Preoperative anemia and female gender as risk factors for transfusion in patients undergoing coronary artery bypass grafting with a restrictive transfusion strategy

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ABSTRACT

Background:

Red blood cell (RBC) transfusion increases morbidity and mortality after cardiac surgery. Despite the use of patient blood management methods, blood transfusions may still be needed in cardiac surgery. This study aims to determine the risk factors for blood transfusions in isolated coronary bypass graft surgery with the use of a restrictive transfusion strategy along with individualized patient blood management.

Methods:

A total of 198 consecutive patients (28 females, 170 males; age range 38–87) who underwent isolated CABG surgery in single private hospital using a restrictive transfusion strategy between April 2015 and October 2020 were included in the study. Patients were divided into two groups: with RBC transfusion and without RBC transfusion. Preoperative, intraoperative, and postoperative values were compared between groups. The risk factors for transfusion and transfusion probability were analyzed.

Results:

Preoperative hematocrit level and female gender (OR: 0.752; 95% CI 0.639–0.884; p = 0.001; OR: 7.874; 95% CI 1.678–36.950; p = 0.009, respectively) were the statistically significant independent risk factors for red blood cell transfusion. In female patients, the RBC transfusion probability was 61.08% when the preoperative

hematocrit was 30%. The intensive care unit and hospital stay were longer in the blood transfusion group.

Conclusions:

The risk factors for RBC transfusion were preoperative anemia and female gender in isolated CABG surgery with restrictive blood transfusion strategies.

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

Introduction

Red blood cell (RBC) transfusion increases morbidity and mortality after cardiac surgery[1]. On the other hand, the aging of the population is leading to an increase in consumption of blood products and a decrease in donation, which poses a global challenge for blood services globally[2,3]. For these reasons, restrictive versus liberal blood transfusions in cardiac surgery have been compared in various studies[4,5]. Guidelines have been created to limit the use of RBC[6,7]. However, despite all efforts, blood transfusion may not be completely avoidable.

Patient blood management is the major method for reducing RBC transfusion in three stages: detecting/treating preoperative anemia, reducing perioperative blood loss, and managing anemia[8]. One of the main tools for blood conservation during cardiac operations is cell saving[9]. Although the cell salvage system can decrease the odds of blood transfusion by recovering blood loss, blood transfusion may still be required.

This study aims to determine the independent risk factors for RBC transfusion patients who undergo isolated coronary bypass graft (CABG) surgery with the use of a restrictive transfusion strategy along with individualized patient blood management.

Materials and Methods

After receiving institutional review board approval, patient data were retrieved from the electronic medical records in our institution's database. Written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 198 consecutive patients (28 females, 170 males; age range 38–87) who underwent first-time isolated CABG surgery using a restrictive transfusion strategy between April 2015 and October 2020 were included in the study. Patients who had previous cardiac surgery, off-pump surgery, and concomitant surgeries were excluded from the study.

All operations were performed by the same surgeon and team and the same anesthesiologist. If possible, enoxaparin sodium, rivaroxaban, apixaban, and antiplatelet drugs (clopidogrel and ticagrelor) were discontinued for at least 24 hours, 3 days, and for 5 to 7 days, respectively.

Patients were monitored perioperatively with a 5-lead electrocardiogram, pulse oximeter, invasive blood pressure, central venous pressure, bispectral index, and cerebral oximeter. Transesophageal echocardiography was used routinely. All patients received balanced anesthesia using clinical protocols. An initial dose of heparin (300 U/kg) was given. After achieving an activated clotting time of >400 s, aortic, and caval cannulation was 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/m2 at 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 and extubated once weaning criteria were met.

The patients' demographic data, logistic EuroSCORE, ejection fraction (EF), hematocrit (Hct), creatinine levels, use of medication, and the presence of comorbidities were analyzed. The cross-clamp (CC) and CPB time and the number of distal anastomoses were also analyzed. The durations of endotracheal intubation,

intensive care unit (ICU) stay, morbidity, mortality rates, and hospital stay were evaluated.

Patients were divided into two groups: with RBC transfusion and without RBC transfusion.

Restrictive transfusion strategy:

Tranexamic acid (25 mg/kg, iv) was infused with the induction of anesthesia to all patients in 10 minutes. The meticulous hemostasis and careful tissue handling were of paramount importance in all steps of the operation. An autotransfusion device was used in all patients (Sorin Xtra LivaNova USA Inc., Arvada, CO). Blood was collected throughout the whole cardiac procedure from the pericardial and pleural spaces into the collection reservoir of the cell salvage device. The bloody sponges were strongly squeezed and blood suctioned to the cell saver system. All remaining pump contents were added to the cell saver reservoir and washed before being returned to the patient. After the closure of the sternum, chest drainage tubes were connected to the autotransfusion circuit. The autotransfusion system was continued postoperatively for the first 6 hours in the ICU. In case of continuing drainage, a new device was used after 6 hours. If the patient bled more than 200 mL/h in more than two consecutive hours in the absence of a coagulation disorder, re-exploration for bleeding was carried out.

Blood transfusion was not driven by a numerical trigger value alone, but by a restrictive RBC transfusion policy based on Hct levels and hemodynamic and clinical parameters. If the hematocrit value was below 17% during the hypothermic period of CPB, below 20% after CPB, and below 21% during the postoperative period, RBCs were transfused.

The hematocrit level was measured at least at the following intervals: preoperatively, before cardiopulmonary bypass, during cardiopulmonary bypass, after cardiopulmonary bypass, on arrival in the ICU, and on days 1, 2, 4, and 7 while the patient was still hospitalized. If the hematocrit concentration fell below the appropriate threshold at any time, one unit of red cells was administered at a time and was followed with a reassessment of the hematocrit level.

Statistical analysis

Discrete variables were compared with the chi-square test and are presented as numbers and percentages. Continuous variables were compared with the Student t test and analysis of variance and are presented as means standard deviations. If significant at $p < 0.05$, they were included into the binary logistic regression model. Hosmer and Lemeshow goodness-of-fit test was used for the logistic regression model. Binary logistic backward regression analysis was performed to investigate the impact of several preoperative and perioperative factors on receiving one or more transfusions of RBCs. A p value <0.05 was used to indicate statistical significance for all tests. Exp (B) values with 95% confidence intervals are reported. Statistical analysis was performed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). The probability of the blood transfusion was calculated with the probability formula.

Results

Baseline demographic and clinical characteristics of the patients were compared (Table 1). A total of 198 patients underwent CABG with the use of a restrictive transfusion strategy, and only 11 (5.6%) patients had a RBC transfusion. The patients who received RBC transfusions were significantly older and had higher logistic

EuroSCORE values compared to patients who did not receive RBCs. There were also more reoperations and female patients among these patients. Preoperative Hct levels were significantly lower and total average fluid balance was higher in the transfusion group compared to the nontransfusion group.

Intubation time, ICU, and hospital stay were statistically longer in the blood transfusion group than in the nontransfusion group. ICU readmission was higher in the blood transfusion group than in the nontransfusion group. (Table 2). There was no new onset dialysis or stroke in any of the patients. There were no hospital readmissions within four weeks after discharge and no mortality during hospital stay or in the first month after the operation.

RBC was transfused in three patients during the CPB period and in three patients after CPB because of low Hct (<17 g/dL during CPB and <20 g/dL after CPB). Three patients had an RBC transfusion on postoperative second and fourth days because of low Hct (<21 g/dL). One patient had an RBC transfusion because of hemodynamic instability during revision for bleeding at the operation date. One patient had an RBC transfusion because of gastrointestinal bleeding on postoperative day 4.

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

We calculated the blood transfusion probability that corresponds to the Hct level by the probability formula. (Table 3)

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

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

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

By this formula, if the preoperative Hct is 25, 30, and 35 g/dL, the probabilities of the blood transfusion are 86.7%, 61.08%, and 27.3% in female patients and 45.4%, 16.6%, and 4.5% in male patients, respectively, in isolated CABG surgery (Figure 1).

Discussion

This study focused on identifying risk factors for blood transfusion during isolated CABG surgery under standardized operative techniques and restrictive transfusion protocols. Age, sex, EuroSCORE levels, previous cardiac operations, total fluid balance after CPB, and preoperative Hct level were identified as risk factors for blood transfusion in univariate analysis; however, preoperative anemia and female gender were the only significant independent factors.

Data from recent studies have disclosed perioperative anemia as an independent risk factor for unfavorable outcomes, such as acute renal failure, neurologic injury, and mortality following CABG[10-12]. Although hemoglobin value alone does not accurately

reflect the real state of available oxygen carriers or the actual RBC volume, it is still the most widely used transfusion trigger, and perioperative anemia is frequently managed with blood transfusion[13,14]. However, independent of anemia, blood transfusions have also been shown to increase major complications, including kidney and lung injury, infections, and mortality after cardiac surgery[15].

In light of these findings, many studies have been conducted on preventing the possible damage due to both anemia and blood transfusion. Importantly, protocols have been prepared for guiding allogeneic red blood cell transfusion in cases of anemia[4,16].

Despite the evidence from numerous randomized clinical trials, meta-analyses, and guidelines, blood transfusion strategies after cardiac surgery differ in many centers; some groups use liberal blood transfusions, and others prefer restrictive strategy[4,16,17]. In a study on variations in the use of blood transfusion in coronary artery bypass graft surgery in 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[18].

The literature shows that the factors influencing blood transfusion include preoperative anemia, older age, female gender, small body size, preoperative anti-platelet or anti-thrombotic medication, redo and complex procedures, and emergency operations[19,20]. However the risk factors for blood transfusion, despite restrictive strategies, have not been adequately investigated.

We have been following the restrictive blood transfusion policy in our clinic for a long time and have shown the benefits of this strategy. In our previous study, the total blood transfusion rate was 29.6% in isolated CABG [21]; which gradually decreased to 5.6%, due to the blood conservation methods and the restricted transfusion strategy.

In univariate analysis, female gender, older age, higher logistic Euroscore, previous cardiac surgeries, fluid balance after CPB, and preoperative low Hct were the factors associated with RBC transfusion in the present study. Nevertheless, when we calculated the effects of independent variables on the result variable via logistic regression analysis, preoperative anemia and female gender remained to be the only independent risk factors for RBC transfusion.

The presence of preoperative anemia and female gender as risk factors for RBC transfusion in our study can be explained by attributing other factors, such as older age or higher Euroscore, to preoperative low Hct levels. Females have lower body mass index, lower circulating blood volume, and lower Hct levels, which influence RBC transfusion[22]. As the priming volume of the CPB circuits is identical in all patients, female patients are more prone to dilutional anemia, and eventually, to RBC transfusion.

One of the most important causes of transfusion need in cardiac surgery is an excessive amount of operational or postoperative bleeding. However, the amount of bleeding and the rate of blood transfusion were not found to be correlated in our study. This result might be related to factors such as meticulous bleeding control, application of autotransfusion not only during the operation but also in the first 6 hours postoperatively, and perioperative strict transfusion policy. These might explain the failure to determine the factors detected in univariate analysis but not in multivariate analysis.

Another issue that should be taken into consideration about blood transfusion is the increase in the aging population. It has been shown that 70- to 80-year-olds have an eightfold higher RBC consumption than 20- to 40-year-olds[2]. It should be kept in mind that in the future, older, more complicated and anemic patients will be

undergoing cardiac surgery. Additionally, the frequency of anemia in the elderly population will increase due to various age-related reasons, so the already limited donor shortage will increase even more. The Finnish transfusion registry data simulated a long-term aging population and suggest some alarming signals and future challenges that are likely to be faced by transfusion services as populations continue to age[2].

The main limitations of our study were that it was non-randomized, observational, and comprised a relatively small group of patients. Nevertheless, all operations were done by the same team using similar practices for blood transfusion, which was the strength of the study.

Conclusions:

Although many risk factors have been identified in patients undergoing cardiac surgery in the literature, we observed that preoperative anemia and female gender were risk factors for transfusion in patients undergoing restrictive blood strategy. Other risk factors identified in the literature may be associated with preoperative anemia. Undoubtedly, prospective randomized controlled studies with a large number of patients are needed to further validate our findings.

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