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Original research

Bleeding, transfusion and the risk of stroke after coronary surgery: A prospective cohort study of 2357 patients

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HIGHLIGHTS

- The mechanisms underlying stroke after cardiac surgery are not fully understood.
- Bleeding and blood transfusion independently increase the risk of stroke after coronary surgery.
- The risk of postoperative stroke is highest in case of severe postoperative bleeding.

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ABSTRACT

Introduction: This study was planned to investigate the impact of severe bleeding and blood transfusion on the development of stroke after coronary surgery.
Methods: This cohort study includes 2357 patients undergoing isolated CABG from the prospective European Coronary Artery Bypass Grafting (E-CABG) registry. Severity of bleeding was categorized according to the Universal Definition of Perioperative Bleeding (UDPB), E-CABG and PLATO definitions.

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Results: Thirty patients (1.3%) suffered postoperative stroke. The amount of transfused red blood cell (RBC) (OR 1.10, 95%CI 1.03–1.18), preoperative use of unfractioned heparin (OR 4.49, 95%CI 1.91–10.60), emergency operation (OR 3.97, 95%CI 1.47–10.74), diseased ascending aorta (OR 4.62, 95%CI 1.37–15.65) and use of cardiopulmonary bypass ($p = 0.043$, OR 4.85, 95%CI 1.05–22.36) were independent predictors of postoperative stroke. Adjusted analysis showed that UDPB classes 3–4 (crude rate: 3.6% vs. 1.0%; adjusted OR 2.66, 95%CI 1.05–6.73), E-CABG bleeding grades 2–3 (crudes rate: 6.3% vs. 0.9%; adjusted OR 5.91, 95%CI 2.43–14.36), and PLATO life-threatening bleeding (crude rate: 2.5% vs. 0.6%, adjusted OR 3.70, 95%CI 1.59–8.64) were associated with an increased risk of stroke compared with no or moderate bleeding.
Conclusions: Bleeding and blood transfusion are associated with an increased risk of stroke after CABG, which is highest in patients with severe bleeding.

1. Introduction

Postoperative stroke is one of the most severe complications after cardiac surgery. Recent studies reported on a possible association between blood transfusions and the development of postoperative stroke [1–6]. However, investigation of the mechanistic role of excessive bleeding requiring transfusion in the pathogenesis of postoperative neurological complications is made difficult by the multifactorial causation of postoperative stroke [7–10], the lack of adequate stratification methods of the severity of bleeding, and of prospective data. The on-going European multicenter registry E-CABG [11] collects prospectively a number of variables on the amount of bleeding, severity of anemia, and use of any blood products in patients undergoing isolated coronary artery bypass grafting (CABG). This allows a stratification of the severity of bleeding according to the E-CABG bleeding severity definition [11], the Universal Definition of Perioperative Bleeding (UDPB) [12], and Platelet Inhibition and Patient Outcomes (PLATO) bleeding definition for major hemorrhage [13]. The prospective E-CABG registry was used to investigate the impact of increasing severity of bleeding and use of blood products on the development of stroke after isolated CABG.

2. Methods

The E-CABG registry is a prospective, multicenter study enrolling patients undergoing isolated CABG at 15 European cardiac surgery centers (Besançon, France; Catanzaro, Italy; Genoa, Italy; Hamburg, Germany; Milan, Italy; Nuremberg, Germany; Naples, Italy; Oulu, Finland; Parma, Italy; Pedara, Italy; Rennes, France; Rome, Italy; Stockholm, Sweden; Trieste, Italy; Verona, Italy). This study is registered in Clinicaltrials.gov (Identifier: NCT02319083) and its study protocol and definition criteria are reported in detail elsewhere [11]. For the purpose of the present analysis, we included a consecutive series of patients with coronary artery disease undergoing isolated CABG from January 2015 to September 2015. This analysis was planned before starting the E-CABG project. Patients undergoing carotid angioplasty or endarterectomy immediately before CABG ($n = 97$) and those with missing data ($n = 28$) were excluded from this analysis. Data on preoperative antithrombotics, postoperative blood loss, anemia, and use of any type of blood products were collected prospectively in order to stratify the severity of bleeding according to the E-CABG bleeding severity definition [11], UDPB criteria [12], and PLATO major and life-threatening bleeding criteria [13]. Preoperative anemia was defined as hemoglobin <12 gr/dL in women and <13 gr/dL in men. Data on preoperative ultrasound screening of the status of carotid arteries and intraoperative use of epiaortic ultrasound were available according to institutional policies and were considered as covariates in multivariate analyses.

The main outcome measure of this study was any temporary or permanent ischemic stroke occurring during the in-hospital stay after CABG. Stroke was defined as any focal or global neurological syndrome occurring during the in-hospital stay caused by ischemia not resolving within 24 h. The diagnosis and nature of stroke was made on the basis of findings at computed tomography and/or magnetic resonance imaging of the brain and confirmed by a neurologist. When neurological signs and symptoms disappeared before discharge, stroke was defined temporary, otherwise it was defined as permanent.

3. Statistical analysis

Summary statistics are presented as means ± standard deviation for continuous variables and as counts and percentages for categorical variables. Odds ratios (ORs) and 95% confidence interval (CIs) are reported. No attempt to replace missing values was made. Fisher exact test, Chi-square test and Mann-Whitney tests were used for univariate analysis. Logistic regression with backward selection was used to identify risk factors associated with postoperative stroke. Since the incidence of stroke was less than 2%, we included in the regression models only variables with a $p < 0.05$ in univariate analysis in order to avoid model overfitting. The fit of the final multivariate logistic regression analysis was assessed using the Hosmer-Lemeshow goodness-of-fit test and the discriminatory power was quantified by C-statistics. In a subsequent analysis, a logistic regression model was conducted to adjust the risk of stroke associated with increasing UDPB classes, E-CABG bleeding grades and PLATO bleeding classes for any baseline, operative and postoperative covariate potentially associated with the development of stroke as defined by a $p < 0.05$. According to this criterion, critical preoperative state, emergency operation, preoperative use of unfractioned heparin, diseased ascending aorta, use of cardiopulmonary bypass, amount of chest tube output 12 h after surgery, units of transfused RBC, administration of fibrinogen and of prothrombin complex were included in to the regression model for prediction of stroke. Along with these variables, also postoperative atrial fibrillation ($p = 0.054$), prolonged use of inotropics after surgery ($p = 0.029$), use of intra-aortic balloon pump ($p = 0.126$), and use of extracorporeal mechanical oxygenation ($p = 0.008$) were included in to the regression models because of their potential causative role in the development of postoperative stroke. Furthermore, participating centers, baseline and nadir levels of hemoglobin, and hematocrit on the operation day were forced in to this regression models. All tests were two-sided with the alpha level set at 0.05 for statistical significance. All statistical analysis