

Tranexamic Acid Administration after Cardiac Surgery

A Prospective, Randomized, Double-blind, Placebo-controlled Study

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***Background*: Many different doses and administration schemes have been proposed for the use of the antifibrinolytic drug tranexamic acid during cardiac surgery. This study evaluated the effects of the treatment using tranexamic acid during the intraoperative period only and compared the results with the effects of the treatment continued into the postoperative period.**

***Methods:* Patients undergoing elective cardiac surgery with use of cardiopulmonary bypass (N = 510) were treated intraoperatively with tranexamic acid and then were randomized in a double-blind fashion to one of three postoperative treatment groups: group A: 169 patients, infusion of saline for 12 h; group B: 171 patients, infusion of tranexamic acid, 1 mg · kg^{-1} · h^{-1} for 12 h; group C: 170 patients, infusion of tranexamic acid, 2 mg · kg^{-1} · h^{-1} for 12 h. Bleeding was considered to be a primary outcome variable. Hematologic data, allogeneic transfusions, thrombotic complications, intubation time, and intensive care unit and hospital stay duration also were evaluated.**

***Results:* No differences were found among groups regarding postoperative bleeding and outcomes; however, the group treated with 1 mg·kg^{-1}·h^{-1} tranexamic acid required more units of packed red blood cells because of a significantly lower basal value of hematocrit, as shown by multivariate analysis.**

***Conclusions:* Prolongation of treatment with tranexamic acid after cardiac surgery is not advantageous with respect to intraoperative administration alone in reducing bleeding and number of allogeneic transfusions. Although the prevalence of postoperative complications was similar among groups, there is an increased risk of procoagulant response because of antifibrinolytic treatment. Therefore, the use of tranexamic acid during the postoperative period should be limited to patients with excessive bleeding as a result of primary fibrinolysis.**

EXCESSIVE bleeding is a common complication after cardiac surgery performed with use of cardiopulmonary bypass (CPB) and exposes the patients to the risks related to increased occurrences of postoperative complications (*e.g.*, increased risk of postoperative infection, see Dacey *et al.*[2]).[1–3] Antifibrinolytic drugs are one type of agent used to prevent hemostatic dysfunction.[4] Recently, there has been increased interest in tranexamic acid. Previously published studies described different doses and timing of administration: some authors[5–7] advocated pharmacologic protocols limited to the duration of surgery, whereas others[8–10] proposed prolonged administration of tranexamic acid during the first postoperative hours. None of these studies separately analyzed the effects of prolonging antifibrinolytic treatment during the postoperative period, with respect to the treatment limited only to the duration of surgery, on postoperative bleeding and the need for allogeneic transfusions. The aim of the current study was to compare the hemostatic effects of prolonging administration of tranexamic acid during the postoperative period with the effects of treatment limited to the duration of surgery. Postoperative bleeding was the primary outcome. In addition, allogeneic transfusions, thrombotic complications, and the duration of intensive care unit and hospital stay were recorded.

Materials and Methods

After institutional review board approval and informed consent were obtained, 510 consecutive adult patients participated in the study. Participants were older than 18 yr and scheduled to undergo elective cardiac surgery during September 1, 1998 to January 31, 1999 that necessitated the use of CPB. Criteria for preoperative exclusion included chronic renal insufficiency (plasmatic creatinine concentration more than 2 mg/kg), history of hematologic disorders, hepatic dysfunction (active hepatitis, cirrhosis), history of pulmonary embolism, deep venous thrombosis, and cerebrovascular injury. Following these criteria, 18 patients were excluded from randomization.

Operative Procedures

Anesthetic management was standardized. Premedication included oral diazepam (0.1 mg/kg), intramuscular morphine (0.1 mg/kg), and scopolamine (0.5 mg). Induction and maintenance of anesthesia were achieved using propofol (bolus of 2 mg/kg and infusion of 6–10 mg · kg^{-1} · h^{-1}) and fentanyl (bolus of 20 μg/kg; total dose up to 50 μg/kg); muscle relaxation was obtained using pancuronium bromide (bolus of 0.1 mg/kg

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and successive administrations of 0.03 mg/kg as needed). In patients with a left ventricular ejection fraction (LVEF) less than 35%, midazolam (bolus of 0.15 mg/kg and infusion of 0.1–0.2 $mg \cdot kg^{-1} \cdot h^{-1}$) was substituted for propofol, and intraoperative monitoring was performed using a pulmonary artery catheter and transesophageal echocardiography. All patients were administered an intraoperative infusion of tranexamic acid according to the protocol of our institution: a bolus of 1 g 20 min before sternotomy, followed by a continuous infusion of 400 mg/h until the completion of the operation, with 500 mg injected in the priming of the extracorporeal circuit. Before cannulation, porcine heparin (300 IU/kg) was administered, and supplemental doses were added, as needed, to maintain a kaolin activated clotting time (ACT) more than 480 s. A hollow-fiber membrane oxygenator was used in each patient, and CPB was performed with moderate hypothermia (typically 33–35°C, but if indicated, as low as 30°C); mean arterial pressure was maintained between 60 and 85 mmHg, with a blood flow of 2–2.4 $l \cdot min^{-1} \cdot m^{-2}$ and, if needed, by using phenylephrine or sodium nitroprusside. Myocardial protection was performed according to the Buckberg protocol.[11] Difficulty weaning from CPB was managed with use of inotropic and vasodilator drugs and, if indicated, by use of an intraaortic balloon pump. After discontinuation of CPB, the dose of heparin was "antagonized" using protamine (1:1 ratio). Further doses were administrated if activated clotting time was greater than the basal value. A cell separator was used to concentrate the remaining cellular content of the oxygenator and the blood in the cardiotomy. Before chest closure, mediastinal and pleural drains were positioned, and low-grade suction was instituted. Intraoperative criteria for allogeneic transfusions were standardized: Packed red blood cells (PRBCs) were transfused during CPB if the hemoglobin concentration was less than 6 g/dl and if the hematocrit concentration was less than 18% but after CPB if the hemoglobin concentration was less than 8 g/dl and the hematocrit concentration was less than 24% accompanied by signs or symptoms of hypovolemia (hypotension or tachycardia, or both). Fresh frozen plasma was infused after protamine administration if the prothrombin time value was 1.5 times the basal value and was accompanied by diffuse bleeding. Platelet concentrates were transfused if diffuse bleeding occurred and if the platelet count was less than 50×10^9/l.

Treatment Groups and Hematochemical Evaluation

By using a computer-generated random number sequence, 510 consecutive patients were assigned in a double-blind manner to one of three treatment groups: group A: control, 169 patients, infusion of saline for 12 h; group B: 171 patients, infusion of tranexamic acid, 1 $mg \cdot kg^{-1} \cdot h^{-1}$ for 12 h; group C: 170 patients, infusion of tranexamic acid, 2 $mg \cdot kg^{-1} \cdot h^{-1}$ for 12 h. The double-blind procedure was ensured by means of coded infusion syringes, prepared by an anesthesiologist in training who was not involved directly in intra- and postoperative treatment of the randomized patients. Samples for the evaluation of plasma concentrations of hemoglobin and hematocrit, of platelet count, prothrombin time, and activated thromboplastin time, of concentrations of creatinine, creatine phosphokinase, and creatine phosphokinase myocardial band (MB) isoenzyme were performed before the induction of anesthesia (basal), after the arrival in the intensive care unit (ICU; time 1), 4 h after arrival in the ICU (time 2), and at 6 AM of the first and second postoperative days (times 3 and 4). Blood loss was recorded during the first 24 h. Chest drains were removed when bleeding was less than 100 ml in the previous 4 h.

Postoperative Transfusion Protocol and Criteria for Surgical Reexploration for Bleeding

During postoperative period transfusion, criteria for administration of allogeneic blood–derivative products were the same as those described for the intraoperative period after CPB. Surgical reexploration was considered when bleeding during the first 2 h was greater than 300 ml/h or was greater than 200 ml/h for 4 h consecutively, with normal coagulation variables. Intubation time, ICU stay, and hospital stay were considered to be the time from admission to the ICU until removal of the endotracheal tube and the time from admission to the ICU until transfer to the cardiosurgical division, respectively. During the first 24 h postoperatively, the following thrombotic complications were recorded as possible consequences of antifibrinolytic therapy: myocardial infarction (defined as new Q waves during electrocardiography, and a creatine phosphokinase myocardial band isoenzyme and creatine phosphokinase ratio greater than 10%), acute renal insufficiency (defined as a creatinine value twice that of the baseline with a need for administration of diuretic drugs to maintain a diuresis rate of at least 1 $mg \cdot kg^{-1} \cdot h^{-1}$, or as needed for dialysis), major neurologic dysfunction (transient ischemic attack or cerebrovascular injury), deep venous thrombosis, and pulmonary embolism. Neurologic examination was performed during awakening of the patients by the anesthesiologist of the ICU and in all cases of suspected altered neurologic conditions by the consultant specialist in neurology, who indicated the eventual need for instrumental examination for diagnosis (electroencephalography, computed tomography).

Statistical Analysis

Considering as a primary outcome total bleeding, the sample size was calculated, assuming a standard deviation for bleeding equal to 250 ml. In this manner, the

Table 1. Baseline Characteristics

	Placebo (N = 169)	TA (1 mg · kg^{-1} · h^{-1}) (N = 170)	TA (2 mg · kg^{-1} · h^{-1}) (N = 170)	*P**
Age (yr)	64 [19–85]	64 [21–85]	61 [20–87]	0.1
Sex, no. (%) of male	113 (67)	102 (60)	118 (69)	0.1
BMI	24.8 [16.4–36.5]	25.4 [15.6–45.8]	26.2 [16.8–36]	0.01†
Base-line ejection fraction (%)	60 [20–75]	62 [20–77]	60 [25–88]	0.07
Patients with baseline ejection fraction < 35%, no. (%)	13 (7.7)	13 (7.6)	15 (8.8)	0.8
Coexisting illness, no. (%)				
Hypertension	48 (28)	50 (29)	53 (31)	0.8
Diabetes	25 (15)	25 (15)	27 (16)	0.9
Peripheral vascular disease	8 (5)	7 (4)	11 (6)	0.6
COPD	17 (10)	15 (9)	12 (7)	0.6
Preoperative aspirin, no. (%)	30 (18)	32 (19)	31 (18)	0.9
Preoperative heparin, no. (%)	24 (14)	23 (13)	22 (13)	0.9

Data are expressed as median [minimum–maximum], or as indicated.

* Mann-Whitney U test or chi-square test as appropriate: significance for $P < 0.05$. † *Post hoc* comparison by Dunn procedure: differences between group A (placebo group) and group C (TA, 2 mg · kg^{-1} · h^{-1}).

BMI = body mass index kg/m^2; COPD = chronic obstructive pulmonary disease; TA = tranexamic acid.

current study had 95% power to detect a difference of 100 ml in bleeding among groups, with an α error equal to 0.05. To test the normality of the distribution of the continuous variables, the Shapiro-Wilk statistic was performed. Because variables did not have a Gaussian distribution, comparisons among the groups were performed using the Kruskal-Wallis analysis. *Post hoc* comparisons were performed using the Dunn procedure. Categoric data were compared using the chi-square test. $P < 0.05$ was considered to be statistically significant. Because the amount of the units of PRBCs transfused was significantly greater in the patients of group B and because of the multifactorial nature of the decision to administer allogeneic transfusions, multiple logistic analysis was performed. All preoperative and intraoperative variables, that presented with $P \leq 0.1$ during univariate analysis were applied to the multivariate model to adjust the comparison between patients transfused and patients not transfused with PRBCs for all possible differences among groups. Odds ratios (ORs; see Results) for each increment of variables (tables 1–3) and 95% confidence intervals (CIs; see Results) are presented. Data were analyzed using SAS statistical software (SAS Institute, Cary, NC).

High-risk Patients for Bleeding. To analyze the hemostatic effects of tranexamic acid on patients considered to have an increased risk of bleeding, we performed the same analysis described previously for 108 patients (group A: 31 patients; group B: 37 patients; group C: 40) undergoing cardiac reintervention or intervention in which more than one surgical heart procedure was requested (combined intervention; table 3).

Results

Following the "intention to treat" rule, all but one patient enrolled in the study were considered for statistical analysis. The excluded patient belonged to group B, had a reduced left ventricular ejection fraction, and was scheduled for myocardial revascularization and mitral valve anuloplasty. The study could not be completed because the patient died of cardiogenic shock while in the operating room. Therefore, 509 patients were used for statistical analysis. As shown in table 1, body mass index was the only demographic variable that was significantly different among the groups. Table 2 shows baseline hematochemical data: basal hematocrit concentration was significantly different and lower in group B. The same differences also were observed for the minimum hematocrit concentration obtained during CPB, as shown in table 3, in which operative variables are reported. Table 4 shows postoperative bleeding and number of allogeneic transfusions in the groups: although no differences were found regarding bleeding, significant differences were observed in the number of allogeneic transfusions. The patients in group B received more units of PRBCs than did the patients of the other two groups, and the number of patients transfused was significantly greater in group B. In a multiple logistic model, to estimate the risk of PRBC transfusion, we tested the following variables, which showed different results among treatments in the univariate analysis at $P \leq 0.1$: sex, age, type of intervention, body mass index, LVEF, baseline hemoglobin and hematocrit concentrations, minimum hematocrit concentration during CPB, and minimum temperature during CPB. The variables that were significantly associated with transfusions of PRBCs included age (OR: 1.05; CI: 1.03–1.08), basal hematocrit concentration (OR: 0.77; CI: 0.61–0.97), and minimum hematocrit concentration during CPB (OR: 0.80; CI: 0.74–0.88). On the contrary, postoperative treatment with tranexamic acid was not significantly related to the number of allogeneic transfusions. As shown in table 5, we did not find significant differences among the groups regarding intubation

Table 2. Baseline Hematochemical Data

	Placebo (N = 169)	TA (1 mg · kg^{-1} · h^{-1}) (N = 170)	TA (2 mg · kg^{-1} · h^{-1}) (N = 170)	P*
Hemoglobin (g/dl)	14 [7.9–17.4]	13.6 [8.7–17.7]	13.9 [8.7–17]	0.09
Hematocrit (%)	40.8 [25.4–50.7]	40.2 [26.9–50]	41.1 [26–51]	0.05§
Platelet count ($\times 10^3$/mm^3)	192 [93–555]	199 [91–388]	187 [87–350]	0.2
Prothrombin time (s)	12 [11–29]	12 [11–31]	11 [10–30]	0.2
Thromboplastin time (s)	34 [23–83]	33 [24–89]	33 [23–82]	0.4
Activated clotting time (s)	141 [82–266]	141 [96–224]	144 [100–204]	0.7
Creatinine (mg/dl)	0.9 [0.49–2]	0.86 [0.42–2]	0.87 [0.35–1.8]	0.5
Creatinephosphokinase (mg/dl)	68 [16–408]	69 [19–288]	69 [20–450]	0.6

Values are expressed as median [minimum–maximum].

* Mann-Whitney U test: significance for $P < 0.05$. † *Post hoc* comparison by Dunn procedure: differences between group B (TA 1 mg · kg^{-1} · h^{-1}) and group C (TA, 2 mg · kg^{-1} · h^{-1}).

TA = tranexamic acid.

time, duration of ICU stay, duration of hospital stay, and prevalence of postoperative complications. In particular, the same number of patients in the three groups were treated in the ICU with an infusion of tranexamic acid for excessive postoperative bleeding, on the basis of alterated values of D-dimers (3 times the baseline) and fibrinogen (<150 mg/dl): they received an infusion of 200 mg/h tranexamic acid until normalization of hematologic values of fibrinolysis. Twenty patients (3.9%) required early postoperative surgical reexploration; of these, 13 (2.6%, 4 in group A, 4 in group B, and 5 in group C; P = NS) showed evidence of a surgical cause of bleeding. One patient in group B, with a preoperative history of peptic ulcer, had significant blood loss caused by the gastric tube on the first postoperative day. Gastric endoscopy showed a bleeding ulcer that was treated locally, and the patient required transfusion of PRBCs because of anemia. Finally, one patient in group C required early reoperation for myocardial ischemia, and venous bypass was performed for the right coronary artery.

High-risk Patients for Bleeding. Analysis of the subgroup of patients considered to have an increased risk for bleeding did not show significant differences regarding demographics and hematochemical data. Also, operative data were not significantly different (data not shown). Table 6 shows total postoperative bleeding and the number of allogeneic transfusions. No significant differences were found among the groups. Finally, incidence of postoperative complications and outcome were similar in the three groups (data not shown).

Discussion

Among antihemorrhagic drugs used to prevent hemostatic derangement in cardiac surgery performed concomitant with CPB, ϵ-aminocaproic acid and tranexamic acid (two synthetic, low-cost, antifibrinolytic drugs) recently were studied as alternatives to the more expensive drug aprotinin.[12] ϵ-Aminocaproic acid and tranexamic acid both act by forming a reversible complex with plasminogen and

Table 3. Operative Data

	Placebo (N = 169)	TA (1 mg · kg^{-1} · h^{-1}) (N = 170)	TA (2 mg · kg^{-1} · h^{-1}) (N = 170)	P*
CABG, no. (%)	73 (43)	77 (45)	81 (48)	0.5
Valvular surgery, no. (%)	62 (37)	54 (32)	46 (27)	0.2
ASD repair, no. (%)	3 (1)	2 (1)	3 (2)	0.9
Combined interventions, no. (%)	23 (14)	27 (16)	30 (18)	0.2
Cardiac reinterventions, no. (%)	8 (5)	10 (6)	10 (6)	0.9
Pulmonary artery catheter, no. (%)	2 (13)	28 (16)	29 (17)	0.3
CPB time (min)	76 [28–250]	77 [18–188]	78 [20–250]	0.5
ACC time (min)	52 [7–120]	55 [7–129]	55 [20–190]	0.2
Total heparin dose (mg)	260 [130–500]	250 [150–530]	260 [125–750]	0.2
Total protamin dose (mg)	260 [130–500]	250 [150–550]	260 [150–750]	0.1
Minimum hematocrit during CPB (%)	23 [14–35]	23 [13–34]	24 [15–32]	0.04†
Minimum temperature during CPB (°C)	34.2 [30.6–36.1]	34 [30–36.4]	34 [30–36.4]	0.1
ACT post-CPB (s)	131 [92–183]	130 [94–174]	132 [100–168]	0.5

Data are expressed as median [minimum–maximum], or as indicated.

* Mann-Whitney U test or chi-square test as appropriate: significance for $P < 0.05$. † *Post hoc* comparison by Dunn procedure: differences between group B (TA, 1 mg · kg^{-1} · h) and group C (TA, 2 mg · kg^{-1} · h).

ACC = aortic cross clamping; ACT = activated clotting time; ASD = atrial septal defect; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; TA = tranexamic acid; combined interventions = CABG and valve repair/replacement, CABG and ventricular aneurismectomy; multiple valve repairs/replacements.

Table 4. Postoperative Bleeding and Allogeneic Transfusions

	Placebo (N = 169)	TA (1 mg · kg^{-1} · h) (N = 170)	TA (2 mg · kg^{-1} · h) (N = 170)	*P**
Bleeding 0–4 h (ml)	150 [0–1000]	150 [0–1050]	150 [0–1000]	0.5
Total bleeding (ml)	300 [50–2500]	300 [0–1700]	350 [0–2000]	0.6
PRBC OR, units (patients transfused)	64 (24)	95 (35)	75 (31)	0.3
Total PRBC, units (patients transfused)	118 (41)	179 (59)	129 (41)	0.04†
FFP OR, units (patients transfused)	9 (4)	6 (2)	5 (2)	0.4
Total FFP, units (patients transfused)	38 (9)	30 (7)	42 (9)	0.8
PLTC OR, units (patients transfused)	8 (1)	0	0	0.4
Total PLTC, units (patients transfused)	15 (2)	19 (3)	18 (2)	0.8
Total number of patients transfused (%)	41 (24)	59 (35)	39 (23)	0.04†

Data are expressed as median [minimum–maximum], or as indicated.

* Mann-Whitney U test or chi-square test as appropriate: significance for $P < 0.05$. † *Post hoc* comparison by Dunn procedure: differences between group B (TA, 1 mg · kg^{-1} · h^{-1}) and group A (placebo), and differences between group B (TA, 1 mg · kg^{-1} · h^{-1}) and group C (TA, 2 mg · kg^{-1} · h^{-1}).

FFP = fresh frozen plasma; OR = operating room; PLTC = platelet concentrate; PRBCs = packed red blood cells; TA = tranexamic acid.

plasmin through the lysine-binding sites, thus blocking interaction with the specific lysine residues of fibrin. Tranexamic acid is approximately 10 times more potent than ϵ-aminocaproic acid.[13] Since 1997, in our institution, tranexamic acid has been administered intraoperatively to all patients undergoing cardiac surgery concomitant with extracorporeal circulation. This is a consequence of the results of previous comparative studies of this drug with ϵ-aminocaproic acid and aprotinin.[14,15] Therefore, we did not include a placebo control group that did not receive tranexamic acid during surgery. The optimal doses, timing, and methods of administration of tranexamic acid are controversial. One group of authors,[5–7,16–19] using different protocols, proposed limited use during surgical procedures. Another group,[9,10,20–23] starting from the original study of Horrow *et al.*,[8] suggested administration of tranexamic acid infusion during the first hours of the postoperative period. Nevertheless, in these studies, the independent effects of postoperative administration are not discussed. One result of the current study is that, paradoxically, a greater number of patients in group B, treated with tranexamic acid, required significantly more units of PRBCs than did the patients in group C, treated with a larger postoperative dose of tranexamic acid, and the patients in group A, who were not treated with postoperative antifibrinolytic therapy. Multivariate analysis showed that the principal factor that conditions perioperative transfusions is the hematocrit concentration. The patients of group B showed hematocrit concentrations before and during CPB that were significantly lower then those of the other groups; for this reason they required a significantly greater number of units of PRBCs to maintain the hematocrit concentration up to the limit considered to be the least acceptable. However, the most important conclusion of the current study is that prolonged treatment with tranexamic acid did not reduce postoperative bleeding. Antifibrinolytic treatment during the postoperative period did not reduce postoperative bleeding and the need for allogeneic transfusions compared with treatment during the surgical procedure. The same conclusion is derived from the analysis of the subgroup of patients considered to be at high risk for bleeding. In addition, for these patients, there are no ad

Table 5. Postoperative Complications and Outcomes

	Placebo (N = 169)	TA (1 mg · kg^{-1} · h^{-1}) (N = 170)	TA (2 mg · kg^{-1} · h^{-1}) (N = 170)	*P**
Excessive blood loss, no. (%)	27 (16)	25 (15)	31 (18)	0.2
Reexploration for bleeding, no. (%)	7 (4)	6 (3.5)	7 (4)	0.9
Antifibrinolytic treatment for excessive postoperative bleeding, no. (%)	2 (1.2)	2 (1.2)	1 (0.6)	0.8
Early reoperation for ischemia, no. (%)	0	0	1 (0.6)	0.4
Perioperative AMI, no. (%)	3 (1.8)	4 (2.4)	2 (1.2)	0.6
Postoperative renal insufficiency				
Creatinine twice the baseline, no. (%)	4 (2.4)	6 (3.5)	10 (5.9)	0.1
Postoperative dialysis, no. (%)	1 (0.6)	2 (1.2)	2 (1.2)	0.8
Major neurologic dysfunctions, no. (%)	2 (1.2)	3 (1.8)	2 (1.2)	0.9
Intubation time (h)	9 [2.4–144]	8 [2–648]	9 [2.5–408]	0.7
ICU stay (days)	1 [1–8]	1 [1–27]	1 [1–37]	0.1
Hospital stay (days)	9 [5–33]	8 [5–30]	9 [5–66]	0.6
Death, no. (%)	1 (0.6)	2 (1.2)	2 (1.2)	0.8

Data are expressed as median [minimum–maximum], or as indicated. Excessive bleeding is considered to be greater than 600 ml in the first 24 h.

* Mann-Whitney U test or chi-square test as appropriate: no differences among the groups.

AMI = acute myocardial infarction; ICU = intensive care unit; TA = tranexamic acid.

Table 6. Postoperative Bleeding and Allogeneic Transfusions in High-risk Patients for Bleeding

	Placebo (N = 31)	TA (1 mg · kg^{-1} · h^{-1}) (N = 37)	TA (2 mg · kg^{-1} · h^{-1}) (N = 40)	P*
Total bleeding (ml)	300 [100–2500]	300 [100–1300]	350 [100–1700]	0.7
Total PRBC, units (patients transfused)	39 (11)	50 (12)	38 (12)	0.6
Total FFP, units (patients transfused)	13 (2)	14 (4)	15 (3)	0.9
Total PLTC, units (patients transfused)	8 (1)	9 (1)	8 (1)	0.9
Total number of patients transfused (%)	11 (35)	12 (32)	12 (30)	0.7

Data are expressed as median [minimum–maximum], or as indicated. High-risk patients for bleeding were considered as patients undergoing cardiac reintervention and patients undergoing combined intervention.

* Mann-Whitney U test or chi-square test as appropriate: no differences among the groups.

PRBC = packed red blood cells; FFP = fresh frozen plasma; PLTC = platelet concentrate; TA = tranexamic acid.

vantages to prolonging the administration of tranexamic acid during the postoperative period in terms of reduction of amount of blood loss and allogeneic transfusions. There are various explanations for these observations. The first consideration concerns the half-life of tranexamic acid, which is approximately 80 min. Approximately 30% of the dose administered is recovered in the urine during the first hour, approximately 45% during the first 3 h, and approximately 90% after 24 h.[13] Probably, the doses administered during the operative time are sufficient to last the immediate postoperative period without additional doses. Other important considerations include the multifactorial origin of hemostatic dysfunction induced by CPB, such as dilution and consumption of coagulation factors; activation, degranulation, and deposition of the platelets; heparin rebound; primary fibrinolysis; and complement activation.[1,24,25] The circuit for performing extracorporeal circulation is a large foreign surface for the blood cells and, despite attempts to ameliorate the biocompatibility of the materials,[26] is a powerful stimulus for blood cell activation.[27] Fibrinolysis is only one alteration, and as previously shown, an increased level of fibrin-split products alone after CPB is not related to excessive bleeding.[28] In addition to being first caused by surgical maneuvers (surgically dissected surfaces, sternotomy, manipulation of the heart), excessive fibrinolysis primarily is amplified by the contact of the blood with the surface of the circuit for CPB. During extracorporeal circulation, the degradation of fibrinogen and fibrin is common, but, after the cessation of CPB, concentrations return rapidly to the normal value. The interactions among the different systems involved in the hemostatic pathways were evaluated in previous studies, which obtained different results.[29,30] Gelb *et al.*[29] evaluated the variations of the most important variables of coagulation and fibrinolysis during and after CPB, demonstrated the lack of a significant relation between laboratory measurements and postoperative bleeding, and demonstrated the absence of differences in laboratory measurements between patients with normal postoperative bleeding and patients with excessive bleeding. They concluded that the coagulopathy induced by extracorporeal circulation in most cases is transient and infrequently results in clinically important hemostatic abnormalities.[29] Very different conclusions have been proposed by Holloway *et al.*,[30] who observed that the combination of changes of platelet number and function and increased fibrinolysis significantly correlated with postoperative blood loss, whereas the single changes did not. The importance of the role of platelets is well-evidenced by the study of Harker et al.,[31] who hypothesized that the severity of postoperative hemorrhage can be caused largely by a defective platelet plug formation as a result of a decrease in agonist-induced platelet aggregation during bypass. The heterogeneity of the fibrinolytic response to CPB is described by Chandler *et al.*,[32] who also demonstrated that fibrinolysis is suppressed in the postoperative period by high levels of plasminogen activator inhibitor type 1 (PAI-1), produced as a part of the systemic acute-phase response to surgical trauma. Paramo *et al.*[33] demonstrated a fibrinolytic shut down during the postoperative period after CPB with a reduction of tissue plasminogen activator (t-PA) levels and an increase of plasminogen activator inhibitor type 1 activity, suggesting a possible role in postoperative thrombotic complications. Slaughter *et al.*[34] reached the same conclusions: they stated that antifibrinolytic therapy ε-aminocaproic acid determines a reduction in fibrinolytic activity in the absence of a concomitant reduction of thrombin generation and soluble fibrin, suggesting possible potentiation of a hypercoagulable prothrombotic status. CPB induces dysregulation of the complex system of fibrinolysis, caused by an imbalance between endothelial-derived circulating plasminogen activator and plasminogen activator inhibitor type 1, that results at first in fibrinolysis and later in a propensity toward thrombosis. Therefore some patients seem to have a greater propensity toward clot lysis and others toward forming clots, which suggests that there is considerable individual variation in the response to the stress of surgery.[35] We did not find significant differences among patients in terms of outcome and postoperative complications; however, many previously published case reports described thrombotic complications as consequences of antifibrinolytic therapy.[36,37] The three groups did not differ regarding prevalence of perioperative thrombotic complications. Nevertheless, we noted that the number of patients whose creatine value was twice the baseline value during the postoperative period is greater in the two treatment groups, suggesting a possible implica-

tion of antifibrinolytic treatment, as previously described in the literature.[38] However, as suggested by a recent meta-analyses of the works that considered use of hemostatic drugs in cardiac surgery, only a large, prospective, controlled study with complications and mortality as primary outcomes can provide definitive evidence.[39]

To conclude, antifibrinolytic therapy is important in the prevention of perioperative bleeding; however, there are potential, and not completely clarified, adverse effects. The routine prolongation of antifibrinolytic therapy in the postoperative period is not indicated.

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