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Ankaferd Blood Stopper Decreases Postoperative Bleeding and Number of Transfusions in Patients Treated with Clopidogrel: A Double-blind, Placebo-controlled, Randomized Clinical Trial

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ABSTRACT

Background: The risk of reoperation due to bleeding after open heart surgery is 2.2%-4.2%. Extracorporeal circulation and emergency operations are the important risk factors. In coronary artery bypass graft (CABG) patients who are treated preoperatively with antiplatelets plus clopidogrel are the sources of postoperative bleeding. The aim of this study was to research the effect of local Ankaferd blood stopper (ABS) to prevent mediastinal bleeding in on-pump CABG patients who were treated with clopidogrel and acetylsalicylic acid (ASA) preoperatively.

Methods: Twenty-five emergency CABG patients premedicated with clopidogrel and ASA were included in the study (Group 1). An additional twenty-five patients who were premedicated with the same antiplatelet agents were selected as a control group (Group 2). At the end of the surgery, 4-10 mL of ABS solution was applied on the mediastinal and epicardial tissue following protamine administration in Group 1. We compared postoperative total mediastinal bleeding, reoperation rate and total blood and blood products transfused between the two groups.

Results: There was no mortality in either of the two groups. Mean postoperative bleeding was 430 mL in the ABS group, and 690 mL in the CG group (P = .044). In the ICU, bleeding in groups 1 and 2 was 610 mL and 980 mL, respectively (P = .025); total bleeding from the mediastinum was 830 mL and 1490 mL, respectively (P = .001) and the amount of autotransfusion was 210 mL and 400 mL (P = .003). Total transfusion of PRBCs in the operating room in groups 1 and 2 was 0.3 and 0.8, respectively (P = .003). No patients in the ABS group needed surgical revision due to severe bleeding or cardiac tamponade.

Conclusion: The use of local ABS reduces bleeding, transfusion requirements of packed red blood cells, platelets and total blood units in patients premedicated with clopidogrel and ASA undergoing emergent CABG .

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INTRODUCTION

The risk of reoperation due to mediastinal bleeding after cardiac surgery is 2.2%-4.2% [Wallentin 2000; Yende 2001; Yusuf 2001; Steinhubl 2002]. Risk factors include older age, low body mass index, time on extracorporeal circulation, five or more anastomoses and non-elective operations [Wallentin 2000; Yende 2001; Steinhubl 2002]. Re-operated patients have a two to six times greater mortality rate [Wallentin 2000; Yende 2001; Yusuf 2001; Steinhubl 2002] and greater morbidity from compromised renal and pulmonary function, sepsis and arrhythmias [Wallentin 2000; Yende 2001; Yusuf 2001; Hongo 2002; Steinhubl 2002]. In addition, re-exploration is associated with deep and superficial wound infections. Postoperative bleeding can be due to surgical bleeding or coagulopathy [Yusuf 2001].

Antiplatelet therapy, such as aspirin and clopidogrel, is frequently used preoperatively in a number of unstable patients with coronary artery disease who will undergo CABG. The use of antifibrinolytic drugs has resulted in an increased incidence of postoperative bleeding. Bleeding from the mediastinum after open heart surgery is one of the primary postoperative complications. The most recent ACS guidelines make early clopidogrel treatment a Class I recommendation. However, caution must be exercised in the decision to administer clopidogrel to patients scheduled to undergo surgical revascularization. Current guidelines support the discontinuation of clopidogrel 5 to 7 days before elective CABG; more urgent surgery, if necessary, can be performed by experienced surgeons if the increased bleeding risk is acceptable.

Ankaferd blood stopper is composed of a standardized mixture of the plants Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum and Urtica dioica. Each of these individually have some effect on the endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics and mediators [Royston 1987; Alderman 1998]. However, the basic mechanism of action for the hemostatic effects of ABS

Table 1. Baseline Characteristics and Operative Data

	ABS(n =25)	PG	*P*
Male/female	19/6	18/7	.74
Age (years)	54.2 (48.6–69.8)	56.4 (49.3–63.5)	.89
Last clopidogrel intake before surgery			
< 24 hours	10	9	.96
≥ 24 < 48 hours	15	16	.96
The mean time between the last administration of clopidogrel(h)	5	6	.32
Aspirin	25	25	
Low-molecular-weight heparin	23	21	.89
Hemoglobin (g/L)	123 (109–134)	130 (114–139)	.94
Operative risk evaluation			
Number of grafts	3.4 (2.6–3.9)	3.7 (3.1–4.3)	.59
Saphenous vein	2.7 (2.2–3.2)	2.3 (1.7–3.0)	.37
Left internal thoracic/ radial artery	1.3 (1.0–1.4)	1.4 (1.0–1.6)	.70
Surgery (minutes)	161 (155–192)	175 (139–202)	.06
Cardiopulmonary bypass (minutes)	88 (65–94)	93 (72–104)	.78
Aortic cross-clamping (minutes)	51 (42–61)	53 (39–59)	.61

Data presented as mean with 95% confidence intervals, or number.

Table 2. Postoperative Data

	ABS Group (n =25)	Control Group (n =25)	*P*
Early mortality	0	0	1.0
Reoperation(%)*	0	5(20%)	.036
Creatine kinase-MB, post-operative day 1 (μg/L)	41 (19–64)	44 (26–63)	.91
Troponin-T, postoperative day 1 (μg/L)	0.51 (0.23–0.55)	0.64 (0.34–0.66)	.93
Time to extubation (hours)	6.6 (4.5–10.1)	11.5 (6.9–16.1)	.023
Hemoglobin at discharge (g/L)	121 (96–139)	113 (92–119)	.74
Length of intensive care unit stay (hours)*	17 (15–23)	36 (19–49)	.001
Length of hospital stay (days)*	5.8 (5.2–7.2)	8.4 (5.8–9.3)	.034
Stroke	0	0	1.0
Q-wave infarction	0	0	1.0
Atrial fibrillation	3	4	.940

*Data presented as mean with 95% confidence interval, or number.

is currently unknown. In 2008 Goker and colleagues investigated the basic mechanism of Ankaferd Blood Stopper (ABS) as a new hemostatic drug. They demonstrated that ABS induces a very rapid (< 1 sec) formation of a protein network within the plasma and serum; consecutive measurements showed that individual clotting factors were not affected. In our previous study, we clearly showed that ABS use after off-pump CABG patients decreased postoperative bleeding [Atalay 2015]. Thus, we researched the anticoagulant effects of ABS during surgery in on-pump CABG patients.

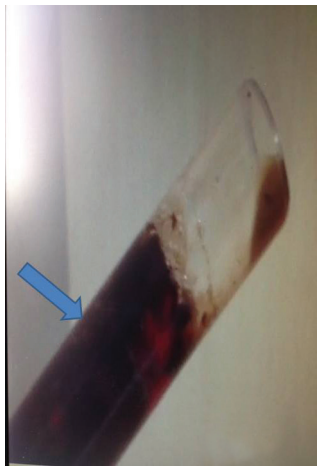
MATERIALS AND METHODS

After the ethics committee approval of the study, informed consent was signed by the patients. Twenty-five consecutive patients at our hospital with unstable angina unsuitable for percutanous coronary intervention who were scheduled for urgent or acute CABG were included. All patients were given an oral starting dose of 600 mg clopidogrel and 300 mg ASA. Only patients in whom oral clopidogrel treatment had been discontinued < 5 days before surgery were eligible. Blood platelet counts, activated partial thromboplastin time (aPTT), international normalized ratio (INR), activated coagulation time (ACT) and bleeding time (BT) were measured preoperatively. Patient history included bleeding and bleeding disorders. Patients with chronic renal failure, bleeding disorders (von Willebrand disease, hemophilia) and chronic obstructive pulmonary disease were excluded from the study. The preoperative characteristics of the patients are summarized in Table 1. When we compared the patient characteristics, there was no statistical difference between the two groups. There were no differences in the ACT values between the groups before and after heparin administration, and no difference was found in the total dose of heparin and protamine given between the two groups (Table 2). Mediastinal drainage was measured postoperatively at hourly intervals in the intensive care unit. The ICU team was not informed about the bleeding control measures and ABS use.

The effect of ABS in heparinized blood is demonstrated in Figures 1, 2 and 3. After in vitro ABS application a microscopic examination demonstrated erythrocyte aggregation (Figure 4). Mean postoperative bleeding is shown in Figure 5. The total blood transfusions and blood products, including PRBCs, plasma and platelets given is shown in Figure 6.

OPERATIVE TECHNIQUE

All operations were performed under cardiopulmonary bypass (CPB). After median sternotomy, aortic and single venous cannulas were placed, patients were heparinized (300 U/kg) and CPB was initiated under moderate hypothermia. The saphenous vein and left internal thoracic artery were used as conduit in all patients. The aorta was cross



Figures 1 and 2. After application of ABS rapid coagulation of heparinized blood from the fully heparinized CABG patient (ACT level 560). Thrombus formation is constituted immediately after Ankaferd injection into the tube.

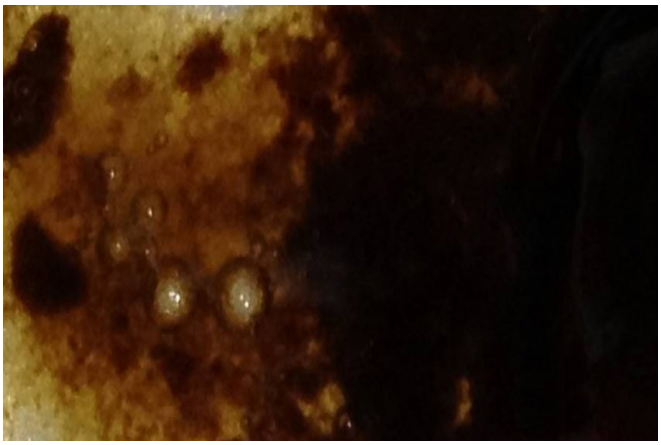


Figure 3. Thrombus formation removed from the tube.

clamped for distal coronary anastomosis. Proximal anastomoses were made using an aortic side clamp. All patients were weaned from CPB uneventfully. For neutralization of heparin, protamine sulphate® was administered. Electrocautery and hemoclips were used for bleeding control from the peripheral tissue. After the completion of the CABG procedure, a 4-10 mL Ankaferd solution was sprayed over the mediastinum including over the ITA and epicardium via a simple rapid ejection method using a syringe. Protein network formation was clearly seen immediately after the use of ABS and bleeding was easily controlled in every patient. Ankaferd was also applied to epicardial fat and aortic and atrial cannulation sites. Chest tubes were inserted into the mediastinum and left thorax, and the sternotomy incision was re-approximated using surgical steel wire. Postoperative coagulation test results, including ACT, hemoglobin and hematocrit, INR, platelet counts, and PTT were recorded for each patient every 8 hours during ICU follow-up. There

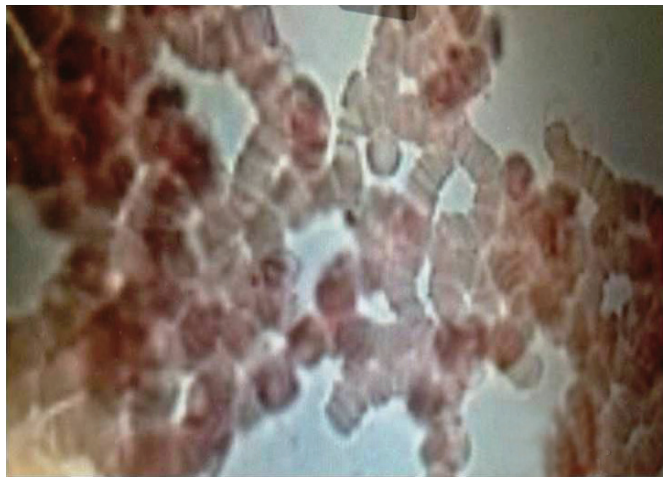


Figure 4. Microscopic examination of erythrocyte aggregation after in vitro ABS application.

was no statistical difference between the two groups in results of coagulation tests and platelet counts. The amount of mediastinal bleeding and the amount of PRBC and blood products transfusion were compared in both groups. The decision to perform resternotomy was based on conventional guidelines: 1) chest tube drainage of > 500 mL in the first hour; total drainage of > 800 mL in the first 2 h; > 900 mL in the first 3 h; >1,000 mL in the first 4 h or > 1,200 mL in the first 5 h and 2) sudden massive bleeding or cardiac tamponade. Postoperative measurements of bleeding from the mediastinum, the amount of PRBC transfusion, aortic cross clamp time, and the number of bypass grafts are summarized in Table 3.

STATISTICAL ANALYSIS

Variables are reported as mean ± and 95% confidence interval (CI). Differences were considered significant at $P \leq .05$. Wilcoxon test was used for comparison of repeated measurements. The chi-square test was used for categorical variables. For continuous variables, we used either the Student t test or the Mann-Whitney U test depending on whether the data were normally distributed. The relationships between different treatment variables were assessed before and during regression analysis. The correlation was assessed by using the Pearson correlation coefficient. If the correlation coefficient between 2 variables was > 0.7 and statistically significant, then only one of the variables was used in the regression model. The primary outcomes of the study were assessed by univariate analysis, followed by logistic regression analysis, to identify independent predictive variables from the categorical and continuous variables. Potential confounders were entered into models if they were clinically relevant or showed statistical significance at $P \leq .05$ during the univariate analysis between the two groups. We also used the propensity scores risk adjustment method to adjust baseline characteristics and/or clinical factors that could impact the decision to give patients clopidogrel and ASA. All analyses were performed

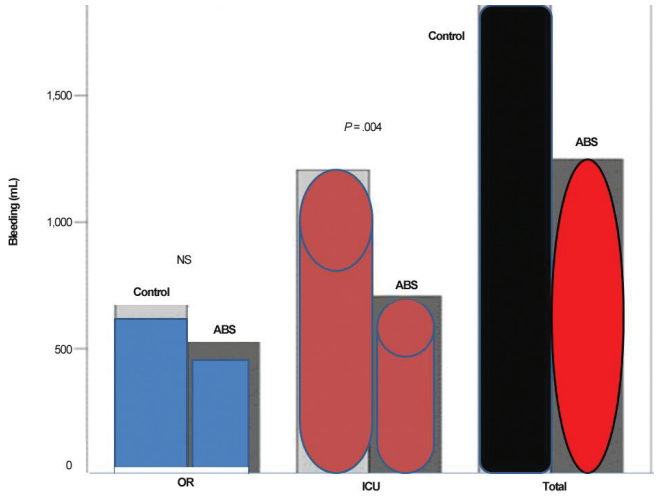


Figure 5. Mean postoperative bleeding (95% confidence interval) in patients undergoing CABG and randomized to treatment with ABS or saline.

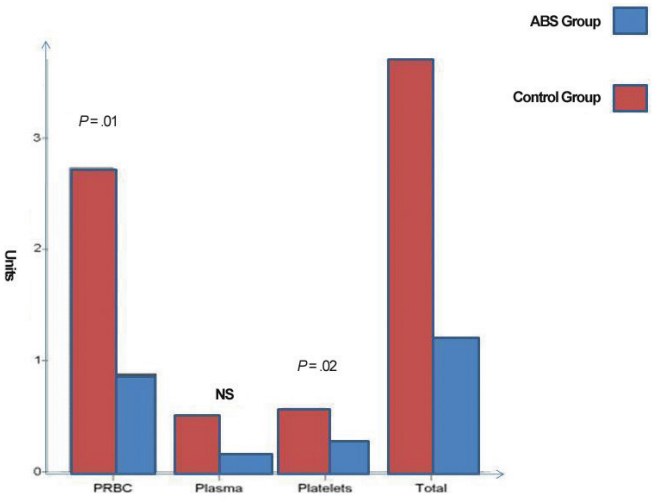


Figure 6. Transfusions during the hospital stay (operating room, ICU and total) in patients randomized to treatment with ABS or saline (95% confidence interval).

using SPSS version 15.0 (SPSS, Inc., Chicago, Illinois), and STATA (STATA Corp., College Station, Texas).

RESULTS

There was no mortality in either of the two groups due to any reason. No re-operations were performed in the ABS group. The mean amount of bleeding after operation was 430 mL in ABS group, and 690 mL in the CG (P = .044). In ICU, bleeding in the ABS and control groups was 610 mL and 980 mL, respectively (P = .025). Total bleeding from the mediastinum was 830 mL and 1490 mL in the ABS and CG groups, respectively (P = .001). Autotransfusion was 210 mL in the ABS group and 400 mL in the CG (P = .003). Total

Table 3. Bleeding and Transfusiona

	ABSG (n = 25)	CG (n = 25)	P
Bleeding (mL)			
Operating room*	230 (270–510)	230 (270–510)	.023
Intensive care unit*	400 (360–540)	750 (620–1200)	.025
Total*	630±280	1200±440	.001
Autotransfusion (mL)	210 (120–430)	400 (280–620)	.001
Transfusions (U), (Operating room)			
PRBC*	0.3 (0–0.9)	0.8 (0.2–1.1)	.003
Plasma*	0 (0–0.2)	0.7(0.4-1.6)	.36
Plateletsb	0.3 (0.2–0.6)	1.2 (0.9–1.4)	.21
Transfusions (U) (intensive care unit)			
PRBC*	0.3 (0–0.6)	1.5 (0.3–2.6)	.03
Plasma*	0	0.5 (0–1.0)	.036
Platelets†	0.1 (0–0.2)	0.4 (0–0.7)	.021
Transfusions (U), (total)			
PRBC*	0.7 (0.2–1.1)	2.4 (1.1–4.1)	.001
Plasma*	0.1 (0–0.3)	1.4 (0.5–2.2)	.004
Platelets†	0.2 (0–0.4)	1.9 (0.6–1.3)	.002
Total blood products (U)*	1.0 (0.1–2.1)	3.9 (2.2–6.3)	.002

PRBC = packed red blood cells.
*Data presented as mean and 95% confidence interval.
†One unit is equal to 500 mL from 6 donors.

transfusion of PRBCs in the operating room in ABS group and control groups was 0.3 and 0.8, respectively (P = .003). The mean transfused plasma and platelets in the ABS group was 0.0 and 0.1; in the CG these were 0.5 and 0.4 (P values of transfused plasma and platelets for group 1 and group 2 were .36 and .21). Transfusions of PRBC in ICU for the ABS and CG was 0.4 and 1.8, respectively (P = .003). In ICU, the mean amount of transfused plasma was 0.0 and 0.5 in ABS and CG, respectively (P = .036). In ICU, the mean platelet transfusion in ABS and CG groups was 0.1 and 0.4 units, respectively (P = .021). Total transfusions of PRBCs in the ICU in ABS group and CG group was 0.7 and 2.4 (P = .001). Total blood products in ABS group 1.1, and 3.9 in control group (P = .002). A summary of the postsurgical bleeding from the mediastinum in different periods and amount of transfusions of various blood products is given in Table 3.

No patient needed surgical revision due to severe bleeding or cardiac tamponade in the ABS group. Seven patients (28%) from group 1 and 16 patients (64%) from group 2 required blood transfusions (P = .001). In group 2, five patients (20%) required surgical re-exploration due to cardiac tamponade as a result of mediastinal hemorrhage in the early postoperative period. There was no evidence of

surgical bleeding requiring suture or hemoclips in these patients. In the ABS group, the mean hematocrit was 22 ± 2, and blood products and/or PRBCs were administrated in 9 of these patients (36%). In the control group, the mean hematocrit in 9 patients postoperatively was 19 ± 3. A total of 19 patients (76%) required PRBC transfusion in the early postoperative period.

DISCUSSION

Because our previous study showed positive effects of ABS use in our off-pump CABG surgery [Atalay 2015], we evaluated whether it has positive effects or not during on-pump CABG patients. We presented the effects of ABS use on bleeding from mediastinum and transfusion requirements in urgent on-pump emergent CABG patients who were treated with high dose clopidogrel plus aspirin within 5 days prior to surgery.

Ankaferd blood stopper is composed of a standardized mixture of the plants Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum, and Urtica dioica. All of these plants individually have some effects on the endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics and mediators [Royston 1987; Alderman 1998]. However, the basic mechanism of action for the hemostatic effects of ABS is currently unknown. Three Ankaferd phase III studies [Goker 2008; Al 2009; Meric 2010] on vascular port insertion bleeding, anterior epistaxis, and post-tonsillectomy hemorrhage have led to its approval as a hemostatic agent. Experimental studies have set the preclinical stage for the development of this hemostatic product [Teker 2009; Kalayci 2010]. The hematological and biochemical safety of systemic administration of Ankaferd to rabbits has previously been reported. Acute mucosal toxicity, hematotoxicity, hepatotoxicity, nephrotoxicity, and biochemical toxicity were not observed in the follow-ups of the animal or human studies [Chen 2004; Al 2009; Cipil 2009].

Since 2007, ABS has been increasingly used topically after or during gastrointestinal tract bleeding, bronchial hemorrhage and severe hemoptysis, and dental surgery in Europe and Asia. Since individual clotting factors, namely coagulation factors V, VII, VIII, IX, X, XI, and XIII, are not affected in the network formation, the possible driver for hemostasis is based on protein agglutination. Erythrocytes and platelets have been shown in the network formation. A possible hypothesis is that the development of the ABS network of might involve the entire physiological hemostatic process without unequally affecting individual clotting factors. Biochemical tests also revealed that total protein, albumin, and globulin levels significantly decreased with the interactions of ABS. Red blood cells form vital erythrocyte mass blocks in the presence of ABS [Ulus 2011]. The basic mechanism of action for ABS appears to be the formation of an encapsulated protein network for erythrocyte aggregation.

We know that with interventional angiography clinicians are frequently using high doses of clopidogrel along with 300 mg oral aspirin and additional anticoagulants. Clopidogrel and aspirin affect platelet function and result in increased bleeding time in these patients. Therefore, we hypothesized that the use of local ABS solution in our 25 urgent CABG patients would decrease the possibility of re-exploration resulting from cardiac tamponade due to excessive mediastinal bleeding. To provide blinded study protocol, we did not inform ICU personal or our colleagues about the ABS application protocol in either group. There was a > 2.5 fold increase in blood product transfusions in the control group compared to the ABS.

Kalayci et al. (2010) reported the intraabdominal hemostatic effect of ABS in an experimental liver injury in rat models. They suggested that the use of ABS shortened hemorrhage from experimental liver injury. In another study published in 2009, Cipil and collegues have shown that the amount of bleeding after ABS administration to amputed legs decreased by 53.8% in warfarin-treated group in animal models. Previous published research has clearly demonstrated that ABS is effective in producing local hemostasis, and may provide a therapeutic potential for the management of patients with deficient primary hemostasis. Ulus and colleagues in 2011 published a report on the surgical and histopathological efficacy of topical ABS used for major arterial vessel injury. They found that vessel lumens were enriched with erythrocyte aggregates following ABS administration. Uzun and collegues (2014) demonstrated successful application of ABS in 23 of 25 bronchoscopy procedures for bronchial hemoptysis. Endobronchial local application of ABS was effective in the management of bronchial bleeding in patients with endobronchial malignant lesions. Ozaslan et al. (2011) had success with topical application of ABS in four patients with severe gastric and duodenal varices. In two separate studies, Beyazit et al. and Kurt and collegues reported successful use of ABS in patients with gastrointestinal bleeding [Kurt 2010; Beyazit 2011]. Another study by Kurt and collegues in 2010 reported success with ABS use in 26 patients with benign lesions of the gastrointestinal tract. The authors suggested that ABS should be considered as a primary treatment or as an adjuvant to conventional modalities to control gastrointestinal bleeding. In CABG patients who were treated with high doses of antiplatelets and anticoagulants, bleeding sometimes cannot be controlled with current conventional methods, even during re-operations, when the focal surgical bleeding point cannot be found and bleeding is massive and originates from the surrounding tissues. Therefore, we advocate for the use of the local ABS in these particular patients.

Several nonrandomized studies have demonstrated benefits of the use of clopidogrel in acute coronary syndrome [Fox 2004]. In a 2002 paper, Hongo and collegues investigated the effects of preoperative clopidogrel in combination with aspirin on CABG outcomes of 224 patients and found higher postoperative bleeding and morbidity in those patients premedicated before surgery. Chen et al. (2004) found that clopidogrel use prior to CABG is associated with increased blood loss and reoperation rates, requiring the use of blood products in these patients.

With urgent cardiac surgery after coronary intervention, excessive bleeding induced by clopidogrel and aspirin is also an issue. It is known that blood transfusion during and after cardiac surgery is associated with increased hospital morbidity

and mortality due to infectious complications, and longer ICU stays and hospitalization [Schreiber 1996]. The recently published Atalay study demonstrated that the use of ABS during on-pump CABG surgery was an effective approach to inhibit bleeding from mediastinum [Atalay 2015]. Therefore, in our opinion, ABS should be considered in this context. Our study showed that intraoperative use of ABS decreases postoperative mediastinal bleeding and transfusion requirements in urgent CABG patients treated with high dose clopidogrel in combination with aspirin within 5 days prior to surgery.

CONCLUSION

Current guidelines recommend discontinuing clopidogrel for at least 5 days before elective CABG, and at least 24 hours before urgent CABG, to reduce major bleeding complications. However, emergency CABG surgery is inevitable in some cases of acute coronary syndrome. In cardiovascular surgery, major postoperative bleeding is a significant complication that leads to morbidity, mortality and longer hospitalization and ICU stays. Our study demonstrated that a significant reduction in bleeding and requirement for transfusion can be achieved with the use of ABS in CABG patients premedicated with a high dose of clopidogrel.

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