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Efficiency of Preoperative Tranexamic Acid in Coronary Bypass Surgery: An Analysis Correlated with Preoperative Clopidogrel Use

Sahin Senay,[1] Fevzi Toraman,[2] Hasan Karabulut,[1] Cem Alhan[1]

Departments of [1]Cardiovascular Surgery and [2]Anesthesiology, Acıbadem University School of Medicine, Istanbul, Turkey

ABSTRACT

Objective: This study evaluates the efficiency of prophylactic tranexamic acid in coronary bypass surgery with respect to preoperative clopidogrel use.

Methods: We analyzed data for 3754 consecutive patients who underwent isolated coronary bypass surgery with cardiopulmonary bypass between January 1999 and August 2008. The patients were placed into 4 groups according to the perioperative use of clopidogrel and tranexamic acid. Group 1 included patients administered neither of these medications (n = 3160, 84.2%); group 2 included patients who received tranexamic acid only (n = 444, 11.8%); group 3 included patients who received clopidogrel only (n = 113, 3.0%); and group 4 included patients who received both medications (n = 37, 1.0%).

Results: In patients who received tranexamic acid, we noted significant decreases in postoperative drainage (615 ± 336 mL versus 458 ± 289 mL, group 1 versus group 2 [P = .0001]; 740 ± 399 mL versus 570 ± 408 mL, group 3 versus group 4 [P = .03]) and the use of fresh frozen plasma (1.4 ± 1.4 units/patient versus 0.2 ± 0.7 units/patient, group 1 versus group 2 [P = .0001]; 2.2 ± 1.7 units/patient versus 0.5 ± 1.3 units/patient, group 3 versus group 4 [P = .0001]), irrespective of the use of clopidogrel. We found significant decreases in postoperative blood transfusion (0.59 ± 1.1 units/patient versus 0.39 ± 1.1 units/patient, group 1 versus group 2 [P = .0001]; 1.2 ± 1.8 units/patient versus 0.7 ± 1.1 units/patient, group 3 versus group 4 [P > .05]) and in the percentage of patients who received transfusions (31.3% versus 19.3%, group 1 versus group 2 [P = .0001]; 54.5% versus 37.8%, group 3 versus group 4 [P > .05]) only in the patients who did not receive clopidogrel.

Conclusion: Prophylactic tranexamic acid reduces bleeding and the need for transfusion. This effect exists in patients using clopidogrel but is less prominent. Preoperative use may be beneficial in patients using clopidogrel without any need for delaying the surgical procedure.

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Correspondence: Sahin Senay, Department of Cardiovascular Surgery, Acıbadem Maslak Hospital, Istanbul, Turkey; +90-533-310-52-02; fax: +90-216-325-87-59 (e-mail: sahinsenay@gmail.com).

INTRODUCTION

Postoperative bleeding in cardiac surgery is related to increased transfusion rates and an adverse outcome. Different factors, including advanced age, increased preoperative creatinine level, low body surface area, emergency surgery, low temperature on bypass, duration of cardiopulmonary bypass (CPB), and preoperative anticoagulant therapy, have been reported to contribute to the likelihood of excessive bleeding [Sellman 1997; Skubas 2001; Parr 2003; Hartman 2006].

Platelets play an important role in hemostasis, and platelet dysfunction is considered a major pathophysiological cause of postoperative nonsurgical bleeding [Woodman 1990]. During CPB, hemodilution caused by the priming volume of the system leads to a decrease in the platelet count. The concurrent adhesion, activation, and mechanical destruction of platelets may cause severe hemostatic dysfunction. Moreover, CPB contributes to this pathology by decreasing coagulation factors and activating fibrinolysis [Hartman 2006].

An antiplatelet drug, clopidogrel, is commonly used in acute coronary syndromes and coronary stenting. It produces a dose- and time-dependant inhibition of platelet aggregation, with a maximum of 40% to 60% inhibition of aggregation reached after 3 to 5 days. After discontinuation of the drug, platelet function gradually increases, and recovery is seen 5 to 7 days after the last clopidogrel dose. Bleeding time is significantly prolonged with clopidogrel. It has an irreversible action and has no specific antidote [Fox 2004].

Tranexamic acid (*trans*-4-aminomethylcyclohexane-1-carboxylic acid), a synthetic lysine analog, reversibly binds to the lysine-binding site on plasminogen, thus inhibiting the conversion of plasminogen to plasmin and inhibiting fibrinolysis. Administration of tranexamic acid decreases blood loss and blood transfusion requirements in cardiac surgery patients [Mannucci 1998].

There is a clear recommendation for clopidogrel use in special coronary pathologies; thus, patients with either acute coronary syndrome or previous stent implantation and who have been anticoagulated with clopidogrel have increasingly been referred for coronary surgery in recent years [Yusuf 2001; King 2008; Pollack 2008]. The routine recommendation for this group of patients is discontinuation of the drug 5 or more days before surgery when the clinical situation permits it [Eagle 2004]; however, there is a subgroup of patients

Table 1. Comparison of Demographics and Perioperative Variables for the Groups*

	No Clopidogrel (n = 3604)			Clopidogrel (n = 150)		
	No Tranexamic Acid (n = 3160, 84.2%; Group 1)	Tranexamic Acid (n = 444, 11.8%; Group 2)	*P*	No Tranexamic Acid (n = 113, 3.0%; Group 3)	Tranexamic Acid (n = 37, 1.0%; Group 4)	*P*
Age, y	60.5 ± 9.5	62.1 ± 10.0	.001	61.2 ± 9.9	57.4 ± 11.0	.050
Age >65 y, %	32.5	39.2	.006	36.3	18.9	NS
CCS class ≥3, %	33.8	39.2	.0001	43.4	48.6	NS
NYHA ≥3, %	7.4	14.5	.0001	8.9	10.8	NS
Male sex, %	77	75	NS	73	89	NS
BMI <25 kg/m^2, %	25.0	16.2	.0001	30.9	13.9	NS
Left main coronary disease, %	4.8	5.9	NS	3.5	2.7	NS
Preoperative heparin use, %	4.2	7.9	.001	12.4	29.7	.02
≥4 Distal anastomoses, %	34.1	46.8	.0001	32.7	48.6	NS
EuroSCORE	3.6 ± 2.5	3.7 ± 2.8	NS	4.1 ± 2.7	4.3 ± 2.9	NS
LVEF <30%, %	4.7	2.7	NS	4.4	—	NS
Preoperative CHF, %	1.7	2.5	NS	4.5	2.8	NS
Hypertension, %	52.8	41.2	.0001	44.2	51.4	NS
Diabetes mellitus, %	22.5	30.4	.001	28.3	16.2	NS
Preoperative aspirin use, %	58.4	54.1	NS	59.3	54.1	NS
Nonelective operation, %	9.5	18.7	.0001	30.1	40.5	NS
Redo operation, %	1.8	3.2	NS	1.8	—	NS
CPB time, min	58 ± 21	60 ± 18	.04	53 ± 18	61 ± 16	.02
Cardiac arrest time, min	33 ± 13	43 ± 12	.02	29 ± 9	33 ± 10	.01

*Data are presented as the mean ± SD where indicated. NS indicates not statistically significant; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; BMI, body mass index; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; CPB, cardiopulmonary bypass.

who are receiving clopidogrel anticoagulation therapy and require emergency surgery or may benefit from not discontinuing this drug owing to previous coronary stenting or the presence of a severe coronary lesion. Thus, there may be a group of patients who will undergo emergent surgery with clopidogrel or will gain benefit from continuing clopidogrel therapy unless postoperative bleeding is controlled.

The aim of the study was to evaluate the effect and safety of prophylactic tranexamic acid in coronary bypass surgery with respect to the use of preoperative clopidogrel.

METHODS

We included in the study 3754 consecutive patients who underwent isolated on-pump coronary artery bypass surgery with a single surgical and anesthesia team between January 1999 and August 2008. No patient was excluded from the study for any reason.

Patients were divided into 4 groups according to their preoperative medication with clopidogrel and/or tranexamic acid. Group 1 included patients who received neither of these medications (n = 3160, 84.2%); group 2 included patients who received tranexamic acid alone (n = 444, 11.8%); group 3 included patients who received clopidogrel alone (n = 113, 3.0%); and group 4 included patients who received both medications (n = 37, 1.0%). Outcome variables were measured.

Anesthesia and Operative Technique

On the night before the operation, all patients received 0.5 mg alprazolam (Xanax) orally. Midazolam (125 μg/kg) was administered intramuscularly 30 minutes before the operation, and a 16-gauge intravenous cannula was inserted in the operating room in all patients. The patients were then administered NaCl solution at a rate of 100 mL/hour. Anesthesia induction consisted of 50 μg/kg midazolam, 0.15 mg/kg pancuronium, and 25 to 35 μg/kg fentanyl. After endotracheal intubation, 50% O_2, 50% N_2O, and desflurane (3%-4%) were administered to all hemodynamically stable patients. Desflurane and N_2O were discontinued at times of hemodynamic instability. Maintenance anesthesia and muscle relaxation was accomplished with midazolam and vecuronium (80 μg/kg per hour). Furosemide (0.5 mg/kg) was administered routinely. Tranexamic acid (20 mg/kg over 20 minutes) was administered before CPB in patients who received this medication. This protocol was performed consecutively in all patients who underwent their operations between October 2006 and August 2008. The CPB priming solution included 900 mL Ringer lactate solution, 150 mL 20% mannitol, and 60 mL

Table 2. Comparison of Outcome Variables for the Groups*

	No Clopidogrel (n = 3604)			Clopidogrel (n = 150)		
	No Tranexamic Acid (n = 3160, 84.2%; Group 1)	Tranexamic Acid (n = 444, 11.8%; Group 2)	*P*	No Tranexamic Acid (n = 113, 3.0%; Group 3)	Tranexamic Acid (n = 37, 1.0%; Group 4)	*P*
Mean drainage, mL	615 ± 336	458 ± 289	.0001	740 ± 399	570 ± 408	.03
Blood transfusion, units/patient	0.59 ± 1.1	0.39 ± 1.1	.0001	1.2 ± 1.8	0.7 ± 1.1	NS
FFP transfusion, units/patient	1.43 ± 1.46	0.26 ± 0.73	.0001	2.2 ± 1.7	0.5 ± 1.3	.0001
Patients with transfusion, %	31.3	19.3	.0001	54.5	37.8	.09
ICU stay, h	21.9 ± 19.2	25.9 ± 38.9	.001	25.3 ± 33.5	32.3 ± 28.6	NS
Hospital stay, d	5.2 ± 3.4	6.0 ± 4.8	.001	5.7 ± 5.8	6.6 ± 3.8	NS
Reoperation for bleeding, %	1.6	1.6	NS	1.8	5.4	NS
Postoperative inotrope use, %	2.1	3.6	NS	4.4	16.2	.03
Postoperative IABP, %	1.4	1.4	NS	0.9	—	NS
Stroke, %	0.8	1.1	NS	1.8	1.3	NS
New-onset renal failure, %	0.2	1.1	.0001	0.9	0.7	NS
Hospital readmission, %	2.7	5.5	.006	5.3	6.7	NS
ICU readmission, %	1.8	2.9	.09	3.5	—	NS
Mortality, %	0.9	1.6	NS	0.9	0.7	NS

*Data are presented as the mean ± SD where indicated. NS indicates not statistically significant; FFP, fresh frozen plasma; ICU, intensive care unit; IABP, intra-aortic balloon pump.

8.4% sodium bicarbonate. During CPB, the mean arterial pressure was kept between 50 and 80 mm Hg, and the pump flow was kept between 2.2 and 2.5 L/m^2. Moderate hypothermia was used during CPB, and the midazolam and vecuronium dose was decreased to 60 µg/kg per hour when the body temperature reached 32°C. Myocardial viability was preserved with antegrade cold hyperkalemic crystalloid cardioplegia (Plegisol®; Abbott Laboratories, Abbott Park, IL, USA) except in patients with a left ventricular ejection fraction <25%, who received antegrade plus retrograde blood cardioplegia associated with terminal warm blood cardioplegia. During rewarming, the midazolam and vecuronium dose was increased back to 80 µg/kg per hour. After the termination of CPB, the midazolam and vecuronium dose was decreased to 50 µg/kg per hour and discontinued upon skin closure.

Postoperative Clinical Management

On arrival in the intensive care unit (ICU), patients were placed on mechanical ventilation. The ventilator mode was switched to synchronized intermittent mandatory ventilation plus pressure support, and ventilator settings were adjusted as follows: respiratory rate, 12/min; tidal volume, 8 to 10 mL/kg; fraction of inspired oxygen (FIO_2), 0.6; peak end-expiratory pressure, 0 to 5 mm Hg; pressure support, 10 mm Hg; trigger sensitivity, –2 cm H_2O. All patients were warmed by forced-air warming until the rectal temperature reached 37°C. The basic fluid substitution rate during the first 20 postoperative hours was 40 mL/kg per day. Six hundred to 800 mL of this solution was the autologous blood derived from the CPB circuit, and the rest was balanced crystalloid solution. Meperidine (0.4 mg/kg intravenously) to a total dose of 50 mg over 6 hours was used to treat shivering. All patients were evaluated every half hour for extubation. As soon as spontaneous breathing resumed, the respiratory rate was gradually decreased to 4/min, and pressure support was reduced to 4 mm Hg. If there were no contraindications to the use of beta-blockade, metoprolol was used intravenously to control hypertension. All hemodynamically stable patients without excessive chest tube drainage and a $PaCO_2$ value <48 mm Hg, a pH >7.30, and a PaO_2/FIO_2 ratio >250 were extubated. After the patient was extubated, 40% to 50% oxygen was administered by face mask. Oxygen saturation of hemoglobin and the respiratory rate were monitored continuously. Arterial blood gases were measured 30, 60, and 120 minutes after extubation. Inotropes were used only when hemodynamic stabilization could not be achieved by fluid administration or when there was other evidence of impaired contractility. In cases of an insufficient response to inotropes, intra-aortic balloon counterpulsation was initiated. We aimed to discharge all patients on the fifth postoperative day. The decision to discharge is based on a satisfactory routine checkup on day 4, which consists of a clinical examination, a complete blood cell count, measurements of urea and electrolyte levels, an electrocardiogram, and a chest radiograph. If the patient is medically unfit on day 5, hospitalization is prolonged, and further investigations may be performed, depending on the clinical status. Because the objective of our fast-track recovery protocol was to extubate the patient within 6 hours of the completion of cardiac procedure and to discharge the patient from the ICU within 24 hours and from the hospital on the fifth postoperative day, these time points were taken as references in this study.

Table 3. Risk Factors for Drainage >1000 mL (Univariate Analysis)

	Drainage <1000 mL (n = 3337)	Drainage >1000 mL (n = 417)	*P*
Age >65 y, %	32.1	42.9	.0001
Body mass index <25 kg/m^2, %	22.9	32.1	.0001
Male sex, %	75.7	91.0	.0001
Preoperative tranexamic acid use, %	13.3	8.0	.002
Preoperative clopidogrel use, %	3.5	7.3	.0001
Peripheral arterial disease, %	5.6	8.3	.04
Preoperative cerebrovascular disease, %	4.7	7.1	.053
Preoperative heparin use, %	4.8	7.1	.055
Preoperative creatinine >1.2 mg/dL, %	8.4	15.0	.0001
>4 Distal anastomoses, %	35.1	41.0	.02
EuroSCORE >5, %	20.9	26.3	.01
Smoking, %	66.2	73.7	.002
Left ventricular ejection fraction <30%, %	4.0	7.1	.002
Hypothyroidism, %	2.1	0.7	.058
Left main disease, %	4.7	7.1	.053

Data Source and Definitions

Our clinical database is used for outcomes analysis. It is a prospectively collected record containing relevant patient demographic data, comorbidities, intraoperative variables, and postoperative outcomes, including postoperative drainage, ventilation time, length of ICU stay, length of hospital stay, transfusion rate, new-onset postoperative renal failure, postoperative stroke, rate of readmission to the ICU, rate of readmission to the hospital, and mortality. Hospital mortality included all deaths within 30 days of the operation, irrespective of where the death occurred, and all deaths in the hospital after 30 days among patients who had not been discharged after the operation. Postoperative blood loss was defined as the total drainage from the chest tube. Renal complications included acute renal failure, which was defined as the requirement of permanent or temporary hemodialysis postoperatively. Stroke included postoperative permanent or temporary neurologic dysfunction.

Statistical Analysis

Data are reported as a percentage or as the mean ± SD. Univariate comparisons were evaluated with the χ^2 test or Fisher exact test for categorical variables and with Student *t* tests for continuous variables. Any factor with a *P* value <.1 in the univariate analysis was entered into the multiple logistic regression analysis. Statistical analysis was performed with SPSS statistical analysis software (version 11.0; SPSS, Chicago, IL, USA). Differences were considered statistically significant at *P* values <.05.

RESULTS

Perioperative data and demographic variables are included in Table 1. In patients who received tranexamic acid, we noted significant decreases in postoperative chest tube drainage (615 ± 336 mL versus 458 ± 289 mL, group 1 versus group 2 [*P* = .0001]; 740 ± 399 mL versus 570 ± 408 mL, group 3 versus group 4 [*P* = .03]) and in the use of fresh frozen plasma (1.4 ± 1.4 units/patient versus 0.2 ± 0.7 units/patient, group 1 versus group 2 [*P* = .0001]; 2.2 ± 1.7 units/patient versus 0.5 ± 1.3 units/patient, group 3 versus group 4 [*P* = .0001]), irrespective of the use of clopidogrel (Table 2). We found significant decreases in postoperative blood transfusion (0.59 ± 1.1 units/patient versus 0.39 ± 1.1 units/patient, group 1 versus group 2 [*P* = .0001]; 1.2 ± 1.8 units/patient versus 0.7 ± 1.1 units/patient, group 3 versus group 4 [*P* > .05]) and in the percentage of patients who received transfusions (31.3% versus 19.3%, group 1 versus group 2 [*P* = .0001]; 54.5% versus 37.8%, group 3 versus group 4 [*P* > .05]) only in the patients who did not receive clopidogrel (Table 2).

The univariate analysis revealed the following risk factors for a postoperative drainage volume >1000 mL: an age >65 years, a body mass index <25 kg/m^2, male sex, preoperative tranexamic acid use, preoperative clopidogrel use, peripheral arterial disease, preoperative cerebrovascular disease, preoperative heparin use, preoperative creatinine >1.2 mg/dL, >4 distal anastomoses, a EuroSCORE >5, smoking, a left ventricular ejection fraction <30%, hypothyroidism, and left main disease (Table 3). The multivariate regression analysis revealed the following to be independent risk factors for a postoperative bleeding volume >1000 mL: clopidogrel use (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.4-3.6), an age >65 years (OR, 1.6; 95% CI, 1.2-2.1), male sex (OR, 2.8; 95% CI, 1.9-4.3), no tranexamic acid use (OR, 2.3; 95% CI, 1.5-3.5), a preoperative creatinine concentration >1.2 mg/dL (OR, 1.7; 95% CI, 1.2-2.4), a body mass index <25 kg/m^2 (OR, 1.3; 95% CI, 1.08-1.7), and a left ventricular ejection fraction <30% (OR, 1.6; 95% CI, 1.002-2.7) (Table 4).

Table 4. Risk Factors for Postoperative Bleeding >1000 mL (Multivariate Analysis)*

	Odds Ratio (95% CI)	*P*
Preoperative clopidogrel use	2.3 (1.4-3.6)	.0001
Male sex	2.8 (1.9-4.3)	.0001
No tranexamic acid use	2.3 (1.5-3.5)	.0001
Preoperative creatinine >1.2 mg/dL	1.7 (1.2-2.4)	.01
Left ventricular ejection fraction <30%	1.6 (1.002-2.7)	.049
Age >65 y	1.6 (1.1-2.1)	.001
Body mass index <25 kg/m^2	1.3 (1.08-1.7)	.009

*CI indicates confidence interval.

DISCUSSION

In this study, we observed that preoperative use of tranexamic acid reduced postoperative blood loss in patients undergoing coronary bypass surgery with CPB. Evidence in the literature suggests that tranexamic acid use reduces the number of patients receiving blood transfusions [Zabeeda 2002; Andreasen 2004; Casati 2004; Diprose 2005; Vanek 2005; Santos 2006; Henry 2007; Umscheid 2007; Fergusson 2008]. Our study also revealed a clear benefit with respect to postoperative blood loss, even in preoperatively anticoagulated patients, whom surgeons are likely to increasingly face in the near future as the numbers of percutaneous coronary interventions and emergency coronary surgeries increase.

The data for outcomes (including intubation time, length of ICU stay, length of hospital stay, and rates of new-onset renal failure and hospital readmission) were higher in patients who were treated preoperatively with tranexamic acid and no clopidogrel use. We note, however, that the patients in this study included more patients with an older age, a Canadian Cardiovascular Society class ≥3, a New York Heart Association class ≥3, diabetes mellitus, a preoperative creatinine concentration >1.2 mg/dL, nonelective operation, a longer CPB time, and a longer period of cardiac arrest. All of these variables might have an effect on an observed adverse outcome. The same outcome data were more homogeneous for patients who received clopidogrel therapy, with the exception that postoperative use of inotropic agents was higher in patients who also received tranexamic acid. This result, however, might be a consequence of the higher incidence of nonelective patients in this group (40% versus 30%, statistically nonsignificant). Previous studies detected no impact of the use of tranexamic acid on or had inadequate evidence for its association with reoperation for bleeding, stroke, cognitive dysfunction, renal dysfunction, myocardial infarction, and mortality. One study found that compared with aprotinin, tranexamic acid was associated with a decreased rate of death in high-risk cardiac surgery patients [Umscheid 2007; Fergusson 2008].

Our multivariate analysis revealed the following risk factors for bleeding: preoperative clopidogrel use, an age >65 years, male sex, a preoperative creatinine concentration >1.2 mg/dL, a body mass index <25 kg/m^2, and a left ventricular ejection fraction <30%. In addition, other reports have defined emergency surgery, low body temperature on bypass, and CPB duration as risk factors for postoperative bleeding [Sellman 1997; Skubas 2001; Parr 2003; Hartmann 2006].

Regarding our results, the following 2 important points about the administration of tranexamic acid during coronary bypass surgery should be evaluated:

Timing

The literature has defined different timing options regarding the preoperative, perioperative, and postoperative use of tranexamic acid as effective [Zabeeda 2002; Andreasen 2004; Casati 2004; Santos 2006; Umscheid 2007; Fergusson 2008]. As we know, CPB is the main cause of the systemic inflammatory response produced by the kinin-kallikrein, fibrinolytic coagulation, and complement system. Increased plasma concentrations of plasmin and thrombin lead to platelet dysfunction following CPB [Paparella 2004; Vedin 2005; Hartmann 2006; Vanek 2007]. Fibrinolysis occurs mainly in conventional coronary artery bypass grafting at the time of extracorporeal circulation. Indeed, fibrinolytic activity during cardiac surgery is initiated by the release of tissue plasminogen activator. This activity begins with the skin incision and sternotomy and continues throughout the surgical manipulation of tissues. Additional massive activation of coagulation occurring during CPB is related to the contact of the blood with foreign, negatively charged nonendothelial surfaces and the consequent activation of the fibrinolytic system. The subsequent reinfusion of the fluids suctioned from the surgical field (shed blood from the pericardium contains large amounts of cytokines, tissue factors, and tissue plasminogen activator) exacerbates these pathologic processes [Vanek 2007]. Thus, any attempt at preventing these processes should include preoperative actions, and preoperative administration of tranexamic acid may provide such a benefit and reduce bleeding.

Patient Selection

Acute coronary syndromes include a spectrum of severe angina and acute myocardial infarction processes. Some of these patients are treated with new and more potent antithrombotic and antiplatelet therapies that include clopidogrel. Coronary artery bypass grafting offers a survival advantage compared with medical therapy in patients with unstable angina and left ventricular dysfunction, particularly in those with 3-vessel disease. Discontinuation of this drug is recommended by 5 days before surgery [Eagle 2004]. Earlier surgery for acute infarction may be more appropriate for patients with residual ongoing ischemia, however, despite nonsurgical therapy and if urgent surgery is warranted by other conditions, including left main or 3-vessel disease, associated valve disease, mechanical complications, and an anatomy unsuitable for other forms of therapy. In this group of patients, administration of tranexamic acid may be beneficial and decrease the already elevated risk of surgery. This approach may also be adopted for patients who have open coronary stents and have been referred for elective coronary surgery for other coronary vessel surgery. Although the data for tranexamic acid is not as great as the data for aprotinin, recent studies have revealed

no relationship with an adverse outcome [Brown 2007]. Currently, tranexamic acid might be suggested for use at least in patients with a high risk for bleeding.

CONCLUSION

In conclusion, prophylactic use of tranexamic acid reduces bleeding and the need for transfusion. This effect exists in patients who also receive clopidogrel but is less prominent. Its preoperative use may be beneficial in patients at high risk for bleeding.

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