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Fibrinogen levels compensation of thrombocytopenia-induced bleeding following cardiac surgery

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ABSTRACT

Background: After cardiopulmonary bypass (CPB) thrombocytopenia is a relatively common pattern which may trigger postoperative bleeding. The purpose of this study is to verify if the endogenous fibrinogen levels are independent determinants of chest drain blood loss and need for allogeneic blood products transfusions in a clinical model of post-CPB thrombocytopenia.

Methods: Retrospective analysis on 445 consecutive patients having a platelet count <100 × 1000 cells/μL after CPB. Based on the fibrinogen levels the patients were divided into three groups with similar platelet count and low (LF, median 170 mg/dL), intermediate (IF, median 215 mg/dL), and high (HF, median 280 mg/dL), fibrinogen levels. Chest drain blood loss (mL/12 h), transfusion rate of red blood cells (RBC), fresh frozen plasma (FFP) and platelet concentrates were assessed and compared between groups.

Results: There was a significant (P = 0.001) difference in chest drain blood loss with higher values in the LF group (487 mL/12 h, IQR 300–600 mL/12 h) than in the IF group (350 mL/12 h, IQR 200–500 mL/12 h) and the HF group (300 mL/12 h, IQR 200–475 mL/12 h). Transfusion rates of FFP significantly (P = 0.014) differed between groups (LF: 18.4%, IF: 7.9%, HF: 9.2%) and platelet concentrate transfusions significantly (P = 0.020) differed between groups (LF: 23.5%, IF: 16.5%, HF: 10.7%). In multivariable models, these differences were confirmed. Thromboelastography parameters showed an effective compensation of clot firmness in group HF vs. IF and LF.

Conclusions: Levels of fibrinogen >240 mg/dL compensate the decrease in clot firmness observed in thrombocytopenic patients following CPB, and reduce bleeding and transfusion needs.

1. Introduction

Clot firmness is an important determinant of a correct hemostasis under different clinical conditions, including cardiac surgery [1–4].

Determinants of clot firmness are the interaction between fibrin(o-gen) and platelets, factor XIII activity, and fibrinolysis. Platelet count is an important determinant of clot firmness, and thrombocytopenia is accompanied by signs of poor clot firmness at visco-elastic tests [5,6]. Thrombocytopenia is relatively common after cardiac surgery with cardiopulmonary bypass (CPB), due to platelet activation, aggregation, and destruction [7–9], and severe patterns of thrombocytopenia are one of the possible determinants of postoperative bleeding [10].

The possibility of a fibrinogen-based compensation of clot firmness in the setting of thrombocytopenia was raised by different laboratory-based studies [11–13]. However, there is no clinical evidence of a positive role of fibrinogen levels in thrombocytopenic patients following cardiac surgery.

The present study investigates the hypothesis that postoperative bleeding (primary endpoint) and allogeneic blood products transfusions and surgical re-exploration due to bleeding (secondary endpoints) in thrombocytopenic patients following cardiac surgery are determined by the fibrinogen level.

2. Methods

This study is a retrospective analysis of the hemostasis/coagulation cardiac surgery database of the IRCCS Policlinico San Donato, a Clinical Research Hospital partially funded by the Italian Ministry of Health. The Local Ethics Committee (San Raffaele Hospital Ethics Committee) gave the approval (March 2016) to the study design and waived the need for an informed consent from the patients.

2.1. Patient selection

Data from 2878 consecutive adult patients were available in the period March 2012–January 2015. A selection was applied based on the entry criterion (postoperative thrombocytopenia). Thrombocytopenia was defined as a platelet count <100,000 cells/μL at the arrival in the ICU. Four hundred forty-five patients remained available for the subsequent step. The patient population was divided into tertiles based on the distribution of the concentration of fibrinogen (mg/dL), with the first tertile defined as "low fibrinogen" (LF),

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the second as "intermediate fibrinogen" (IF) and the third as "high fibrinogen" (HF). The three groups were checked for homogeneity of platelet count values, and re-defined according to a propensity-matching in case of heterogeneity. This procedure resulted in a final total sample size of 406 patients. A sub-analysis of patients with a platelet count <80,000 cells/μL is included.

2.2. Variables and definitions

The database contains clinical data on preoperative (demographics, co-morbidities, laboratory data), intraoperative (surgical details, CPB details), and postoperative variables (outcome data, laboratory data at the arrival in the intensive care unit [ICU]). When performed, data on post-CPB thromboelastograpy (TEG, Haemoscope, Niles, IL) were available for the analysis.

For the purposes of the present study we have retrieved and analyzed the following variables. Preoperative: demographics; left ventricular ejection fraction (%); hematocrit (HCT, %); serum creatinine (mg/dL); main co-morbidities (diabetes, previous cerebrovascular accident, chronic obstructive pulmonary disease, congestive heart failure); urgent or emergent procedures, redo surgery, preoperative coagulation tests included activated partial thromboplastin time (aPTT, sec), international normalized ratio (INR) of the prothrombin time, platelet count (cells/μL), antithrombin activity (%); preoperative use of P_2Y_{12} platelet inhibitors, salycilates, or warfarin. Intraoperative: type of operation; CPB duration (minutes). Postoperative: bleeding (chest drain blood collected in the first 12 postoperative hours); severe bleeding (defined according to modified criteria of the Universal Definition of Perioperative Bleeding [14] as a chest drain blood loss >1000 mL/12 h or surgical re-exploration due to bleeding); transfusion of allogeneic RBCs, fresh frozen plasma (FFP), platelet concentrates; surgical re-exploration due to bleeding. Surgical re-exploration is usually applied at our Institution in presence of a severe chest drain blood loss in the ICU in absence of clear coagulopathy or despite the treatment of the coagulopathy. Postoperative coagulation tests included activated partial thromboplastin time (aPTT, sec), international normalized ratio (INR) of the prothrombin time, platelet count (cells/μL), antithrombin activity (%). When available, postoperative TEG data were retrieved and defined in terms of clotting time (R, minutes), alpha angle (degrees), K-time (minutes), maximum amplitude (MA, mm). All the TEG tests were performed with and without heparinase.

2.3. Surgery and CPB

Surgery was generally performed under moderate (32–33 °C) hypothermia on CPB. Antegrade cold crystalloid cardioplegia was generally used (500 mL for the first dose, and 300 mL–500 mL for subsequent doses).

The perfusion circuit was minimized in order to limit the amount of dynamic priming volume. The priming volume consisted of a mixture of 80% gelatin and 20% tromethamine (THAM) solution. The volume of the priming varied according to the baseline HCT of the patient and to the body surface area. The general aim was to obtain a nadir HCT on CPB not lower than 26%. The median priming volume at our institution is 600 mL (interquartile range 450 mL–700 mL).

A cell-saver was routinely used only for redo-surgery. The residual volume in the cardiotomy reservoir at the end of CPB was usually re-infused to the patient via the aortic cannula. Anticoagulation was achieved with unfractionated heparin according to our standard protocol to reach and maintain an activated clotting time of 450–480 s. Heparin reversal was achieved with a dose of protamine at a 1:1 ratio with the heparin loading dose. All the patients received tranexamic acid at a dose of 15 mg/kg before CPB and 15 mg/kg after protamine administration, without continuous infusion.

Transfusions of allogeneic blood products were guided by our transfusion protocol(s) based on standard coagulation tests [15] or on TEG results [16]. In particular, the trigger value for RBC transfusions is settled at a hemoglobin level <8.0 g/dL. Transfusion of RBC is however possible in case of signs of inadequate oxygen delivery (end organ ischemia) even for a hemoglobin value between 8 and 10 g/dL. These signs include a central venous oxygen saturation <68%, low cardiac output (requiring high-dose inotropes and/or mechanical assistance), poor urine output, and of course clinical signs of myocardial ischemia at the electrocardiographic examination, stroke, and mesenteric infarction.

2.4. Statistics

All data are expressed as median with interquartile range (IQR) for continuous variables, or as number and percentage for binary variables.

Differences in platelet count between the three groups were assessed with a Kruskall–Wallis analysis, and the groups were rendered homogeneous for platelet count with a propensity-matching (limited to platelet count). Other differences between groups were considered as co-variates in multivariable analyses (regression analysis for continuous variables and logistic regression for binary variables).

The primary and secondary endpoints were explored for differences between groups using an ANOVA (continuous normally distributed variables) or a Kruskall–Wallis analysis (non-normally distributed variables) with post-hoc comparisons based on Bonferroni correction, and with a Pearson's chi-square for binary variables.

Subsequently, the differences in primary and secondary endpoints were checked using multivariable models (linear regression and logistic regression) including as co-variates all the factors being significantly different between groups. The independent factors associated with the endpoints were identified, producing the relative odds ratios with 95% confidence interval.

For all the tests, a P level <0.05 was considered statistically significant. All the calculations were done using a computerized statistical package (SPSS 13.0, IBM, Chicago, IL, USA and GraphPad Prism 6, San Diego, CA).

3. Results

The 445 patients with thrombocytopenia demonstrated a significant (P = 0.01) difference in platelet count at the arrival in the ICU according to the level of fibrinogen: LF (N = 147): 81,000 (67,000–90,000) cells/μL; IF (N = 152): 85,000 (72,000–93,000) cells/μL; HF (N = 146): 88,000 (76,000–94,000) cells/μL. Therefore, a propensity-matching was applied to obtain three groups homogeneous for platelet count. This resulted in the exclusion of 39 patients, and a final patient population of 406 patients.

The three final experimental groups were formed based on the tertiles of distribution of fibrinogen levels. LF group had a median value of fibrinogen of 170 mg/dL (IQR 154–181 mg/dL, range 38–192 mg/dL); group IF had a median value of 215 mg/dL (IQR 204–227 mg/dL, range 193–240 mg/dL), and group HF had a median value of 280 mg/dL (IQR 256–334 mg/dL, range 241–679 mg/dL), with a P value of 0.001 for between group difference. The correspondent platelet count values were 82,000 cells/μL (IQR 72,000–91,000 cells/μL) for LF group, 84,000 cells/μL (IQR 72,000–91,000 cells/μL) for IF group and 86,000 cells/μL (IQR 75,000–93,000 cells/μL) for HF group, with non-significant (P = 0.418) between group differences. The distribution of the clinical and laboratory variables in the three groups is shown in Table 1. The three groups had significant differences in terms of age, weight, left ventricular ejection fraction, serum creatinine, hematocrit, rate of non-elective operations, and baseline aPTT.

Postoperative chest drain blood loss (Fig. 1) was significantly (P = 0.001) different between groups, with higher values in the LF group (487 mL/12 h, IQR 300–600 mL/12 h) than in the IF group (350 mL/12 h, IQR 200–500 mL/12 h) and the HF group (300 mL/12 h, IQR 200–475 mL/12 h). Transfusion rate of packed red cells did not differ between groups, whereas there was a significantly higher rate of fresh frozen plasma transfusions in patients in the LF group (18.4%) vs. patients in the IF (7.9%) and HF (9.2%) groups (P = 0.014), and a significant (P = 0.020) between groups difference for platelet concentrate transfusions, accounting for 23.5% in LF group, 16.5% in IF group, and 10.7% in HF group.

Severe bleeding was found in 9.6% patients in the LF group, 6.5% in IF group, and 5.3% in HF group; surgical re-exploration rates were 4.4% in LF group, 3.6% in IF group, and 1.5% in HF group. These differences were not significant.

To investigate the independent association of fibrinogen levels on the primary and secondary outcome endpoints, multivariable models including the potential confounders (age, weight, serum creatinine, hematocrit, ejection fraction, non-elective surgery, and preoperative aPTT) were built and are shown in Table 2. After correction for the other confounders, the fibrinogen group remained an independent predictor of postoperative bleeding, FFP and platelet concentrates transfusion. Chest drain output was reduced by 110 mL/12 h per each fibrinogen concentration class increase. FFP transfusion and platelet concentrate transfusions decreased by 37% and 43% respectively per each fibrinogen concentration class increase.

In a subgroup of 152 patients, showing signs of microvascular bleeding after protamine administration, TEG data were available and are shown in Table 3. Microvascular bleeding was defined on a clinical basis, as the evidence of an abnormal blood loss (either by visual inspection or by amount of blood collected in the cell-saver). When residual heparin effects were eliminated, patients in the HF group had a significantly shorter clot formation kinetics (alpha angle and K-time) and greater clot firmness (MA tract).

3.1. Sub-analysis of patients with platelet count <80,000 cells/μL

One-hundred forty-six patients (81 in HF group, 34 in IF group, and 31 in LF group) had a platelet count <80,000 cells/μL at the arrival in the ICU.

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