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Preoperative Fibrinogen Levels as a Predictor of Postoperative Bleeding after Open Heart Surgery

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ABSTRACT

Background. Open heart surgery still involving major bleeding continues to be a major challenge after cardiac surgery and is also a significant cause of morbidity and mortality. Most hemostatic factors are intercorrelated with postoperative bleeding, and fibrinogen seems the most fundamental hemostatic risk factor for open heart surgery.

Methods. The study included 97 patients who underwent elective coronary artery surgery (78 men and 19 women; mean age, 60.9 ± 10.3). Preoperative blood samples were obtained and preoprative quantitative determination of plasma fibrinogen levels were measured by the clotting method of Clauss using the fibrinogen kit. Patients were operated on by the same team and the same tecnique. The total amount of drainage blood from chest tubes was recorded after termination of operation.

Results. There were statistical significance between the fibrinogen levels and the drainage ($r = -0.897$, $P < .001$). Chest drainage was a mean of 972 mL (range, 240-2445 mL) in the first 48 hours after sternotomy closure. Fibrinogen level and relation to age was statistically significant ($P = .015$). There was no statisticaly significance between fibrinogen levels and gender (male gender = 400.7 ± 123.0 versus female gender = 395.6 ± 148.1; $P = .877$) and between drainage and gender (male gender = 968.2 ± 538.5 versus female gender = 990.0 ± 554.7; $P = .876$). Two patients (2%) died early after the surgery. There were no significant differences between the postoperative bleeding and cardiopulmonary bypass time ($P = .648$) or cross-clamp time ($P = .974$).

Conclusions. The results of this study suggested that low preoperative fibrinogen level appears to be a useful diagnostic marker to assess the activity of the coagulation system, and that its preoperative level may serve as a potential risk factor for postoperative bleeding after coronary artery bypass surgery.

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INTRODUCTION

Cardiac surgery including cardiopulmonary bypass (CPB) induces marked abnormalities of primary and secondary hemostasis [Czer 1989; Taylor 1990; Woodman 1990; Kestin 1993; Despotis 1996; Dacey 1998; Bishop 2006]. These abnormalities occur due to blood contact with the large nonendothelial surfaces of the extracorporeal circuit, the release of tissue factor after surgical trauma, reinfusion of tissue factor and activated coagulation factors, and the shear forces generated by cardiotomy suction [Pappalardo 2006]. The amount of transfused allogenic blood and blood components per CPB procedure has decreased in recent years as a result of improved technology, autologous blood conservation techniques, and the use of antifibrinolytic agents [Blome 2005]. However, major bleeding and hemorrhaging continues to be a major challenge after cardiac surgery and is also a significant cause of morbidity and mortality, prolonged hospital stay, and increased cost after cardiac operations [Taylor 1990; Dacey 1998; Karkouti 2004; Bishop 2006]. Numerous risk factors induce systemic inflammatory activation and alterations in the hemostatic cascade. The responses contribute to postoperative complications but may also have protective effects [Aljassim 2006]. Fibrinogen seems the most fundamental hemostatic risk factor and it is a moderator of platelet aggregation and a determinant of plasma viscosity. Fibrinogen is an acute-phase reactant synthesized in the liver that is elevated in inflammatory states and mediates the thrombogenic effect of other risk factors [Kannel 2005]. Elevated fibrinogen levels lead to enhanced coagulation activity and are associated with increased cardiovascular disorders, atherosclerosis, peripheral vascular disease, and other thromboembolism [Kirmizis 2006; Odeberg 2006].

There is little clinical data available concerning the relationship between preoperative fibrinogen levels and postoperative bleeding after coronary artery bypass grafting (CABG). The present study aimed to clarify the association between preoperative plasma fibrinogen levels and postoperative bleeding after CABG.

MATERIAL AND METHODS

Selection of Patients and Study Design

The study was approved by the local ethics committee. Informed consent was obtained from all participants. This clinical trial was conducted in accordance with the amended Declaration of Helsinki and Good Clinical Practice regulations. Ninety-seven patients were enrolled in this study (78 men [80.4%] and 19 women [19.6%]; mean age, 60.9 ± 10.3 years; median age, 60.0; range 40-80 years). Patients were included consecutively when they met the inclusion criteria. Patients were excluded when body weight was greater than 100 kg or less than 60 kg, age was under 40 or over 80 years, or in cases of severe liver dysfunction; patients with a history of hemorrhagic events, known platelet dysfunction, platelet count lower than 100/nL, partial thromboplastin international normalized ratio greater than 1.50, and who received intravenous or subcutaneous heparin less than 48 hours before surgery or who were administered platelet-active medication before surgery were excluded from the study. No patients were using antiplatelet agents other then acetylsalicylic acid (aspirin); aspirin usage was discontinued at least one week prior to surgery. We also excluded patients with recent (<3 months) venous or systemic thromboembolism, myocardial infarction, stroke or acute coronary syndrome, infection, inflammatory disease, surgery, malignancy and renal impairment, patients with valvular heart disease, and those being treated with hormone replacement therapy or oral anticoagulation.

Sample Collection and Laboratory Assay

Blood samples were drawn from central venous lines by means of a two-syringe technique preoperatively. Central venous catheters were placed immediately before operation. Ten milliters of blood were withdrawn with the first syringe and discarded, and 5 mL obtained in the second syringe. Blood samples were collected into commercially available tubes containing 0.129 M sodium citrate, which contains 9 parts blood to one part trisodium citrate (Becton Dickinson vacutainer systems, Plymouth, UK). Preoprative quantitative determination of fibrinogen levels was measured by the clotting method of Clauss using the fibrinogen kit (Diagnostica Stago, Asnieres sur Seine, France).

Operative Technique and Anesthesia

All patients underwent standardized anaesthesia and surgical techniques. All patients were operated by the same team and the same tecnique. Intravenous penthotal sodium was administered 5 to 7 mg/kg for induction. Anesthesia was continued with sevoflouran or isoflouran. Vecuronium bromide 0.1 mg/kg was used as the myorelaxan drug. Cefazelin sodium and gentamycin sulphate were administered in the preoperative period in all patients. Extra corporeal circulation was performed under moderate hypothermia. The internal mammary artery was harvested in all subjects plus one or more venous grafts. Heparin was administered as a loading dose of 300 IU/kg of body weight and supplemented to maintain an activated clotting time of > 450 seconds during CPB. CPB was accomplished using a membrane oxygenator (Edwards Vital; Edwards Lifesciences, Irvine, CA, USA), 2000 mL of Ringer's lactate priming, a roller pump, and maintaing a nasopharingeal temperature of 28°C. CPB was instituted via the ascending aorta and single two-stage venous cannulation (maintained at 2.2 to 2.4 l/minute^{-1} per m^{-2}). Following cross clamping of the aorta, Myocardial protection was accomplished by 10 to 15 cc/kg antegrade intermittent cold blood cardioplegia through the aortic root and topical ice slush, continued every 20 minutes. Heparin was neutralized with protamine hydroclorur (Protamin 1000; Roche, Istanbul, Turkey) under monitoring with the activated clotting time. Additional protamine sulfate was given if the activated clotting time was above 120 seconds. Surgical hemostasis was achieved using a standardized protocol. The cardiotomy reservoir was used to collect mediastinal blood loss. The chest tubes were connected to the reservoir before closure of the chest. Chest tube drainage was recorded hourly until removal of drains on the morning after surgery. Shed blood was not reinfused. Transfusion of packed red cells was considered below a hemoglobin value of 9 g/dL, particularly in a bleeding patient. Fresh frozen plasma was given if the blood loss through the mediastinal drains was more than 200 mL for 3 consecutive hours. The total amount of drainage blood from chest tubes was recorded after termination of operation.

Statistical Analysis

Data were expressed as mean ± standard deviation. Pearson's correlation test was used for analysis of continuous variables. Correlations between the measured laboratory indices and clinical and demographic data were performed using the *t* test. A multivariate regression analysis was done to determine the influence of all variables and the incidence of postoperative bleeding. A two-tailed *P* value less than .05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS 11.5 for Windows; SPSS, Chicago, IL, USA).

Baseline and Cardiopulmonary Bypass Characteristics of the Study Group

Age, y	60.9 ± 10.3
Sex, F/M	19/78
Current smoker, %	60
Hypertension, %	69
Diabetes mellitus, %	29.9
Hypercholesterolemia, %	81.4
Body mass index, kg/m^2	27.2 ± 3.4
Body surface area, m^2	1.8 ± 0.1
Fibrinogen level	399.7 ± 127.5
Cardiopulmonary bypass duration, min	80.7 ± 32.0
Cross-clamp time, min	48.0 ± 21.8
Flow, cc	4467.7 ± 324.7

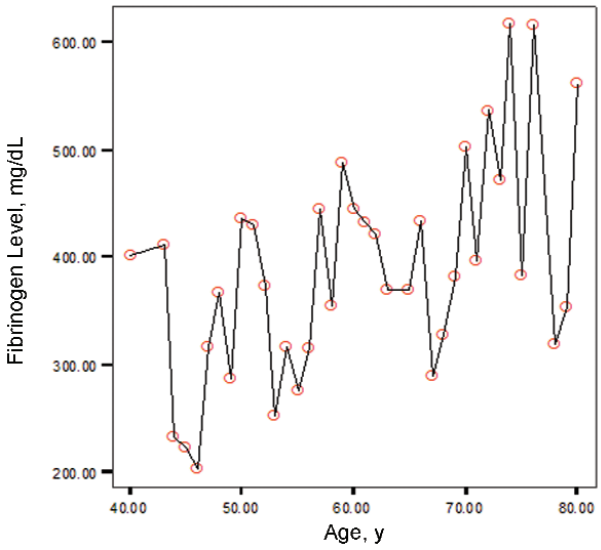

Figure 1. Relation between age and fibrinogen levels.

RESULTS

Baseline and CPB characteristics of the study population are summarized in Table 1. There were negative linear relation between the fibrinogen levels and the postoperative bleeding. This relation was statistically significant ($r = –0.897$, $P < .001$). Chest drainage was a mean of 972 mL (range, 240-2445 mL) in the first 48 hours after sternotomy closure. Fibrinogen level and relation to age was also statistically significant ($P = .015$) (Figure 1).

There was no statistical significance between fibrinogen levels and gender (male gender = 400.7 ± 123.0 versus female gender = 395.6 ± 148.1; $P = .877$) or between drainage and gender (male gender = 968.2 ± 538.5 versus female gender = 990.0 ± 554.7; $P = .876$). Additionaly, there was no relation between the body surgafe area ($P = .817$), body mass index ($P = 837$), and the fibrinogen level. A multivariate regression analysis showed preoperative fibrinogen level as the most valuable predictor for postoperative bleeding after coronary artery bypass surgery ($R = .897$, and adjusted R square was .802).

In particular, there were no thromboembolic events, no cardiac ischemic events, and no allergic reactions. Two patients (2%) died early after the surgery. There were no significant differences between the postoperative bleeding and CPB time ($P = .648$) and cross-clamp time ($P = .974$).

DISCUSSION

Cardiac surgery induces a systemic inflammatory activation and alterations in the hemostatic cascade. The responses contribute to postoperative complications including postoperative excessive bleeding. We investigated the relationship between fibrinogen levels and bleeding after on-pump coronary artery bypass surgery.

CABG is one of the most frequent surgical procedures actually performed in cardiac sugery. The technical and technological improvements that have occurred in the last decade have rendered this operation safer, reducing to acceptable levels the surgical risk even in very old and sick patients [Gaudino 2002]. Bleeding and inflammation are major complications of open heart surgery. The management of postoperative hemorrhaging in this setting may require massive transfusion of blood and blood products, which in itself has inherent risks [Czer 1989; Woodman 1990; Despotis 1996]. Within the cardiac surgery population, those with increasing age and long CPB times are especially at risk of postoperative bleeding [Kestin 1993; Despotis 1996; Bishop 2006]. Induced inflammatory response may contribute to organ dysfunction and complications, which have also been associated with myocardial injury [Janesen 1992; Wan 1997; Paparella 2002; Abacilar 2006; Aljassim 2006]. The relationship between inflammatory response, hemostasis, and bleeding after cardiac surgery is not fully understood [Wan 1997; Despotis 2001; Paparella 2002]. There is however, some evidence for such an association. Rinder et al has described adhesion of leukocytes to platelets during CPB [Rinder 1992].

One finding in the present study was the close relationship between preoperative fibrinogen levels and postoperative bleeding (Figure 2), despite the fact that almost all patients had fibrinogen concentrations within the normal range (202-666 mg/dL). The results suggest that preoperative fibrinogen analysis provides important information about risk for postoperative bleeding and may be controlled at least in patients with increased risk for bleeding. One may speculate that individuals with low levels (within the normal range) may benefit from perioperative fibrinogen therapy [Aljassim 2006].

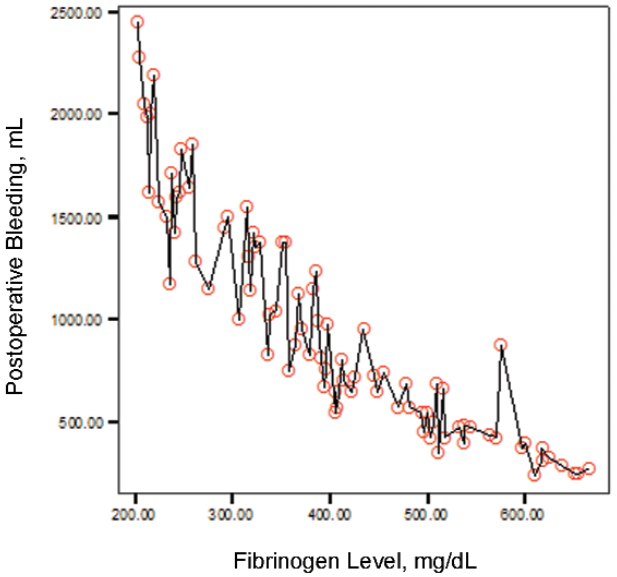

Figure 2. Relation between fibrinogen levels and postoperative bleeding.

Fibrinogen level and association with increased mortality is probably directly related to its ability to promote thromboses, or clots, by causing platelets to clump inside blood vessels. This is one of the main mechanisms underlying ischemia and heart attack. A number of studies show elevated fibrinogen to be a major risk factor for coronary heart disease (heart attacks) and cerebrovascular disease (strokes), which together account for about 60% of deaths in the elderly [Kannel 1987]. Elevated fibrinogen levels are rather associated with increased cardiovascular risk [Jensen 2003]. Thus, it is conceivable that fibrinogen levels modulate postoperative blood loss, which in itself is mainly caused by other factors that have been described previously in detail [Jensen 2004; Aljassim 2006]. We found a strong inverse association between preoperative fibrinogen levels and postoperative bleeding.

General parameters such as age, gender, and duration of CPB and cross-clamp time were analyzed and only fibrinogen levels and age relation were found to be statistically significant. The use of CPB during cardiac surgery influences hemostasis in a number of ways. Hemodilution leads to a reduction of coagulation factors by approximately 50% [Harker 1980]. The abnormalities of hemostasis secondary to contact of blood with the extracorporeal circuit play a significant role in postoperative morbidity and mortality after cardiac operations. The contact of the patient's blood with the surface of the tubing, the oxygenator, and the arterial line filter induces activation of the coagulation cascade [Nutall 1997; Wabha 1997].

Fibrinogen is a key protein in hemostasis synthesized by the liver. Fibrinogen is converted into fibrin at the site of tissue damage in order to minimize blood loss and initiate tissue repair. Fibrinogen may also directly increase cerebrovascular disease risk because of its role in platelet aggregation, plasma viscosity, and fibrin formation and seems the most fundamental hemostatic risk factor for cerebrovascular disease. Preoperative fibrinogen levels are clearly associated with the amount of 24-hour mediastinal blood loss, even when levels are within or above the normal reference range.

In conclusion, preoperative fibrinogen levels are clearly associated with the amount of mediastinal blood loss, and fibrinogen levels obviously modulate postoperative blood loss after open heart surgery. The results of this study demonstrated that low preoperative fibrinogen levels are associated with the development of postoperative bleeding after coronary artery bypass surgery, and fibrinogen determination may be an useful screening tool to identify individuals at added risk for bleeding complication after coronary artery surgery.

REFERENCES

Abacilar F, Dogan OF, et al. 2006. The changes and effects of the plasma levels of tumor necrosis factor after coronary artery bypass surgery with cardiopulmonary bypass. Heart Surg Forum 9:703-9.

Aljassim O, Karlsson M, Wiklund L, Jeppsson A, Olsson P, Berglin E. 2006. Inflammatory response and platelet activation after off-pump coronary artery bypass surgery. Scand Cardiovasc J 40:43-8.

Bishop CV, Renwick WE P, Hogan C, Haeusler M, Tuckfield A, Tatoulis J. 2006. Recombinant activated factor VII: treating postoperative hemorrhage in cardiac surgery. Ann Thorac Surg 81:875-9.

Blome M, Isgro1 F, Kiessling AH, et al. 2005. Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. Thromb Haemost 93:1101-7.

Czer LS. 1989. Mediastinal bleeding after cardiac surgery: etiologies, diagnostic considerations, and blood conservation methods. J Cardiothorac Anesth 3:760-75.

Dacey LJ, Munoz JJ, Baribeau YR, et al. 1998. Reexploration for hemorrhage following coronary artery bypass grafting: incidence and risk factors. Northern New England Cardiovascular Disease Study Group. Arch Surg 133:442-7.

Despotis GJ, Avidan MS, Hogue CW Jr. 2001. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. Ann Thorac Surg 72:1821-31.

Despotis GJ, Filos KS, Zoys TN, Hogue CW Jr, Spitznagel E, Lappas DG. 1996. Factors associated with excessive postoperative blood loss and hemostatic transfusion requirements: a multivariate analysis in cardiac surgery patients. Anesth Analg 82:13-21.

Gaudino M, Nasso G, Andreotti F, et al. 2002. Preoperative C-reactive protein level and outcome following coronary surgery. Eur J Cardiothorac Surg 22:521-6.

Harker LA, Malpass TW, Branson HE, Hessel EA 2nd, Slichter SJ. 1980. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective alpha-granule release. Blood 56:824-34.

Jansen NJ, van Oeveren W, Gu YJ, van Vliet MH, Eijsman L, Wildevuur CR. 1992. Endotoxin release and tumor necrosis factor formation during cardiopulmonary bypass. Ann Thorac Surg 54:744-7.

Jensen E, Andreasson S, Bengtsson A, et al. 2003. Influence of two different perfusion systems on inflammatory response in pediatric heart surgery. Ann Thorac Surg 75:919-25.

Jensen E, Andreasson S, Bengtsson A, et al. 2004. Changes in hemostasis during pediatric heart surgery: impact of a biocompatible heparin-coated perfusion system. Ann Thorac Surg 77:962-7.

Kannel WB. 2005. Overview of hemostatic factors involved in atherosclerotic cardiovascular disease. Lipids 40:1215-20.

Kannel WB, Wolf PA, Castelli WP, D'Agostins RB. 1987. Fibrinogen and risk of cardiovascular disease. The Framingham Study. JAMA 258:1183-6.

Karkouti K, Wijeysundera DN, Yau TM, et al. 2004. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 44:1453-62.

Kirmizis D, Tsiandoulus A, Pangalou M, et al. 2006. Validity of plasma fibrinogen, D-dimer, and the von Willebrand factor as markers of cardiovascular morbidity in patients on chronic hemodialysis. Med Sci Monit 12:55-62.

Kestin AS, Valeri CR, Khuri SF, et al. 1993. The platelet function defect of cardiopulmonary bypass. Blood 82:107-17.

Nuttall GA, Oliver WC, Ereth MH, Santrach PJ. 1997. Coagulation tests predict bleeding after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 11:815-23.

Odeberg J, Freitag M, Odeberg H, Rastam L, Lindblad U. 2006. Severity of acute coronary syndrome is predicted by interactions between fibrinogen concentrations and polymorphisms in the GPIIIa and FXIII genes. J Thromb Haemost 4:909-12.

Paparella D, Yau TM, Young E. 2002. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 21:232-44.

Pappalardo F, Della Valle P, et al. 2006. Phosphorylcholine coating may limit thrombin formation during high-risk cardiac surgery: a randomized controlled trial. Ann Thorac Surg 81:886-91.

Rinder CS, Bonan JL, Rinder HM, Mathew J, Hines R, Smith BR. 1992. Cardiopulmonary bypass induces leukocyte-platelet adhesion. Blood 79:1201-5.

Taylor GJ, Mikell FL, Moses HW, et al. 1990. Determinants of hospital charges for coronary artery bypass surgery: the economic consequences of postoperative complications. Am J Cardiol 65: 309-13.

Wabha A, Rothe G, Lodes H, Barlage S, Schmitz G, Bimbaum DE. 1997. Predictors of blood loss after coronary artery bypass grafting. J Cardiothorac Vasc Anesth 11:824-7.

Wan S, LeClerc JL, Vincent JL, DeSmet JM, Barvais L, Goldstein M. 1997. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. Chest 112:676-92.

Woodman RC, Harker LA. 1990. Bleeding complications associated with cardiopulmonary bypass. Blood 76:1680-97.