



Effect of Tranexamic Acid on Transfusion Requirement in Dual Antiplatelet-Treated Anemic Patients Undergoing Off-Pump Coronary Artery Bypass Graft Surgery

– A Randomized Controlled Study –

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Background: Anemia is not rare in patients presenting for coronary artery bypass graft surgery (CABG) and as these patients are frequently on dual antiplatelet therapy (DAPT), the coexisting conditions could potentially increase the risk of bleeding and transfusion. The aim of this study was to evaluate the effect of tranexamic acid (TA) on blood loss and transfusion in preoperatively anemic patients who continued DAPT until within 5 days of off-pump CABG (OPCAB).

Methods and Results: Seventy-six anemic patients were randomized into 2 groups: TA group receiving TA (1 g bolus followed by infusion at 200 mg/h) and a Control group receiving the same volume of saline. The amount of blood loss and transfusion requirement during, and at 4 and 24 h after the operation were assessed. Patients' characteristics and operative data were similar between the groups. During the perioperative period, which combined the intraoperative and postoperative 24 h data, the TA group received significantly smaller amounts of packed red blood cells and fresh frozen plasma. Total amount of perioperative blood loss was similar between the groups, although the blood loss during the postoperative 4 h was significantly less in the TA group.

Conclusions: TA infusion could reduce the amount of transfusion during the perioperative period in patients with preoperative anemia who continue DAPT until within 5 days of OPCAB. (*Circ J* 2012; **76**: 96–101)

Key Words: Anemia; Dual antiplatelet therapy; Off-pump coronary artery bypass; Tranexamic acid

Increased bleeding and subsequent transfusion of allogeneic blood products are undoubtedly associated with adverse outcome in cardiac surgical patients.¹ Among many risk factors, preoperative anemia is one of the strongest predictors of transfusion.² In coronary patients presenting for coronary artery bypass graft surgery (CABG), mild preoperative anemia is not rare, but surgery often cannot be delayed, especially in patients with acute coronary syndrome.³ Moreover, the need for dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel further complicates the perioperative course of these patients in terms of blood loss and transfusion requirement.^{4–6}

In order to maximize the ischemic benefit and minimize the bleeding risk in patients receiving DAPT until shortly before surgery, off-pump CABG (OPCAB) has been proposed as an alternative technique of surgical revascularization.^{7,8} However, patients with preoperative anemia have a reduced red blood cell reserve that is likely to be depleted by operative

intervention, even without the use of cardiopulmonary bypass (CPB). In addition, anemia per se has been demonstrated to be associated with reversible platelet dysfunction.⁹ Therefore, coexistence of anemia and continued DAPT may potentially result in an increased risk of bleeding and transfusion requirement mandating the need for an effective blood conservation strategy.

Tranexamic acid (TA) is a synthetic antifibrinolytic agent that binds to the lysine-binding sites of plasminogen.¹⁰ TA can reduce postoperative blood loss and transfusion requirement in cardiac surgery with and without CPB.¹¹ TA has improved platelet function in chronic renal failure patients¹² and reduced postoperative blood loss in patients treated with antiplatelet therapy undergoing CABG.^{13,14} Also, a recent study demonstrated that TA actually increased platelet aggregation in patients treated with aspirin and clopidogrel undergoing CABG.¹⁴ Therefore, coronary patients with preoperative anemia who are

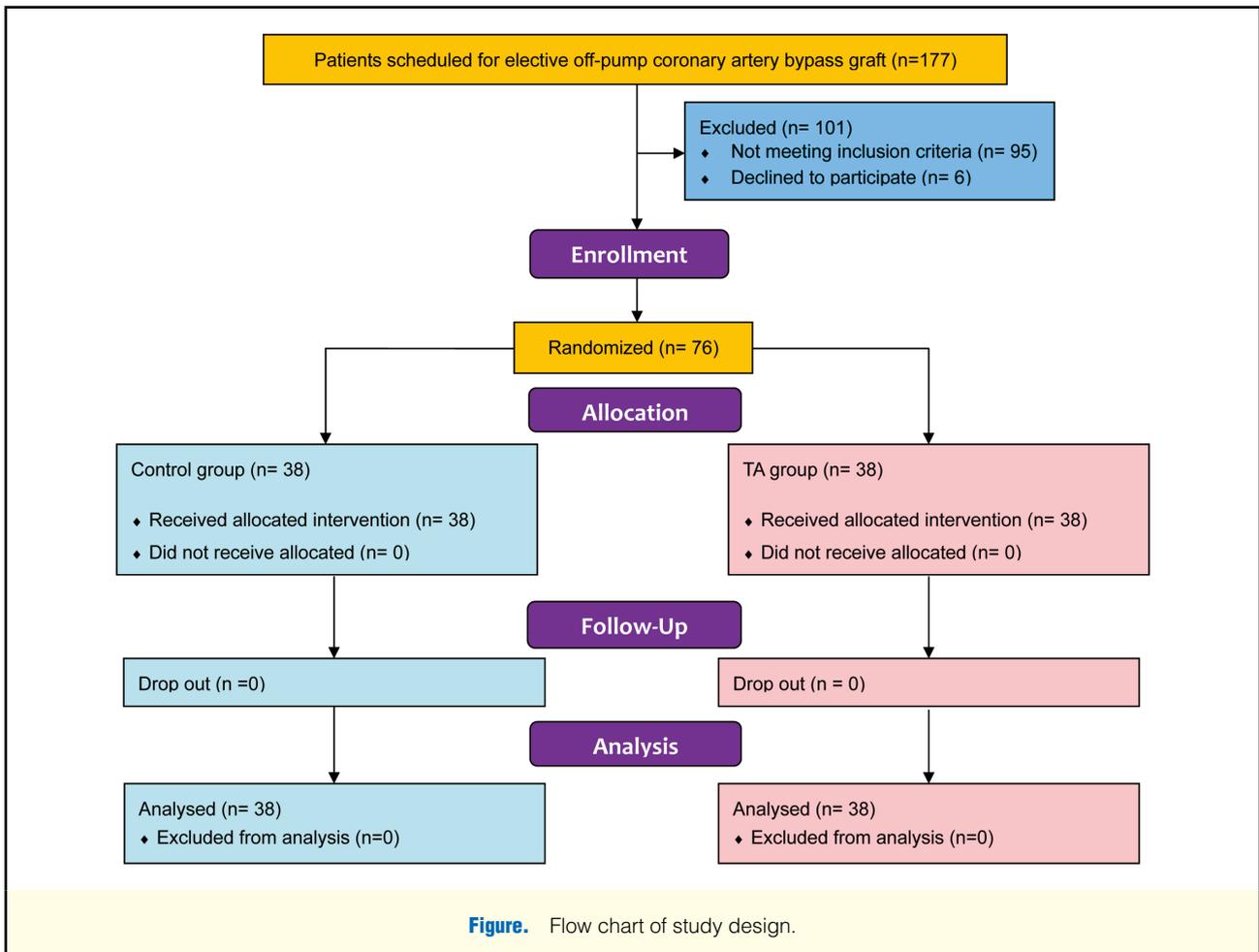
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on continued DAPT until shortly before OPCAB could benefit from TA infusion in terms of blood conservation, yet no comprehensive data exist in that regard.

The aim of this randomized, double-blinded, placebo-controlled study was to evaluate the effect of TA on transfusion requirement and blood loss in preoperatively anemic patients who have been administered DAPT until within 5 days of OPCAB.

Methods

After obtaining the approval of the institutional ethics board and informed written consent from all patients, 76 preoperatively anemic patients (hemoglobin [Hb] ≤ 130 g/L for males, ≤ 120 g/L for females) treated with aspirin and clopidogrel until within 5 days of OPCAB were randomized into 2 groups using the envelope method with random numbers. Patients in the TA group (n=38) received 1 g of TA (Shinpoong, Seoul, Korea) for 20 min before skin incision with subsequent continuous infusion at 200 mg/h during the operation.¹⁵ Patients in the Control group (n=38) received the equivalent amount of saline solution at the same infusion rate. The infusion syringe was prepared by an anesthetic nurse who was not involved in the study. Both the anesthesiologists and cardiac surgeons in the operating room and intensive care unit (ICU) were blinded to the randomization result by the use of unmarked identical syringes for TA and saline administration. Patients with impaired renal function (serum creatinine [sCr] >20 mg/L), hepatic dysfunction,

neurologic dysfunction or hematologic disorders were excluded.

The same, previously described anesthetic technique was used for all patients.¹⁶ Systemic heparinization during anastomosis was achieved with 100 U/kg of porcine heparin to reach a target activated clotting time (ACT) >250 s, which was maintained with additional doses of heparin as necessary. ACT was checked at 30-min intervals until the completion of anastomosis. Adequate graft flow was confirmed and the heart was returned to its natural position by the surgeon. Then, heparin was neutralized with protamine sulfate (0.5 mg/100 U of heparin). The amount of heparin injected and protamine for reversal of heparinization during operation, baseline ACT value before anastomosis, highest ACT value during anastomosis, and ACT value after protamine reversal were recorded. The graft was exposed and stabilized as described previously.¹⁶ Preoperative autologous blood donation was not performed in any patient of either group. A cell salvage device (Cell saver[®], Haemonetics Corp, MA, USA) was used during the operation in all patients, and salvaged blood was reinfused to the patient before the end of the operation. All patients were transferred to ICU after operation.

Allogeneic packed red blood cells (pRBC) were transfused when the Hb level was <85 g/L throughout the study period. Fresh frozen plasma (FFP) was transfused when the postoperative international normalized ratio was >1.5 with excessive bleeding >200 ml/h for 2 consecutive hours. The criteria for transfusion of platelet concentrate were postoperative plate-

	Control (n=38)	TA (n=38)	P value
Age (years)	67 (7)	69 (7)	0.249
Sex (M/F)	18/20	23/15	0.250
BSA (m ²)	1.6 (0.2)	1.6 (0.2)	0.984
EuroSCORE	4.5 (2.3)	4.7 (2.2)	0.578
Ejection fraction (%)	64 (10)	60 (13)	0.109
Diabetes mellitus	19	22	0.490
Hypertension	28	34	0.076
Peripheral obstructive disease	12	7	0.185
Left main coronary disease	7	13	0.118
Triple vessel disease	36	36	>0.999
Prior MI	6	4	0.497
Recent MI (<1 month)	3	4	>0.999
Fibrinogen (mg/dl)	343.9 (108.5)	347.6 (100.6)	0.899
Time of aspirin and clopidogrel discontinuation before surgery (days)	2 [1–3]	2 [1–2]	0.185

Values are mean (SD), median [interquartile range] or number of patients. TA, tranexamic acid; BSA, body surface area; MI, myocardial infarction.

	Control (n=38)	TA (n=38)	P value
Operating time (min)	246 (51)	250 (47)	0.747
No. of grafts	3.1 (0.6)	3.1 (0.6)	>0.999
Heparin (IU)	7,044 (2,716)	7,781 (2,272)	0.84
Protamine (mg)	33 (12)	38 (13)	0.263
Baseline ACT (s)	140 (14)	150 (22)	0.114
Highest ACT (s)	390 (76)	368 (77)	0.396
Reversed ACT (s)	154 (22)	149 (16)	0.435
Crystalloid (ml)	2,421 (726)	2,275 (684)	0.375
Colloid (ml)	1,131 (272)	1,120 (309)	0.874
Urine output (ml)	692 (41)	726 (391)	0.715

Values are mean (SD).

TA, tranexamic acid; ACT, activated clotting time; Baseline ACT, initial level of ACT during operative period; Highest ACT, highest level of ACT during operative period; Reversed ACT, ACT after reversal with protamine.

let count $<50 \times 10^9/L$ with excessive bleeding $>200\text{ml/h}$ for 2 consecutive hours. Surgical re-exploration was indicated when chest tube drainage was $>200\text{ml/h}$ for 4 consecutive hours or $>400\text{ml}$ during the first hour despite normalized ACT and global coagulation status. Anesthesiologists and cardiac surgeons involved in the primary care of the patients during the study period were all blinded to the patients' group allocations.

Hb levels and platelet counts were measured preoperatively, at the end of operation, and 24 h after operation. The lowest Hb level during the postoperative period was also recorded. Prothrombin time (PT), and activated partial thromboplastin time were measured preoperatively and 24 h after operation. During the intraoperative period, fluid balance, amount of pRBC transfusion, and number of patients transfused were recorded. Intraoperative blood loss was recorded as the amount of reinfused salvaged blood by the cell salvage device. Postoperative blood loss was recorded as the volume of chest tube drainage measured at 4 h and 24 h after operation, and the drained blood was not reinfused. The amount of transfused pRBC, FFP, and platelet concentrate during 4 h and 24 h after operation and numbers of patients requiring pRBC transfusion during 4 h and 24 h

after operation were recorded. During hospitalization, possible thromboembolic complications as a result of TA treatment, including myocardial infarction (MI, increase in Tn-T $>0.8\text{ng/ml}$ and/or development of pathologic Q wave on ECG),¹⁷ acute renal insufficiency (sCr $\geq 3\text{mg/L}$ or 50–200% from baseline using modified RIFLE classification),¹⁸ major neurologic dysfunction (transient ischemic attack or stroke), pulmonary embolism, and deep vein thrombosis were recorded.

The primary endpoint of this study was to compare the perioperative (combined period of intraoperative and postoperative 24 h) transfusion requirement between the groups. The secondary endpoint of this study was to compare the amount of perioperative blood loss between the groups.

Statistical analyses were performed with SPSS 15.0 (SPSS Inc, Chicago, IL, USA). A difference of 1 unit transfusion of pRBC between the groups was taken as clinically significant reduction. Based on the OPCAB results of our hospital in patients who continued clopidogrel until within 5 days of surgery, the standard deviation in the amount of perioperative pRBC transfusion was 1.5 units.¹⁶ This calculation generated an estimate of 36 patients in each group with 80% power and an alpha level of 0.05. All data are expressed as the number of patients (percentage) or the mean \pm SD. The normality of distribution was assessed with a q–q plot and the Shapiro-Wilk test. Data between groups were compared by χ^2 test, Fisher's exact test, or independent t-test with post hoc comparison using the Bonferroni test as appropriate. A P value <0.05 was considered significant.

Results

OPCAB was successfully performed in all patients without requiring emergency conversion to an on-pump procedure. Thus, data for all 76 patients were analyzed. None of the patients underwent reoperation because of bleeding (Figure).

Patients' characteristics and the preoperative fibrinogen level were all statistically not different between the groups (Table 1). Operative data, including the number of grafts performed, were also similar between the groups (Table 2).

The amounts of perioperative blood loss and transfusion requirement are listed in Table 3. Overall, during the perioperative period (which combined the intraoperative and 24 h

	Intraoperative	Postoperative 4 h	Postoperative 24 h	Total
Blood loss (ml)				
Control	221 (147)	237 (158)	729 (449)	944±482
TA	236 (196)	167 (134)*	751 (489)	986±520
P value	0.718	0.041	0.832	0.720
Amount of pRBC (units)				
Control	1.0±1.0	0.2±0.4	0.4±0.8	1.4±1.2
TA	0.5±0.7*	0.0±0.2	0.2±0.6	0.8±0.8*
P value	0.016	0.061	0.340	0.010
Patients requiring pRBC (%)				
Control	24 (71)	6 (16)	8 (21)	27 (71)
TA	16 (42)	1 (3)	6 (16)	20 (53)
P value	0.066	0.108	0.554	0.098
Amount of FFP (units)				
Control	0.05±0.32		0.34±0.97	0.39±1.00
TA	0		0.05±0.23	0.05±0.23
P value	0.321		0.076	0.043*
Patients requiring FFP (%)				
Control	1 (3)	0 (0)	4 (11)	5 (13)
TA	0 (0)	0 (0)	2 (5)	2 (5)
P value	>0.999	>0.999	0.674	0.430

Values are mean (SD) or number of patients.

*P<0.05 compared with Control group.

Total, combined data of intraoperative and postoperative 24 h; TA, tranexamic acid; pRBC, packed red blood cells; FFP, fresh frozen plasma.

postoperative period), patients in the TA group received a significantly smaller amount of pRBC transfusion, although the amount of blood loss was similar between the groups. Also, the number of patients requiring pRBC transfusion during the perioperative period tended to be less in the TA group (20 vs. 27, P=0.098). In detail, during the operation, patients in the TA group received significantly smaller pRBC transfusion. Also, fewer patients required pRBC transfusion in the TA group, without statistical significance (P=0.066). For the first 4 h after operation, the TA group lost a significantly smaller amount of blood and required less pRBC transfusion. The amount of FFP transfusion during the perioperative period was significantly less in the TA group. None of the patients was transfused with platelet concentrate during the study period.

Baseline and postoperative hematologic variables were all comparable between the groups. The lowest Hb level during the perioperative period was 76±9 g/L in the Control group and 75±9 g/L in TA group (P=0.823) (Table 4).

The incidence of MI (0 vs. 1, P=0.471) and of renal insufficiency (5 vs. 5, P>0.999) was similar between the groups. There were no reports of stroke or other thromboembolic complications in either group.

Discussion

In this prospective randomized study, we observed significantly smaller amounts of pRBC and FFP transfusion in the TA group during the perioperative study period among this cohort of patients with preoperative anemia who continued DAPT until within 5 days of OPCAB, although the differences in the total amount of blood loss and number of patients requiring pRBC transfusion did not reach statistical significance between the groups.

Platelets play a pivotal role in hemostasis, and platelet dys-

	Preoperative	End of operation	POD 1
Hemoglobin (g/L)			
Control	108 (11)	87 (11)	89 (9)
TA	109 (9)	84 (7)	88 (10)
P value	0.913	0.327	0.823
Platelet count (10⁹/L)			
Control	274 (90)	169 (72)	162 (65)
TA	270 (86)	189 (71)	179 (63)
P value	0.857	0.231	0.260
PT (s)			
Control	11.0 (2.0)		12.2 (1.1)
TA	11.0 (0.8)		12.7 (1.3)
P value	0.960		0.078
aPTT (s)			
Control	40.1 (19.6)		32.1 (7.3)
TA	34.1 (11.5)		33.8 (10.6)
P value	0.113		0.422

Values are mean (SD).

POD, postoperative day; TA, tranexamic acid; PT, prothrombin time; aPTT, activated partial thromboplastin time.

function is regarded as a major pathophysiologic cause of nonsurgical postoperative bleeding.¹⁹ In cardiac surgery using CPB, it is the bypass that mainly contributes to the decrease in platelet number and function through hemodilution, adhesion, activation, and mechanical destruction.²⁰ Not surprisingly, a considerable number of coronary patients presenting for CABG are at high risk of bleeding and hemorrhagic complications if they are receiving DAPT consisting of aspirin and

clopidogrel, and such patients are recommended to discontinue the drugs 5 days prior to surgery.²¹ However, an increasing number of studies warn of the adverse consequences of discontinuing these agents, especially in patients with previous stent implantation or acute coronary syndrome.²² Altogether, the recent literature on antiplatelet agents implies that there may be an ischemic or even a mortality benefit with some degree of platelet inhibition at the time of CABG, despite a possible risk of excessive bleeding.²³ In the context of maximizing the ischemic benefit while minimizing the bleeding and transfusion risk conveyed by DAPT, OPCAB has been proposed as an alternative surgical revascularization technique.⁸

Transfusion of allogeneic blood products carries risks far beyond the risk of disease transmission affecting the patient's outcome after cardiac surgery.¹ Despite efforts to reduce allogeneic blood transfusion, blood transfusion is still common in patients undergoing cardiac surgery, including OPCAB. Among the many risk factors of transfusion, preoperative anemia is not uncommon in patients undergoing CABG partly because of preoperative percutaneous coronary angiography or interventions.²⁴ Mild preoperative anemia (Hct <35%) has been demonstrated to be an independent risk factor of transfusion in patients undergoing OPCAB.² Furthermore, a reduced Hct produces a reversible platelet dysfunction manifested by an increase in bleeding time and blood loss at the bleeding site.⁹ In most cases, however, CABG is usually not delayed based on the presence of mild preoperative anemia and these patients are frequently on DAPT. Thus, for preoperatively anemic patients who are receiving DAPT until shortly before CABG, a strategy to reduce perioperative blood loss and transfusion is essential.

Plasmin has been demonstrated to induce platelet dysfunction by activating the complement cascade, and inducing proteolytic degradation and redistribution of platelet glycoprotein receptors.²⁵ TA reduces the plasma concentration of plasmin by blocking the lysine-binding sites of plasminogen, thus blocking the interaction with specific lysine residues of fibrin and hindering the conversion of plasminogen to plasmin.¹⁰ TA infusion has already been demonstrated to reduce postoperative blood loss and transfusion requirements in various cardiac surgeries, including OPCAB.¹¹ Indeed, although the efficacy of TA on CPB-related platelet dysfunction was less than that of aprotinin, TA partially reversed platelet aggregation dysfunction associated with antiplatelet therapy in an *in vitro* analysis.¹⁴ Still, controversial results of TA had been reported in clinical studies of on-pump CABG involving patients treated with antiplatelet agents. In a retrospective review of patients undergoing on-pump CABG, the beneficial effect of TA on perioperative blood loss and transfusion requirement was less prominent in patients preoperatively treated with clopidogrel.¹³ In contrast, in a prospective study, a single dose of intraoperative TA reduced postoperative bleeding in patients treated with aspirin until the day of on-pump CABG. However, there have been no studies addressing the influence of TA on patients with preoperative DAPT undergoing OPCAB.

In the current trial, TA had a beneficial effect on the amount of pRBC transfusion during the study period. In addition, although it did not reach statistical significance, fewer of the TA group patients required transfusion, even though the overall amount of blood loss during the study period was similar between the groups. The discordance between the reduced transfusion requirement and no difference in the amount of blood loss may be attributed to the following. Firstly, intraoperative use of a cell salvage device appears to mitigate the beneficial influence conferred by TA, especially in terms of

the amount of blood loss. Similar results were observed in a previous study addressing the efficacy of TA in conjunction with cell salvage in OPCAB, which excluded patients treated with clopidogrel.²⁶ In that study, a significant reduction in blood loss at 4 h postoperatively was observed (median difference 50 ml), although there was no difference in total blood loss, as in our study. Secondly, greater FFP requirement in the Control group may have resulted in reduced postoperative bleeding in that group. In a recent meta-analysis, use of TA in OPCAB was associated with a significant reduction in risk of FFP transfusion when PT was used as a transfusion criterion,²⁷ as in our study. Thirdly, inaccurate measurement of intraoperative blood loss may also have masked the beneficial influence of TA in terms of blood loss, which is a limitation of our study. TA might have affected the amount of insensible blood loss soaked up by gauzes and tapes, which is often difficult to assess accurately. The absolute amount of insensible blood loss and its difference between the groups may not be considerable. However, because our patients were preoperatively anemic with marginal Hb levels and little RBC reserve, the difference in insensible blood loss might have been significant enough to result in less pRBC transfusion in the TA group.

More specifically, TA's beneficial influence on blood loss and transfusion requirement was more prominent during the intraoperative period and for the first 4 h after surgery, whereas it did not exert any effects over the postoperative 24 h. This is not surprising considering that TA's half-life is 2–4 h and that it was infused only during the operation, which is in agreement with the results of a recent meta-analysis demonstrating no beneficial influence of TA on midperiod (4–24 h) blood loss.²⁷ Most critical decisions regarding the transfusion of coagulation factors and/or hemostatic re-exploration are decided within the first 4 h after surgery.²⁸ Thus, the findings that TA had a beneficial influence, especially during the intraoperative and first 4 h after surgery, even with concomitant use of intraoperative cell salvage device, suggest a potential role as a blood conservation strategy in this subset of patients.

The use of antifibrinolytic agents carries the risk of various thromboembolic events, as well as increasing the early graft occlusion rate in patients undergoing CABG.²⁹ TA did not increase the risk of thromboembolic complications or compromise early venous graft patency rate in various studies of both on-pump CABG and OPCAB.²⁹ In the current study, any complications related to thromboembolic events or an increase in the rate of perioperative MI were not observed. However, a cumulative warm ischemia–reperfusion injury and systemic inflammatory response elicited by multivessel OPCAB was demonstrated to be associated with a postoperative hypercoagulable state with increased coagulation and fibrinolysis mimicking consumptive coagulopathy.³⁰ Thus, we limited the duration of TA infusion to the intraoperative period, although more definite effects of TA on the transfusion requirement could have been observed by extending TA infusion to the postoperative period.

Another limitation is that we did not assess individual platelet responsiveness, which might have confounded the results of the current trial. However, there is currently no generally accepted platelet function assay for assessing the responsiveness to antiplatelet agents that correlates well with blood loss and with enough clinical evidence to support its influence.

In conclusion, intraoperative TA infusion could be safely used as a blood conservation strategy in preoperatively anemic patients who continue DAPT until within 5 days of OPCAB. Its beneficial influence on blood loss and transfusion requirement was mostly confined to the intraoperative period and the

first 4 h after operation in relation to the duration of TA infusion and its pharmacokinetics, even with routine use of cell salvage during the operation.

Disclosure

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