27 ± 0.9	0.11±0.15	0.36
Fresh frozen plasma use	18.2% (n = 2)	2.7 % (n = 5)	0.051
Fresh frozen plasma use (U/patient)	0.55 ± 1.3	0.05 ± 0.32	0.237
Pulmonary complication	9.1% (n = 1)	0.0% (n = 0)	0.057
Inotropic support >4 hours	9.1% (n =1)	1.06% (n = 2)	0.172
Revision for bleeding	9.1% (n = 1)	0.5% (n = 1)	0.108

Table 2. Continued

	RBC transfusion (n = 11)	No-RBC transfusion (n = 187)	*P* value
Discharge hematocrit	30.87 ± 3.89	29.30 ± 4.07	0.218
Hct level - Female	31.55 ± 4.40	26.94 ± 2.76	0.008
Hct level - Male	30.43 ± 2.66	29.78 ± 4.09	0.785
Discharge creatinine (mg dL^{-1})	1.05 ± 0.27	0.91 ± 0.27	0.163
ICU readmission	18.2% (n = 2)	3.2% (n = 6)	0.029
Reintubation	9.1% (n = 1)	0.0% (n = 0)	0.056
Hospital stay (days)	11.18 ± 6.75	7.07 ± 4.28	0.003
Mortality	0.0% (n = 0)	0.0% (n = 0)	Ns

RBC, red blood cell; AF, atrial fibrillation; ICU, intensive care unit.

There was a significant negative correlation between preoperative Hct and age (r=-0.363, $P < 0.01$). Age, sex, EuroSCORE, previous cardiac operations, total fluid balance after CPB, and preoperative Hct were subjected to logistic regression analysis. The Hosmer and Lemeshow test indicated a good fit (P=0.991). Preoperative Hct (OR 0.752; 95% CI 0.639-0.884; P=0.001) and female gender (OR 7.874; 95% CI 1.678-36.950; P=0.009; "constant variable", 6.967; "coefficient variable", -0.286) were significant independent risk factors for blood transfusion (Table 3).

We calculated the blood transfusion probability according to the Hct using the probability formula in Table 3.

$$p = \frac{1}{1 + e^{-a-bx}}$$

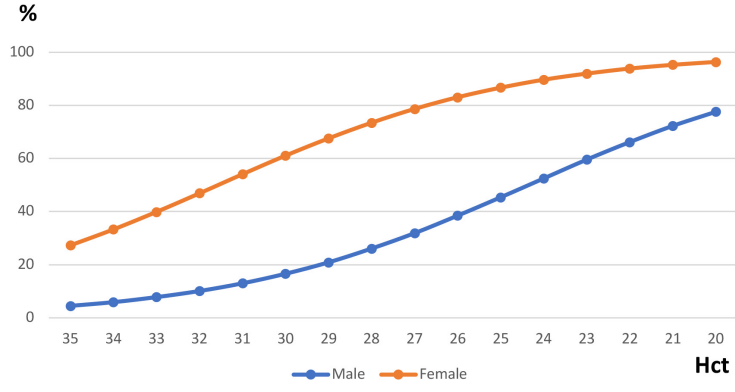
$$P\ \text{female} = \frac{1}{1 + e^{-6.967-(-0.286xHct+2.064)}}$$

$$P\ \text{male} = \frac{1}{1 + e^{-6.967-(-0.286xHct)}}$$

According to this formula, if the preoperative Hct is 25%, 30%, and 35%, the probability of blood transfusion is 86.7%, 61.08%, and 27.3% in females, and 45.4%, 16.6%, and 4.5% in males, undergoing isolated CABG surgery, respectively (Figure 2).

Table 3. Predictive Factors for Blood Transfusion

	Odds ratio	95% Confidence interval	*P* value
Female gender	7.874	1.678-36.950	0.009
Preoperative hematocrit	0.752	0.639-0.884	0.001



% Hct	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20
% P_{MALE}	4.5	5.9	7.8	10.1	13	16.6	20.9	26.1	31.9	38.5	45.4	52.5	59.6	66.2	72.3	77.6
% P_{FEMALE}	27.3	33.3	39.9	46.9	54.1	61.1	67.6	73.5	78.7	83.1	86.7	89.7	92	93.9	95.3	96.4

Figure 2. Preoperative Hct level and blood transfusion probability.

Hct, hematocrit; P, probability.

Discussion

This study identified risk factors for blood transfusion during isolated CABG surgery with a standardized operating technique and restrictive transfusion protocol. Age, sex, EuroSCORE, previous cardiac operations, total fluid balance after CPB, and preoperative Hct were risk factors for blood transfusion in the univariate analyses; however, preoperative anemia and female gender were the only significant independent risk factors.

Recent studies found that perioperative anemia was an independent risk factor for unfavorable outcomes following CABG, such as acute renal failure, neurological injury, and mortality.[11-13] Although Hb alone does not accurately reflect the available oxygen or RBC volume, it is still the most widely used transfusion trigger, and perioperative anemia is frequently managed with blood transfusion.[14,15] However, independent of anemia, blood transfusions have also been reported to be associated with an increase in the rate of major complications, including kidney and lung injury, infections, and mortality after cardiac surgery.[16]

Therefore, many studies have examined how to prevent damage due to anemia and blood transfusion. Importantly, protocols have been prepared for guiding allogeneic RBC transfusion in patients with anemia.[4,17]

Despite evidence from numerous randomized clinical trials, meta-analyses, and guidelines, blood transfusion strategies after cardiac surgery differ among centers; some groups use liberal blood transfusions, while others prefer a restrictive strategy.[4,17,18] In a study of the variation in use of blood transfusion in CABG surgery (involving 82,446 cases at 408 sites), the rates of blood transfusion ranged from 7.8% to 92.8% for RBCs, 0% to 97.5% for fresh-frozen plasma, and 0.4% to 90.4% for platelets.[19]

Factors influencing blood transfusion include preoperative anemia, older age, female gender, small body size, preoperative antiplatelet or anti-thrombotic medication, redo and complex procedures, and emergency operations.[20,21] However, risk factors for blood transfusion in the context of restrictive strategies have not been adequately investigated.

We have long used a restrictive blood transfusion policy in our clinic, and have shown the benefits of this strategy. In our previous study, the total blood transfusion rate was 29.6% in isolated CABG,[22] which decreased gradually to 5.6% when using blood conservation methods and a restricted transfusion strategy. In the univariate analyses in the present study, female gender, older age, higher EuroSCORE, previous cardiac surgery, fluid balance after CPB, and low preoperative Hct were associated with RBC transfusion. However, in logistic regression analysis, only preoperative anemia and female gender remained as independent risk factors for RBC transfusion.

The finding that preoperative anemia and female gender were risk factors for RBC transfusion in our study can be explained by the influence of other factors, such as older age and higher EuroSCORE, on preoperative Hct levels. In females, prior pregnancies, menstruation, nutrient insufficiency in the elderly, and chronic inflammation all lower Hct levels.[22,23] Females also have lower body mass index and circulating blood volume, which influence RBC transfusion.[24,25] The priming volume of the CPB circuit was the same in all of our patients, indicating that females are more prone to dilutional anemia and, ultimately, RBC transfusion.

One of the most important reasons why transfusion is needed in some cardiac surgeries is excessive peri- or postoperative bleeding. However, the amount of bleeding and rate of blood transfusion were not correlated in our study. This might be related to factors such as meticulous bleeding control, the use of autotransfusion during the operation and the first 6 hours postoperatively, and a strict perioperative transfusion policy. These factors might explain why other variables significant in the univariate analyses were not significant in the multivariate analysis.

Study Limitations

The main limitations of our study were the non-randomized, observational design and relatively small number of patients. Moreover, there were no preoperative interventions for patient blood management. However, as a strength of the study, all operations were performed by the same team using similar blood transfusion practices.

Conclusion

Although many risk factors for transfusion have been identified in patients undergoing cardiac surgery, we found that preoperative anemia and female gender were risk factors specifically for those undergoing coronary bypass surgery using a restrictive blood strategy. Other identified risk factors may be associated with preoperative anemia. Prospective randomized controlled studies with large numbers of patients are needed to validate our findings.

Ethics Committee Approval: This study was approved by Institutional Review Board of Acıbadem University (ATADEK; 2022-07/30).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Internally and externally peer-reviewed.

Author Contributions: Concept - M.K., C.A.; Design - Ö.I.K., C.A.; Supervision - F.T., C.A.; Materials - M.K., A.Ü.G., Ş.Ş.; Data Collection and/or Processing - Ö.I.K., M.K. C.A.; Analysis and/or Interpretation - M.K., C.A.; Literature Review - Ö.I.K., A.Ü.G., Ş.Ş.; Writing - Ö.I.K., M.K., A.Ü.G.; Critical Review - A.Ü.G., Ş.Ş., F.T., C.A.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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