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Perioperative changes in platelet count and function in patients undergoing cardiac surgery

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Abstract

Background: Patients undergoing cardiac surgery are at increased risk of bleeding due to multifactorial coagulopathies. In the present study, we aimed at investigating the changes in platelet count and function during and after surgery as well as determining the association of the platelet dysfunction with bleeding and transfusion requirements in these patients.

Methods: A total of 40 adult patients scheduled for elective valve coronary cardiac surgery were included in this prospective observational study. Changes in platelet count and function with ADP, acid arachidonic, and collagen (light transmission aggregometry) were analyzed at three time points: before CPB, after CPB, and 24 hours after end of surgery. Postoperative bleeding and intraoperative transfusion requirements were recorded.

Results: There were a significant reverse correlation between CPB time and ADP-induced aggregation, particularly after CPB and postoperative AA-induced aggregation. There was not any significant correlation between platelet count and function at all-time points. Both platelet count and platelet aggregation significantly reduced during CPB. While platelet aggregation increased on postoperative Day 1, platelet count reduced by about 40% after CPB, and remained at this level postoperatively. Patients with abnormal ADP-induced aggregation had significant increased postoperative bleeding and transfusion requirements.

Conclusion: The results of this study demonstrate that platelet count and platelet aggregation are reduced during CPB. Our results emphasized the effect of platelet dysfunction on increased postoperative bleeding and transfusion requirements. Perioperative monitoring of platelet function can be considered as a bleeding management strategy for implantation of PBM programs.

Keywords: Platelet Function Tests, Cardiovascular Surgical Procedures, Hemorrhage, Blood Transfusion

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Introduction

Multifactorial coagulopathies including defects in both primary and secondary hemostasis increase the risk of bleeding and transfusion requirements in cardiac surgery with cardiopulmonary bypass (CPB). Platelets, as the main component of the primary hemostatic system, play a key role in the development of blood clotting process. Several factors such as preoperative treatment with antiplatelet agents, the use of CPB, hemodilution, hypothermia, etc. can influence platelet count and function in patients undergoing cardiac surgery (1-4). Dual antiplatelet therapy, containing mostly aspirin and clopidogrel, has traditionally been used for patients with coronary artery disease (CAD) to reduce the risk of thrombotic events. According to the recommendations, antiplatelet drugs should be discontinued between 5 to 10 days prior to the surgery to ensure the recovery of platelet function (5-9). However, some studies have reported the relationship of aspirin withdrawal with myocardial infarction (10, 11). Various studies have evaluated platelet function in monitoring antiplatelet agents or CPB effects to guide hemostatic therapy (12-14). However, most of these studies include cardiac surgeries with low or medium risk of bleeding. Patients undergoing valve- coronary surgery are at increased risk of bleeding due to extensive tissue injury, considerable CPB and operation time, and use of anticoagulant agents. Nonetheless, there is limited information

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↑What is "already known" in this topic:
Defects in hemostasis system increase the risk of bleeding and transfusion requirements in cardiac surgery with cardiopulmonary bypass (CPB).

→What this article adds:
Platelet count and platelet aggregation are reduced during CPB. Perioperative monitoring of platelet function can be considered as a bleeding management strategy.

about perioperative platelet function in these patients.

Patient blood management (PBM) is a multidisciplinary, evidence-based approach to reduce the need for transfusion and improve patients' clinical outcomes. The use of perioperative preventative strategies to minimize bleeding in surgery is one of the three pillars of the PBM (15-17). Perioperative monitoring of platelet count and function can be helpful in better managing bleeding and transfusion in cardiac surgery. In the present study, we aimed at investigating perioperative changes in platelet count and function and determining the association of platelet dysfunction with postoperative bleeding and transfusion requirements in valve-coronary surgery.

Methods

Patients

After obtaining an institutional review board approval, we enrolled 40 adult patients (20 male (50%), and 20 female (50%) patients) scheduled for elective valve coronary cardiac surgery at Rajaie cardiovascular medical and research center in this prospective observational study between September 2015 and March 2016. Preoperatively, considering the severity of disease, all patients were into class II or class III based on ASA (American Society of Anesthesiologists) and NyHA (New York Heart Association) classification (18). Patients continued the routine prescription with angiotensin converting enzyme, lipid lowering drugs, beta blocker agents, diuretics, and Ca channel blocker until the night before operation. All patients were on aspirin therapy until the operation day, while clopidogrel was discontinued 5 days prior to the operation. Exclusion criteria were age younger than 18 yrs., known bleeding disorder, emergency operation, severe liver or renal dysfunction, and intake of antiplatelet drugs other than aspirin or clopidogrel.

Data Collection

According to the surgery routine, blood samples were obtained before surgery for hemoglobin (Hb) and routine coagulation testing. To assess changes in platelet, count, and function, three time points were selected: after induction of anesthesia (before CPB), 15 minutes after protamine administration after cessation of CPB (after CPB), and 24 hours after end of surgery (post operation). Those values, which were less than the reference value of platelet count and function, were considered abnormal. Chest tube drainage at 24 hours following admission to the intensive care unit (ICU) was recorded as postoperative bleeding volume. Target Hb for RBC transfusion was 8g/dL. Decision to transfuse with FFP and platelet concentrate in patients with ongoing bleeding was made jointly by the anesthetists and the surgeon.

Anaesthesia and Anticoagulation

Patients were kept NPO from the night before operation for 8 hours. All patients were medicated by intramuscular promethazine (50 mg) and morphine sulfate (15 mg) before being transferred to the operating room. Midazolam, sufentanil, and cisatracurium were used for induction of anaesthesia. Maintenance of anaesthesia was done by sevofloran 0.2%, sufentanil, midazolam, and cisatracurium. During anesthesia, the depth of anesthesia was monitored by the routine usage of bispectotal index (BIS) and nerve stimulator. An initial full dose of heparin (300 IU/kg) was administrated before institution of CPB to achieve a target ACT>480. Additional doses of heparin were administrated in cases of ACT<480. After CPB, heparin was reversed with protamine sulfate to achieve a target ACT<130. After the surgery, we provided all patients with patient controlled analgesia (PCA) with morphine (20 mg/24h) to manage the postoperative pain.

Platelet Function Assay

Blood samples were collected in 5-mL tubes containing 0.5 mL 3.2% buffered sodium citrate (0.105M mol/L) (Becton, Dickinson). Assessment of platelet function was performed by Light transmission aggregometry (LTA). The sample tubes were mixed by gentle inversion before analysis. At first, samples were analyzed for platelet count. Then, PRP was obtained by the centrifugation for 10 minutes. Speed of centrifugation was determined according to the baseline platelet count for PRP containing 200- 400 x 10^9/L. Resultant PRP was separated and transferred into polypropylene tubes. Platelet-poor plasma was obtained by the centrifugation of the remaining plasma for 10 minutes at 2499 RCF. Aggregation was measured with a ChronoLog Aggregometer (ChronoLog 700 model, USA) after stimulation with 5 µM of adenosine diphosphate (ADP), 5 µM arachidonic acid (AA), and 0.5 µg/mL collagen (COL). All agonists were provided from Hyphen-biomed (Neuville sur Oise, France). Aggregation curves were recorded after 10 minutes and the percentage (%) of maximal aggregation was reported. According to the recommendation of Hyphen biomed company, we calculated and established the reference value with normal samples for our laboratory. The reference values for healthy adults were 64-96 % for ADP- induced aggregation, 73-100% for AA-induced aggregation, and 78-100% for COL-induced aggregation.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistic 22 for Windows (IBM Inc, Armonk, NY). Kolmogorov–Smirnov test was applied to investigate the normality assumption of the variables. Nominal data were expressed as the percentage, and Pearson Chi square test was used to find the differences between the 2 groups. The results are presented as mean (±SD). Differences in the scale data between the 2 groups were assessed using the student's t test. Repeated measures ANOVA was used to assess perioperative changes in platelet count and function. Correlation between the scales variables was assessed with Pearson's correlation coefficient (r). P-values less than 0.05 were considered statistically significant.

Results

Patient Characteristic

Patient characteristics are presented in Table 1. Baseline platelet count in all patients was within the reference value (150-450x10^9/L). There was a significant reverse

Table 1. Patients Characteristics and the Results of Perioperative Platelet Count and Function Testing

Variables	Mean (SD)
Age(year)	48 (14.1)
Weight(Kg)	75 (17)
Hb(g/dl)	12.9 (1.7)
INR	1.5 (0.5)
Duration of CPB (min)	106 (33)
Platelet count (x 10 ^{9}/L)	
Baseline platelet count	224 (37)
Before CPB	196 (36)
After CPB	134 (29)
Postoperative	137 (31)
ADP-induced aggregation (%)	
Before CPB	56 (23)
After CPB	44 (22)
Postoperative	47 (22)
AA-induced aggregation (%)	
Before CPB	54 (37)
After CPB	38 (32)
Postoperative	39 (27)
COL-induced aggregation (%)	
Before CPB	59 (28)
After CPB	49 (28)
Postoperative	54 (19)

Abbreviation: Hb, Hemoglobin; INR, International normalized ratio; CPB, cardiopulmonary bypass; ADP, Adenosine diphosphate; AA, Acid arachidonic; Col, Collagen

correlation between CPB time and ADP-induced aggregation, particularly after CPB (r = -0.71, p< 0.001) and postoperative AA-induced aggregation (r= -0.56, p< 0.001). The results of the analyses did not show any significant correlation between CPB time and Col-induced aggregation at any time points. Weight and age were not associated with any of the platelet function tests.

Perioperative Changes in Platelet Count and Function

The results of perioperative platelet count and function testing are demonstrated in Table 1. Of the total of 160 analyses, platelet count less than 100x10^9/L were observed in only 2 (1.6%) and 5 (4.2%) patients after CPB and on the first day after surgery, respectively. Platelet count reduced significantly during surgery, especially after CPB (p< 0.001). Overall, platelet count was reduced by 37 (39%) post operation compared with the baseline platelet count.

Time course of platelet aggregation in the ADP test, AA test, and COL test is shown in Fig. 1. Platelet aggregation in response to all agonists was significantly reduced after CPB compared with before CPB (p< .005). Postoperative ADP-induced aggregation significantly increased but did not reach baseline level (p< 0.05). No significant increase was observed in AA- and Col-induced aggregation after operation (p< 0.05).

The Relationship between Platelet Count and Function

Platelet count showed a poor correlation to the platelet function for ADP-induced aggregation before CPB

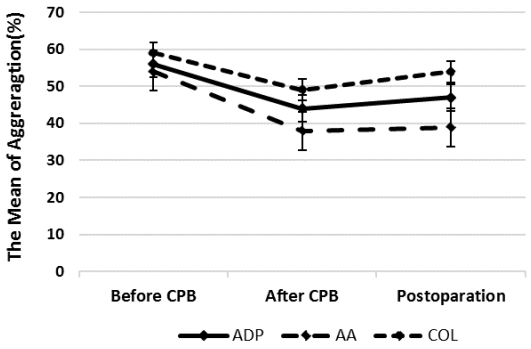

Fig. 1. Perioperative changes in platelet aggregation. Platelet aggregation was analyzed by 3 agonists at 3 time points (before CPB, after CBP, and post operation). In all experiments results were expressed as the mean of maximum percentage of aggregation ± SD. The mean of platelet aggregation was significantly reduced after CPB in response to all agonist versus before CPB (p<0.05). Postoperative platelet aggregation significantly increased in ADP-induced test versus after CPB (p<0.05). Postoperative increase in platelet aggregation was not significant in AA- and Col-induced aggregation tests (p>0.05).

(r=−0.31, p= 0.047). No significant correlation was found between platelet count and function for AA- and COL- induced aggregation at all-time points. Preoperative platelet count did not correlate with platelet aggregation at any time points.

Postoperative Blood Loss and Transfusion Requirements

Table 2 demonstrates the percent of patients with abnormal platelet function in response to each agonist at all-time points. Platelet aggregation was below the reference range in more than half of the patients before CPB. The number of patients with abnormal aggregation increased after CPB in all three platelet function tests. We compared the mean of postoperative bleeding volume between patients with normal and abnormal platelet aggregation. The results revealed that patients with abnormal function in ADP-induced aggregation testing had a more significant postoperative bleeding compared to patients with normal function in this test (646±539 mLvs. 158±147mL, p<0.05). Although the mean of postoperative bleeding volume was higher in patients with abnormal function in AA- and COL- induced aggregation testing compared with patients with normal function in these measurements (584±561mL vs. 368±400mL, and 608±528 mL vs. 316±429 mL, respectively), these increases were not statistically significant (p> 0.05) (Fig. 2).

Transfusion frequencies are summarized in Table 3. Perioperatively, 23 (57.5%) patients received blood products, 21 (52.5%) received RBC, 12(30%) FPP, and 8 (20%) platelet concentrate. Figure 3 displays transfusion

Table 2. Number and Percent of Patients with Abnormal Platelet Function

	Before CPB	After CPB	Post Operation
ADP-induced aggregation	28(70%)	34(85%)	32(80%)
AA-induced aggregation	23(58%)	32(80%)	31(78%)
COL-induced aggregation	25(63%)	28(74%)	34(85%)

Abbreviation: CPB, cardiopulmonary bypass; ADP, Adenosine diphosphate; AA, Acid arachidonic; Col, Collagen

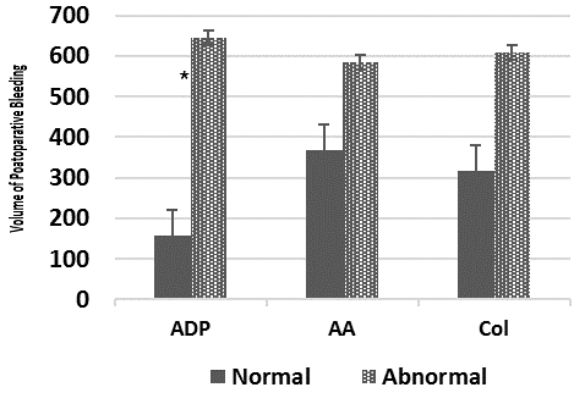

Fig. 2. Comparison of postoperative bleeding volume between normal and abnormal patients in ADP-, AA-, and COL-induced aggregation testing. Data were expressed as mean ±SD. *P<0.05 was considered as significant.

Table 3. Transfusion Requirements Values are expressed as absolute number (percentage) or mean±SD.

Total number of transfused patients	23 (57.7%)
Transfusion with RBC (n)	21 (52.5%)
Transfusion with Platelet concentrate (n)	8 (20%)
Transfusion with FFP (n)	12(30%)
The volume of blood products	
RBC	269±350 ml
Platelet concentrate	350±602 ml
FFP	30±65 ml

Abbreviation: RBC, Red Blood Cell; FFP, Fresh frozen plasma

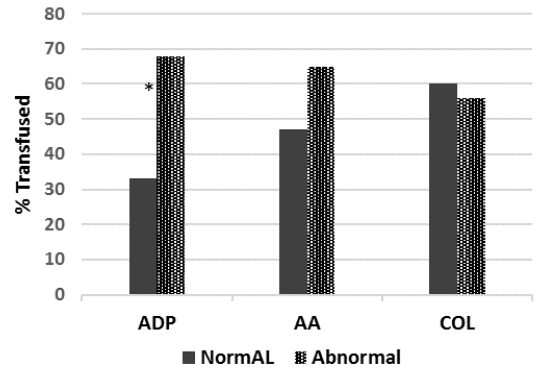

Fig. 3. Prevalence of perioperative transfusion in normal or abnormal patients in ADP-, AA-, and COL-induced aggregation testing. Data were expressed as the percentage of patients transfused. *P<0.05 was considered as significant.

prevalence for patients with normal or abnormal ADP-, AA-, and COL- induced aggregation testing. In patients with abnormal ADP-induced aggregation, transfusion prevalence was 67.9% compared with 33% in patients with normal aggregation (p<0.05). As the figure shows, the differences between groups were not statistically significant in AA- and COL-induced aggregation (65% vs. 45% and 56% vs. 60%, respectively, p> 0.05).

Discussion

A variety of studies have evaluated the platelet function in cardiac surgery (19-22). Here, we focused on the perioperative platelet count and function changes in response to ADP, acid arachidonic, and collagen agonists, as well as their relationship with bleeding and transfusion requirements in valve coronary surgery.

In this study, the baseline platelet count was normal in all patients. In contrast to some previous studies reporting that platelet count and function are associated; our results did not show any significant association between platelet count and aggregation in all- time points (23, 24). We found that both platelet count and aggregation reduced significantly during CPB. Although platelet aggregation increased 24 hours after surgery, we did not observe any significant increase in platelet count. In fact, platelet count reduced by about 40 % after CPB compared with before CPB and remained at this level 24 hours after surgery. These results confirm those of the previous studies reporting a 50% reduction in platelet count during CPB (24-26). Furthermore, similar to other studies, our results showed that platelet function recovered rapidly one day post operation, but it did not reach baseline level (24, 25, 27, 28). However, a slow recovery of platelet aggregation was observed in children (12, 28).

Our results revealed that CPB affects the ability of platelets for aggregation. It is likely that contact of platelets with CPB circuit induces some changes in the expression of molecules involved in adhesion and aggregation or signaling pathway. Furthermore, this issue may be due to the inhibiting effects of heparin on thrombin as the main activator of platelets during CPB.

Based on the traditional recommendations, antiplatelet drugs should be discontinued between 5 to 10 days prior to high bleeding risk procedures (5, 7, 29). Price et al. reported the recovery of platelet function in 75% of patients with coronary diseases by 5 days after cessation of clopidogrel (30). Furthermore, Manach et al. reported highly individual variable platelet recovery after clopidogrel withdrawal in patients undergoing major vascular surgery (31) . In our study, although clopidogrel was discontinued 5 days before surgery, the platelet aggregation was abnormal in more than half of the patients in response to all agonists, especially ADP before CPB. We found that bleeding and transfusion prevalence were higher in patients with abnormal aggregation compared to patients with normal aggregation. However, in contrast to reports of pediatric cardiac surgery, these differences were statically significant only in cases of abnormal ADP-induced aggregation (24). Interestingly, despite the continuation of aspirin until the day of surgery, bleeding and transfusion were not significantly associated with abnormality in AA-induced aggregation. Light transmission aggregometry using ADP agonist is considered as a reference method to evaluate residual platelet reactivity (RPR) in high-risk patients on clopidogrel treatment (32-34).Our results combined with those of the other studies suggested that a 5- day waiting period for surgery after clopidogrel withdrawal is not enough to reach optimal platelet function and it is also associated with risk of bleeding (21).

In conclusion, many studies have been conducted with the aim of optimizing bleeding to reduce the need for transfusion in various types of surgery (35-38). Our results emphasized perioperative changes in platelet function and considerable association between platelet dysfunction and

increased bleeding, as well as increased transfusion requirements in patients undergoing valve coronary surgery. Because of the critical role of the platelet in hemostasis, we recommend perioperative evaluation of platelet function to manage bleeding in these patients. Perioperative monitoring of platelet function can be considered as a bleeding management strategy for implantation of PBM programs.

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Conflict of Interests

The authors declare that they have no competing interests.

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