# Tranexamic acid in emergency coronary surgery. Time for routine use?

## Czy rutynowo stosować śródoperacyjnie kwas traneksamowy u chorych operowanych w trybie pilnym z powodu ostrego zespołu wieńcowego?

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### Abstract

**Aim of the study:** To evaluate retrospectively the blood sparing effect and the side effects of prophylactic treatment with tranexamic acid in patients on antiplatelet medication (aspirin and clopidogrel) requiring emergency coronary surgery.

**Material and methods:** Perioperative data on 120 patients consecutively operated on in our department from July 2009 until June 2010 for coronary artery disease on an emergency basis were analysed retrospectively. During the first 6 months 60 patients were operated on and received no antifibrinolytic treatment (control group). The next 60 patients (TA group) received tranexamic acid according to a new protocol implemented in January 2010. Mortality and morbidity including postoperative bleeding and blood and blood products usage were compared between the groups.

**Results:** The demographic data and operative risk in both groups were similar. Postoperative drainage was lower in the tranexamic acid group (563.0 ml ±384.4 vs. 1047.1 ml ±1025.9 $p < 0.05$). The blood, fresh frozen plasma and platelet transfusion requirements were not statistically different between groups (blood 1.5 units ±2.1 vs. 2.5 units ±3.1, $p = 0.07$, fresh frozen plasma 1.1 units ±1.6 vs. 1.7 units ±2.7, $p = 0.2$, platelets 1.6 units ±2.6 vs. 1.4 units ±3.5, $p = 0.3$). There were no deaths in the tranexamic acid group and 4 deaths (6.7%, $p = 0.04$) in the control group. Myocardial infarction occurred in 3 (5%) and 10 (16.7%) patients respectively ($p = 0.03$). Cerebrovascular accidents occurred in 2 patients (3.3%) in both groups ($p = 0.6$). Two patients (3.3%) from the treatment group and 5 (8.3%) from the control group required re-exploration for bleeding ($p = 0.2$).

**Conclusions:** Perioperative prophylactic therapy with tranexamic acid reduces postoperative bleeding but does not influence the requirements for blood and fresh frozen plasma in patients undergoing emergency coronary artery bypass grafting. No increase in cardiac, neurological, respiratory or renal complications was noted.

### Streszczenie

**Wstęp:** W ostatnich latach obserwuje się wzrost odsetka chorych poddanych operacji pomostowania naczyń wieńcowych w trybie pilnym. Istotnym problemem dla kardiochirurga jest wpływ leków antyagregacyjnych, rutynowo stosowanych u tych pacjentów, na zwiększone ryzyko wystąpienia krwawienia pooperacyjnego.

**Cel pracy:** Celem pracy było zbadanie wpływu śródoperacyjnego stosowania kwasu traneksamowego na krwawienie pooperacyjne, zużycie krwi i preparatów krwiopochodnych oraz wystąpienie powikłań u chorych operowanych w trybie pilnym, u których nie odstawiono leków przeciwpłytkowych przed operacją.

**Materiał i metody:** Zbadano retrospektywnie chorych, u których w trybie pilnym wykonano pomostowanie naczyń wieńcowych w krążeniu pozaustrojowym. Porównano dwie 60-osobowe grupy chorych. W jednej grupie stosowano kwas traneksamowy śródoperacyjnie, w drugiej, kontrolnej, kwasu tego nie stosowano. W obu grupach oceniono pooperacyjny drenaż krwi oraz zużycie krwi i preparatów krwiopochodnych. Porównano także śmiertelność wczesną i wystąpienie powikłań.

**Wyniki:** Dane demograficzne oraz ryzyko operacyjne w obu grupach były zbliżone. Drenaż pooperacyjny w grupie badanej był mniejszy (średni drenaż 563,0 ml ±384,4 *vs* 1047,1 ml ±1025,9, $p < 0,05$). Zużycie krwi, osocza i płytek krwi nie różniło się istotnie statystycznie w obu grupach (średnio na jednego chorego zużyto: koncentratu krwinek czerwonych 1,5 j. ±2,1 *vs* 2,5 j. ±3,1, $p = 0,07$; świeżo mrożonego osocza 1,1 j. ±1,6 *vs* 1,7 j. ±2,7, $p = 0,2$; płytek krwi 1,6 j. ±2,6 *vs* 1,4 j. ±3,5, $p = 0,3$). W grupie badanej nie wystąpiły zgony, natomiast w grupie kontrolnej wystąpiły 4 zgony (6,7%, $p = 0,04$), zawał mięśnia sercowego wystąpił odpowiednio u 3 (5%) i 10 (16,7%, $p = 0,03$) chorych, udar mózgu w obu grupach u 2 pacjentów (3,3%, $p = 0,6$), ostra niewydolność nerek wymagająca zastosowania hemodiafiltracji u 3 i 4 (5% *vs* 6,7%, $p = 0,5$), niewydolność oddechowa

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u 3 (5%) i 5 (8,3%, $p$ = 0,3); reoperacji z powodu krwawienia wymagało odpowiednio 2 (3,3%) i 5 (8,3%, $p$ = 0,2) chorych.
**Wnioski:** Stosowanie kwasu traneksamowego podczas operacji pomostowania wieńcowego wykonywanych w trybie pilnym wpływa na zmniejszenie drenażu pooperacyjnego, natomiast nie wpływa istotnie na ilość przetoczonej krwi i jej preparatów. Nie obserwowano większej liczby zgonów wczesnych, powikłań sercowych, mózgowych czy oddechowych w grupie badanej. Stosowanie kwasu traneksamowego nie wpłynęło na większe ryzyko wystąpienia niewydolności nerek.
**Słowa kluczowe:** pilne pomostowanie naczyń wieńcowych, krwawienie pooperacyjne, kwas traneksamowy.

## Introduction

In recent years a trend towards a higher percentage of patients who require an emergency operation for acute coronary syndrome (ACS) may be observed [1]. Standard pharmacological therapy in these high-risk patients includes antiplatelet agents, the dosage of which may be increased in acute coronary syndromes. The withholding of these agents may expose the patients to an increase in thrombotic complications prior to surgery, especially in those who have recently undergone a percutaneous coronary intervention [2-4]. Antiplatelets increase the risk of postoperative bleeding complications, and the requirement for blood and blood products transfusion [5-9], so platelet function tests and perioperative platelet transfusion are advised in such patients [10]. Other measures to minimize postoperative blood loss include antifibrinolytic medications. Aprotinin was often employed previously, but it was withdrawn from the market by the manufacturer following doubts concerning its safety [11]. Tranexamic acid (TA) is a synthetic amino acid with antifibrinolytic activity. It works by the direct inhibition of plasminogen activators, thus stopping its conversion to plasmin. TA is also a plasmin inhibitor and in high doses inhibits the complement cascade [12].

**Tab. I.** Tranexamic acid administration protocol

| Protocol |
|---|
| Prepare bolus dose: 1000 mg of TA in 100 ml of 0.9% NaCl.<br>Give 5 ml testing dose on induction of anaesthesia.<br>After 10 minutes give the rest of the bolus dose over 10 minutes.<br>Add 500 mg to pump prime.<br>After the bolus start maintenance infusion 400 mg/h. |
| Note: For patients with moderate to severe impaired renal function, the following dosages are recommended:<br>Serum creatinine 1-3 mg/dL<br>Prepare bolus dose: 750 mg of TA in 100 ml of 0.9% NaCl.<br>Give 5 ml testing dose on induction of anaesthesia.<br>After 10 minutes give the rest of the bolus dose over 10 minutes.<br>Add 250 mg to pump prime.<br>After the bolus start maintenance infusion 200 mg/h.<br>Serum creatinine above 3 mg/dL<br>Prepare bolus dose: 750 mg of TA in 100 ml of 0.9% NaCl.<br>Give 5 ml testing dose on induction of anaesthesia.<br>After 10 minutes give the rest of the bolus dose over 10 minutes. |

Our aim was to examine what kind of influence tranexamic acid administration has on postoperative bleeding, the consumption of blood and blood products, and what the side effects of such therapy are in patients on antiplatelet medication (aspirin and clopidogrel) who urgently require an operation.

## Material and methods

The study is based on a retrospective analysis of data collected from all the 120 patients consecutively operated on in our institution between June 2009 and July 2010 for coronary disease on an emergency basis (for unstable angina or acute coronary syndrome). Double antiplatelet medication (aspirin and clopidogrel) was continued until the operation day. Our own protocol (Table I) for tranexamic acid administration was developed and introduced into routine practice in January 2010. All patients ($n$ = 60) operated on after that date were treated with TA and were included in the treatment group of this study. Patients operated on before that date ($n$ = 60) did not receive TA and were included in the control group. The anaesthesia and cardiopulmonary bypass protocols remained unchanged during the study. Cardiopulmonary bypass (CPB) was used in all cases. All the patients received 400 IU of heparin per kg of body weight before aortic cannulation. The adequacy of anticoagulation was confirmed with ACT. During the cardiopulmonary bypass a temperature drift to 35°C was allowed. St. Thomas crystalloid cardioplegia was administered into the aortic root. The internal thoracic artery and vein grafts were used in most patients but 4 of them also received radial artery grafts. All the patients received protamine (1 mg for each 100 IU of received heparin) after the completion of cardiopulmonary bypass. The pericardium was left open and two 32F drains were inserted into the mediastinum or into the pleura if it was open. The drains were put on suction after the operation.

The demographic data (patients' age, sex, body mass index [BMI], logistic EuroSCORE [LES], left ventricle ejection fraction [LVEF]) of patients from both groups were compared. The postoperative results were analysed by comparing mortality, time of hospitalization, incidence of myocardial infarction, atrial fibrillation, cerebrovascular accidents, acute renal failure defined as a necessity of implementation of renal replacement therapy, respiratory failure requiring

ventilation for more than 24 hours and re-exploration for bleeding. The total drainage in all patients was noted and compared between both groups. A cell-saver machine was used in all the cases when the drainage in the first three hours exceeded 600 ml. The transfusion of blood and blood products was also compared between groups. Blood was generally transfused when the haemoglobin was found to be lower than 6 mmol/l. Platelets, plasma and clotting factors were prescribed for coagulation disorders according to the thromboelastometry results. A ROTEM® analyser was used. EXTEM and INTEM tests were applied. The coagulation time (CT), clot formation time (CFT), alpha angle and maximal clot firmness (MCF) were measured to assess the platelet, fibrinogen and fibrin function.

Descriptive statistics for the groups are presented as mean±standard deviation or as a simple percentage. Differences within and between groups were analysed using the two-tailed unpaired or paired Student's *t*-test or Fisher's exact test as appropriate, when continuous and dichotomized variables were compared. The Mann-Whitney *U* test was used to compare postoperative blood loss and transfusion requirements, which do not follow a Gaussian distribution. A $p$ value < 0.05 was considered as statistically significant. The statistical software package Statistica, version 6.0 and Microsoft® Excel 2000 were used to analyse data.

## Results

The demographic and operative data are presented in Table II. Both groups were similar in mean age, percentage of female sex, LES and LVEF. The operative risk calculated with logistic EuroSCORE was not statistically different. The TA group had a higher percentage of diabetic patients. The mean cardiopulmonary bypass time and cross-clamp time were longer in the control group. The mean number of grafts was not statistically different between groups and the haemoglobin levels were similar. It was found that the mean creatinine level before the operation was higher in the TA group. Although there were no deaths in the TA group there were 4 (6.7%; $p = 0.04$) deaths in the control group.

**Tab. II.** Demographic and operative data

| | Tranexamic acid | Control group | *p* value |
|---|---|---|---|
| male/female | 45/15 | 46/14 | 0.5 |
| age (years) | 64.2 ±8.8 | 62.8 ±9.4 | 0.4 |
| operative risk (LES) | 10.4 ±9.6 | 9.6 ±13.0 | 0.1 |
| ejection fraction (% EF) | 46.9 ±10.4 | 46.2 ±13.0 | 0.8 |
| BMI | 29.4 ±3.6 | 27.7 ±3.8 | 0.01 |
| haemoglobin levels (mmol/L) | 6.7 ±0.8 | 6.6 ±0.7 | 0.5 |
| creatinine levels (mg/dL) | 1.2 ±0.8 | 1.0 ±0.8 | 0.01 |
| CPB time (min) | 49.9 ±14.1 | 58.8 ±15.7 | 0.001 |
| cross-clamping time (min) | 28.1 ±8.2 | 32.5 ±9.3 | 0.01 |
| number of coronary grafts | 3.2 ±0.8 | 3.2 ±0.7 | 0.9 |
| diabetes mellitus | 18 (30%) | 13 (21.6%) | 0.2 |

The cause of death in three cases was low output syndrome. One patient died after re-exploration for bleeding with signs of multiple organ failure. Myocardial infarction occurred in 3 patients from the TA group and in 10 control group patients (5% vs. 16.7%; $p = 0.03$). Atrial fibrillation occurred in 17 and 10 patients respectively (28.3% vs. 16.3%; $p = 0.09$). Cerebrovascular accidents occurred in 2 (3.3%) patients from both groups. Renal replacement therapy was necessary for 3 and 4 patients (5% vs. 6.7%; $p = 0.5$) following acute renal failure. Respiratory failure (intubation longer than 24 hours) occurred in 3 and 5 patients (5% vs. 8.3%; $p = 0.3$). Two (3.3%) patients in the TA group and 5 (8.3%; $p = 0.2$) in the control group needed to be reoperated on for bleeding. Among the patients who needed re-exploration for bleeding, in two TA patients surgical bleeding was identified, whereas in the control group patients it was general oozing. Mean postoperative drainage was lower in the TA group (563.0 ml ±384.4 vs. 1047.1 ml ±1025.9; $p = 0.000001$). A cell saving device was used in 2 (3.3%) TA patients and 10 (16.7%; $p = 0.01$) control group patients. Blood and blood products usage was not statistically different between groups: average packed red cells transfusion was 1.5 ±2.1 in the TA group vs. 2.5 ±3.1 units in the control group ($p = 0.07$), fresh frozen plasma 1.1 ±1.6 vs. 1.7 ±2.7 units ($p = 0.2$) and platelets 1.6 ±2.6 vs. 1.4 ±3.5 units, $p = 0.3$. It was found that the creatinine and CRP levels after the operation were not different. The average time spent in hospital was similar for both groups. The postoperative data from both TA and control groups are presented in Table III.

## Discussion

Every surgeon accepting a patient suffering from an acute coronary condition to undergo an emergency operation has to bear in mind the influence that antiplatelets have on such patients. This is due to the fact that in such circumstances platelets are used in much higher doses than in patients with chronic and stable coronary disease. The fear of increased levels of postoperative bleeding in patients may persuade the surgeon to stop the antiplatelets and postpone the operation by a few days, until the platelet function recovers. In some patients, however, exacerbation of their clinical condition may follow. Patients who have had implanted stents placed into their coronary arteries in the last 12 months are at an especially high risk of developing stent thrombosis [13].

The results of our study show that tranexamic acid administration during cardiopulmonary bypass emergency operations leads to a reduction of postoperative bleeding. Therefore it allows a timely surgical intervention, since no time delay is necessary in order to stop the clopidogrel. The blood sparing effect of tranexamic acid has been summarized by Ngaage's meta-analysis [14] of studies performed between 1995 and 2009. Our results show a similar effect of TA on the reduction of blood loss. The fact that no reduction in platelet transfusion was observed may be explained by the fact that platelets were used in most of our patients, whose platelets were blocked with antiaggregants. Similar-

**Tab. III.** Postoperative data

| | Tranexamic acid | Control group | *p* value |
|---|---|---|---|
| mortality | 0 | 4 (6.7%) | 0.04 |
| hospitalisation time (days) | 8.8 ±2.6 | 9.0 ±5.2 | 0.6 |
| myocardial infarction | 3 (5%) | 10 (16.7%) | 0.03 |
| atrial fibrillation | 17 (28.3%) | 10 (16.7%) | 0.09 |
| neurological complications | 2 (3.3%) | 2 (3.3%) | 0.6 |
| dialysis-dependent acute renal failure | 3 (5%) | 4 (6.7%) | 0.5 |
| respiratory failure | 3 (5%) | 5 (8.3%) | 0.3 |
| re-operation for bleeding | 2 (3.3%) | 5 (8.3%) | 0.2 |
| postoperative bleeding (ml) | 563.0 ml ±384.4 | 1047.1 ml ±1025.9 | 0.000001 |
| excluding re-operation | 525.4 ml ±302.6 | 806.6 ml ±363.9 | 0.000001 |
| packed red blood cells PC (u) | 1.5 j ±2.1 | 2.5 j ±3.1 | 0.07 |
| fresh frozen plasma FFP (u) | 1.1 j ±1.6 | 1.7 j ± 2.7 | 0.2 |
| platelet concentrates PLT (u) | 1.6 j ±2.6 | 1.4 j ±3.5 | 0.3 |
| Cell Saver | 2 (3.3%) | 10 (16.7%) | 0.01 |
| creatinine (mg/dL) | 1.6 ±1.5 | 1.27 ±0.87 | 0.1 |
| CRP | 148.3 ±77.4 | 164.5±73.2 | 0.1 |

ly we have also noted the reduction of reoperation risk in TA patients. Patients who needed to be reoperated on for bleeding were also found to have an increased mortality in our material. This was also noted by Choong [15].

The dosage of tranexamic acid in our protocol is dependent on renal function. It never exceeds 50 mg/kg of the patient's body weight. Karski [16] analysed three different doses. He used 50, 100 and 150 mg/kg of body weight. He concluded that 100 mg/kg is the most effective. However, Brown [17] and Lambert [18] stated that there were no significant differences in high and low dosage groups.

Owing to the fact that no higher risk of adverse effects of tranexamic acid treatment was noted either in our or in previous studies, we would like to suggest that tranexamic acid should be considered for patients under the effect of antiplatelet medication who require an emergency cardiac operation. Similar data were collected in meta-analyses mentioned above [14,17]. We did not observe higher incidence of renal failure in the TA group.

Our conclusion is that tranexamic acid should be considered for routine use during all emergency coronary operations performed with cardiopulmonary bypass because it can safely lower postoperative drainage without increasing morbidity. The topic needs to be further explored in order to prove the safety of such treatment in a larger group.

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