Original Article / Özgün Makale

Did blood transfusion increase mortality in patients with diabetes undergoing isolated coronary artery bypass graft surgery?
A propensity score-matched analysis of 816 patients

ÖZ

Amaç: Bu çalışmada izole on-pump koroner arter baypas greftleme yapılan diyabet hastalarında kan transfüzyonu mortalitesi artırdı mı? 816 hastanın eğilim skoru eşleştirme analizi

Muharrem Koçyiğit1, Halim Ulugöl1, Seher İrem Kıran1, Cem Alhan2, Fevzi Toraman1

1Department of Anesthesiology and Reanimation, Acıbadem Mehmet Ali Aydınlar University, Istanbul, Turkey
2Department of Cardiovascular Surgery, Acıbadem Mehmet Ali Aydınlar University, Istanbul, Turkey

ABSTRACT

Background: The aim of this study was to compare clinical outcomes of blood transfusion in patients with diabetes mellitus undergoing isolated on-pump coronary artery bypass grafting.

Methods: The medical records of a total of 1,912 patients (1,300 males, 612 females; mean age 60.7±10.0) with diabetes who underwent isolated on-pump coronary artery bypass grafting between January 1999 and June 2019 were retrospectively analyzed. The patients were divided into two groups as patients with and without blood transfusions. The mortality rates were compared between the two groups.

Results: The mortality rate was 14 times higher in the patients receiving blood transfusion (odds ratio: 14.80; 95% confidence interval 5.05 to 43.34; p<0.001). However, in the multivariate logistic regression analysis, there were no statistically significant difference in mortality between the patient groups, when diabetes mellitus was a covariate factor (Odds ratio: 8.34; 95% confidence interval 3.94 to 17.66 vs. odds ratio 8.36; 95% confidence interval 3.95 to 17.70).

Conclusion: The propensity score-matched analysis of patients with diabetes showed that clinical outcomes were more severely affected by blood transfusion.

Keywords: Blood transfusion, coronary artery bypass grafting, diabetes mellitus, mortality.

Sonuç: Eğitim skoru eşleştirme analizi, diyabet hastalarında kan transfüzyonunun klinik sonuçları daha kötü bir şekilde etkilediğini gösterdi.

Anahtar sözcükler: Kan transfüzyonu, koroner arter baypas greftleme, diabetes mellitus, mortalite.
Diabetes mellitus increased the risk of cardiovascular disease with insulin resistance, inflammation and endothelial dysfunction. The risk of cardiovascular diseases is 1.6 to 2.6 times higher in patients with diabetes, particularly among younger age and in women. After cardiac surgery, the incidences of morbidity and mortality in these patients are higher than those without diabetes.

Blood transfusion are associated with postoperative wound infections, pneumonia, renal dysfunction, multiple organ failure, and increased hospital stay. Additionally, perioperative blood transfusions are known to be associated with an increased morbidity and mortality after cardiac surgery.

In the present study, we aimed to compare clinical outcomes of blood transfusion in patients with diabetes mellitus who underwent isolated on-pump coronary artery bypass grafting (CABG).

**PATIENTS AND METHODS**

Between January 1999 and June 2019, a total of 6,148 patients underwent isolated on-pump CABG in Department of Cardiovascular Surgery of Acibadem Mehmet Ali Aydinlar University. Of these, 1,912 patients (1,300 males, 612 females; mean age 60.7±10.0 year) with diabetes were included in this retrospective study. Patients who underwent off-pump CABG or concomitant surgery were excluded. Patients who had revision for bleeding were also excluded to eliminate the negative outcomes caused by bleeding with hemodynamic instability or blood transfusions. Study flow chart is shown in Figure 1. The medical records were retrieved from the electronic registry and hospital database. A written informed consent was obtained from each patient. The study protocol was approved by the Institutional Review Board of Acibadem Mehmet Ali Aydinlar University, ATADEK. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were divided into two groups as those with (n=515, 26.94%) and without (n=1,397, 73.06%) blood transfusions. Demographic data, EuroSCORE scores, ejection fraction (EF), hematocrit, creatinine levels, use of medication, and the presence of comorbidities were analyzed. The durations of cross-clamp (CC) and cardiopulmonary bypass (CPB) during surgery, durations of endotracheal intubation and intensive care unit (ICU) stay, and morbidity, mortality rates were evaluated.

All operations were performed by a single surgical team. All patients received a balanced anesthesia using clinical protocols. Standard CPB was established and antegrade cold blood cardioplegia was used for myocardial protection. Blood transfusion was not driven by a numerical trigger value alone, but by a restrictive red blood cell (RBC) transfusion policy based on hematocrit levels and hemodynamic parameters. If the hematocrit value was below 17% during the hypothermic period of CPB and below 20% after CPB, RBCs were transfused. The patients receiving at least one unit of RBC were included in the blood transfusion group. All patients were transferred to the ICU after surgery.

**Figure 1.** Study flowchart.
Table 1. Baseline demographic and clinical characteristics of patients with and without blood transfusion

|                                | Before propensity matching | After propensity matching |
|--------------------------------|-----------------------------|--------------------------|
|                                | No transfusion (n=1,397)    | Blood transfusion (n=515) | No transfusion (n=408) | Blood transfusion (n=408) |
|                                | n | %    | Mean±SD       | p     | n | %    | Mean±SD       | p     | n | %    | Mean±SD       | p     |
| Age (year)                     |   |      |                |       |   |      |                |       |   |      |                |       |
|                                | 61.8±8.9 |       | 64.3±8.3 | <0.001 | 64.6±8.8 |       | 64.1±8.3 | 0.430 |
| Body mass index (kg/m²)        | 29.7±9.8 |       | 29.7±24.1 | 0.980 | 30.5±15.0 |       | 30.0±27.0 | 0.770 |
| Sex                            |   |      |                |       |   |      |                |       |   |      |                |       |
| Female                         | 378 | 27 | 234          |       | 177 | 44 | 231          |       | 172 | 44 | 226          |       |
| Male                           | 1019 | 73 | 281          |       | 231 | 56 | 226          |       | 226 | 56 | 220          |       |
| EuroSCORE logistics (%)        |   |      | 3.6±5.5 |       |   |      | 5.4±6.6 |       |   |      | 4.7±6.4 |       |   |      | 4.4±5.3 | 0.390 |
| NYHA Class 3 and 4 (%)         |   |      | 192 | 13.7 | 111 | 19.6 | 0.004 | 67 | 18.4 | 70 | 17.2 | 0.710 |
| Previous cardiac surgery (%)   |   |      | 19 | 1.3 | 22 | 4.2 | <0.001 | 12 | 2.9 | 10 | 2.5 | 0.670 |
| EF <30 (%)                     |   |      | 35 | 2.5 | 25 | 4.9 | <0.001 | 17 | 4.2 | 15 | 3.7 | 0.850 |
| Hypertension (%)               |   |      | 1022 | 73.2 | 379 | 73.6 | 0.840 | 317 | 77.7 | 299 | 73.3 | 0.140 |
| Hypercholesterolemia (%)       |   |      | 871 | 62.3 | 343 | 64.9 | 0.330 | 254 | 62.3 | 274 | 67.2 | 0.160 |
| COPD (%)                       |   |      | 95 | 6.8 | 60 | 11.7 | 0.001 | 45 | 11.0 | 44 | 10.8 | 1.000 |
| Smoking (%)                    |   |      |   |      |    |      |    |      |    |      |    |      |    |
| Smokers                        | 305 | 21.8 | 77 | 15 | <0.001 | 86 | 21.1 | 60 | 14.7 | 0.050 |
| Former smokers                 | 583 | 41.7 | 189 | 36.7 |    | 140 | 34.3 | 154 | 37.7 |    |
| Never smoked                   | 509 | 36.4 | 259 | 48.3 |    | 182 | 44.6 | 194 | 47.5 |    |
| Medications                    |   |      |    |      |    |      |    |      |    |      |    |      |    |
| Beta blockers (%)              | 751 | 53.8 | 288 | 55.9 | 0.390 | 225 | 55.1 | 235 | 57.6 | 0.520 |
| Calcium canal blockers (%)     | 283 | 20.3 | 101 | 19.6 | 0.650 | 95 | 23.3 | 91 | 22.3 | 0.800 |
| ACE inhibitors (%)             | 470 | 33.6 | 173 | 33.6 | 0.980 | 140 | 34.3 | 139 | 34.1 | 1.000 |
| Aspirin (%)                    | 848 | 60.7 | 292 | 56.7 | 0.115 | 222 | 54.4 | 233 | 57.1 | 0.480 |
| Clopidogrel (%)                | 31 | 2.2 | 6 | 1.2 | 0.130 | 7 | 1.7 | 4 | 1.0 | 0.540 |
| Elective surgery (%)           | 1270 | 90.9 | 457 | 88.7 | 0.070 | 372 | 91.2 | 371 | 90.9 | 1.000 |
| Preoperative hematocrit level (%) | 40.3±4.5 |    | 38.0±4.7 | <0.001 | 38.3±4.8 |    | 38.3±4.4 | 0.940 |
| Preoperative creatinine level (mg/dL) | 0.9±0.4 |    | 1.0±0.5 | <0.001 | 0.9±0.4 |    | 1.0±0.5 | 0.300 |
| CC time (min)                  | 39.8±16.2 |    | 40.2±16.9 | 0.680 | 38.9±16.2 |    | 40.3±17.7 | 0.260 |
| CPB time (min)                 | 68.9±24.8 |    | 71.4±29.0 | 0.060 | 67.0±23.7 |    | 70.1±27.2 | 0.080 |
| Number of distal anastomoses   | 3.3±1.0 |    | 3.4±0.9 | 0.040 | 3.3±1.0 |    | 3.5±0.9 | 0.003 |

SD: Standard deviation; NYHA: New York Heart Association; EF: Ejection fraction; COPD: Chronic obstructive pulmonary disease; ACE: Angiotensin-converting enzyme; CC: Cross-clamp; CPB: Cardiopulmonary bypass.
Table 2. Postoperative data of patients with and without blood transfusion

|                                | Before propensity matching | After propensity matching |
|--------------------------------|----------------------------|---------------------------|
|                                | No transfusion (n=1,397)   | Blood transfusion (n=515) |
|                                | n % Mean±SD                | n % Mean±SD               |
| Intubation time (h)            | 7.0±3.8 11.7±43.0          | <0.001                    | 8.2±22.2 9.3±33.5          | 0.610 |
| Chest tube output (mL)         | 495.8±213.9 742.5±545.4    | <0.001                    | 462.4±201.7 659.8±372.3   | <0.001 |
| Blood transfusion unit         | 0.0±0.0 2.2±2.2            | <0.001                    | 0.0±0.0 1.9±1.6           | <0.001 |
| ICU duration (h)               | 21.6±13.1 38.4±58.3        | <0.001                    | 22.5±15.1 31.2±54.7       | 0.002 |
| New onset stroke (%)           |                            |                           |
| Transient                      | 7 0.5                      | 5 1.0                     | 0.030                    | 2 0.5 | 3 0.7 | 0.540 |
| Permanent                      | 0 0.0                      | 2 0.4                     | 0.000                    | 0 0.0 | 1 0.2 |
| Postoperative AF (%)           | 199 14.2                   | 115 22.3                  | <0.001                   | 67 16.4 | 84 20.6 | 0.140 |
| New onset dialysis (%)         |                            |                           |
| Transient                      | 2 0.1                      | 6 1.2                     | 0.001                    | 2 0.5 | 2 0.5 | 0.600 |
| Permanent                      | 1 0.1                      | 3 0.6                     | 0.000                    | 0 0.0 | 1 0.2 |
| Pulmonary complications (%)    | 5 0.3                      | 5 0.9                     | 0.130                    | 3 0.7 | 3 0.7 | 0.220 |
| Sternal dehiscence (%)         | 16 1.1                     | 5 1.0                     | 0.000                    | 6 1.5 | 4 1.0 | 0.750 |
| Overall infections (%)         | 30 2.1                     | 34 6.6                    | <0.001                   | 11 2.7 | 25 6.1 | 0.020 |
| Vasoactive agent infusion >4 h (%) | 143 10.2               | 103 20.0                  | <0.001                   | 51 12.5 | 68 16.7 | 0.280 |
| Discharge hematocrit level (%) | 28.3±4.0                   | 27.0±3.5                  | <0.001                   | 27.8±3.9 | 27.0±3.4 | <0.001 |
| Discharge creatinine level (mg/dL) | 0.9±0.4                  | 1.1±0.8                   | <0.001                   | 0.9±0.5 | 1.0±0.6 | 0.210 |
| Hospital duration (days)       | 6.4±4.6                    | 7.4±6.8                   | <0.001                   | 6.7±4.7 | 7.0±4.8 | 0.320 |
| ICU readmission (%)            | 32 2.3                     | 31 6.0                    | <0.001                   | 11 2.7 | 23 5.6 | 0.030 |
| Reintubation (%)               | 11 0.8                     | 20 3.9                    | <0.001                   | 3 0.7 | 12 2.9 | 0.019 |
| Hospital readmission (%)       | 45 3.2                     | 26 5.0                    | 0.070                    | 13 3.2 | 20 4.9 | 0.210 |
| Mortality (%)                  | 4 0.3                      | 21 4.1                    | <0.001                   | 2 0.5 | 8 2.0 | 0.050 |

SD: Standard deviation; ICU: Intensive care unit; AF: Atrial fibrillation.
Statistical analysis

Statistical analysis was performed using the SPSS version 10 software (SPSS Inc., Chicago, IL, USA). Data were presented in mean ± standard deviation (SD), median (min-max) or number and percentage. Univariate comparisons were made using the chi-square ($\chi^2$) test or Fisher's exact test for categorical variables, and the t-test was used for continuous variables. Transfused patients were matched with non-transfused patients using the propensity score matching analysis to control for the imbalance between the groups. The propensity score was estimated using a regression model. Variables with a $p$ value of $<0.1$ were entered into the logistic regression analysis. A multinomial logistic regression analysis was used to examine the relationships between diabetes mellitus, blood transfusion, and mortality. A two-sided $p$ value of $<0.05$ was considered statistically significant.

RESULTS

Baseline demographic and clinical characteristics of the patients are presented in Table 1. There was no statistically significant difference between the groups in terms of age, sex, body mass index, and pre- and intraoperative values after the propensity score matching.

Before propensity score matching, the length of ICU stay, infection rates (odds ratio [OR]: 3.22; 95% confidence interval [CI]: 1.95 to 5.32; $p<0.001$), hospital stay, and mortality (OR: 14.80; 95% CI: 5.05 to 43.34; $p<0.001$) were significantly higher in the blood transfusion group (Table 2). After propensity score matching, the length of ICU stay was significantly higher in the blood transfusion group than the non-transfusion group; however, there was no significant difference in the duration of hospitalization between the two groups. Additionally, the infection rates were higher in patients who received blood transfusions than those who did not receive blood transfusions (OR: 2.35; 95% CI: 1.14 to 4.85; $p=0.017$).

Furthermore, the mortality rates were four times higher in the patients who received blood transfusions than those who did not receive blood transfusions (OR: 4.06; 95% CI: 0.85 to 19.23; $p=0.05$). However, the multivariate logistic regression analysis revealed no statistically difference in mortality between the groups, when diabetes mellitus was a covariate factor (OR: 8.34; 95% CI: 3.94 to 17.66 vs. OR: 8.36; 95% CI: 3.95 to 17.70).

DISCUSSION

The higher incidence of mortality in patients with diabetes after cardiac surgery was reported in previous studies.[8-11] In a meta-analysis, Zhang et al.[11] found that the incidence of morbidity and mortality was higher in patients with diabetes than those without after CABG.

Blood transfusions have been shown to be associated with a high incidence of infection, transfusion-related lung injury, pneumonia, sternal infections, leg wound infections, circulatory overload, low cardiac output syndrome, renal dysfunction, atrial fibrillation, stroke, and short and long-term mortality rates.[12-14] The independent risk factors for blood transfusions are age, female sex, low body surface area, low EF (<35%), emergency operation, anemia, redo cardiac surgery, use of extracorporeal circulation, prolonged bypass time, and re-exploration for any reason.[15,16] Blood transfusions are also associated with worse survival and increased risk factors, leading to prolonged hospital stay after cardiac surgery.[17-19]

Hemorheological alterations of the storage of RBCs may disturb the microcirculation.[20] Additionally, endothelial dysfunction causes microvascular complications and disturbs the microcirculation in patients with diabetes.[21] A randomized-controlled trial showed that correcting CPB-induced dilutional anemia with blood transfusions in patients with diabetes undergoing CABG increased the risk of renal injury due to the microcirculatory derangements caused by the transfusions.[22] Additionally, this patient population is at an increased risk of renal injury compared to those without diabetes due to possible end-organ damages.[9] Although blood transfusions and diabetes mellitus are associated with a high incidence of renal injury, in our study, there were no statistically significant differences in discharge creatinine levels or the number of new-onset dialysis between the patients with diabetes who received blood transfusion and who did not.

In their study, Vranken et al.[23] reported that the rate of infections increased in female patients, smokers, and patients with advanced age, diabetes mellitus, obesity, chronic obstructive pulmonary disease, low EF, prolonged CPB time, and perioperative administration of inotropes after cardiac surgery. They also reported that the number of blood transfusions was associated with infections in patients after cardiac surgery. Blood transfusions are a predominant factor for all types of postoperative infections. Likosky et al.[24] observed that the incidence of pneumonia increased for every unit of
Blood transfusion in diabetic patients

Blood transfusion in diabetic patients remains comparable between those who receive blood transfusions and those who do not. Nonetheless, further, large-scale, prospective studies are needed to confirm the outcomes due to blood transfusion, although mortality remains comparable between those who receive blood transfusions and those who do not. Nonetheless, further, large-scale, prospective studies are needed to confirm these findings.

In conclusion, propensity score-matched analysis of the patients with diabetes shows worse clinical outcomes due to blood transfusion, although mortality remains comparable between those who receive blood transfusions and those who do not. Nonetheless, further, large-scale, prospective studies are needed to confirm these findings.

Declarations of conflicting interests
The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding
The authors received no financial support for the research and/or authorship of this article.

REFERENCES
1. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J. 2013;34:2436-43.
2. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829-41.
3. Nagendran J, Bozso SI, Norris CM, McAlister FA, Appoo JJ, Moon MC, et al. Coronary Artery Bypass Surgery Improves Outcomes in Patients With Diabetes and Left Ventricular Dysfunction. J Am Coll Cardiol 2018;71:819-27.
4. Moazzami K, Dolmatova E, Maher J, Gerula C, Sambol J, Klapholz M, et al. In-Hospital Outcomes and Complications of Coronary Artery Bypass Grafting in the United States Between 2008 and 2012. J Cardiothorac Vasc Anesth 2017;31:19-25.
5. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006;34:1608-16.
6. D'Agostino RS, Jacobs JP, Badhwar V, Paone G, Rankin JS, Han JM, et al. The society of thoracic surgeons adult cardiac surgery database: 2017 update on outcomes and quality. Ann Thorac Surg 2017;103:18-24.
7. Dixon B, Santamaria JD, Reid D, Collins M, Rechnitzer T, Newcomb AE, et al. The association of blood transfusion with mortality after cardiac surgery: cause or confounding? (CME). Transfusion 2015;53:19-27.
8. Kinnunen EM, Zanobini M, Onorati F, Brascia D, Mariscalco G, Franzese I, et al. The impact of minor blood transfusion on the outcome after coronary artery bypass grafting. J Crit Care 2017;40:207-12.
9. Gallagher S, Kapur A, Lovell MJ, Jones DA, Kirkwood A, Hassan S, et al. Impact of diabetes mellitus and renal insufficiency on 5-year mortality following coronary artery bypass graft surgery: a cohort study of 4869 UK patients. Eur J Cardiothorac Surg 2014;45:1075-81.
10. Ram E, Kogan A, Levin S, Fisman EZ, Tenenbaum A, Raanani E, et al. Type 2 diabetes mellitus increases long-term mortality risk after isolated surgical aortic valve replacement. Cardiovasc Diabetol 2019;18:31.
11. Zhang X, Wu Z, Peng X, Wu A, Yue Y, Martin J, et al. Prognosis of diabetic patients undergoing coronary artery bypass surgery compared with nondiabetics: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2011;25:288-98.
12. Kogan A, Ram E, Levin S, Fisman EZ, Tenenbaum A, Raanani E, et al. Impact of type 2 diabetes mellitus on short- and long-term mortality after coronary artery bypass surgery. Cardiovasc Diabetol 2018;17:151.
13. Bhaskar B, Dullhunty J, Mullany DV, Fraser JF. Impact of blood product transfusion on short and long-term survival after cardiac surgery: more evidence. Ann Thorac Surg 2012;94:460-7.
14. Veenith T, Sharples L, Gerrard C, Valchanov K, Vuyylesteke A. Survival and length of stay following blood transfusion in octogenarians following cardiac surgery. Anaesthesia 2010;65:331-6.
15. Vivacqua A, Koch CG, Yousuf AM, Nowicki ER, Houghtaling PL, Blackstone EH, et al. Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? Ann Thorac Surg 2011;91:1780-90.
16. van Straten AH, Kats S, Bekker MW, Verstappen F, ter Woorst JF, van Zundert AJ, et al. Risk factors for red blood cell transfusion after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2010;24:413-7.
17. Gallo M, Trivedi JR, Monreal G, Ganzel BL, Slaughter MS. Risk factors and outcomes in redo coronary artery bypass grafting. Heart Lung Circ 2020;29:384-9.
18. Crawford TC, Magruder JT, Fraser C, Suarez-Pierre A, Alejo D, Bobbitt J, et al. Less is more: Results of a statewide analysis of the impact of blood transfusion on coronary artery bypass grafting outcomes. Ann Thorac Surg 2018;105:129-36.
19. Galas FR, Almeida JP, Fukushima JT, Osawa EA, Nakamura RE, Silva CM, de Almeida EP, Auler JO, Vincent JL, Hajjar LA. Blood transfusion in cardiac surgery is a risk factor for increased hospital length of stay in adult patients. J Cardiothorac Surg 2013;8:54.
20. Almac E, Ince C. The impact of storage on red cell function in blood transfusion. Best Pract Res Clin Anaesthesiol 2007;21:195-208.
21. Henning RJ. Type-2 diabetes mellitus and cardiovascular disease. Future Cardiol 2018;14:491-509.
22. Aykut G, Kilercek M, Ar turk C, Ulugol H, Aksu U, Kudsioglu T, et al. Correction of dilutional anemia induces renal dysfunction in diabetic patients undergoing coronary artery bypass grafting: a consequence of microcirculatory alterations? J Nephrol 2018;31:417-22.
23. Vranken NP, Weerwind PW, Barenbrug PJ, Teerenstra S, Ganushchak YM, Maessen JG. The role of patient's profile and allogeneic blood transfusion in development of post-cardiac surgery infections: a retrospective study. Interact Cardiovasc Thorac Surg 2014;19:232-8.
24. Likosky DS, Paone G, Zhang M, Rogers MA, Harrington SD, Theurer PF, et al. Red blood cell transfusions impact pneumonia rates after coronary artery bypass grafting. Ann Thorac Surg 2015;100:794-800.