Acute Myocardial Infarction After Tranexamic Acid: Review of Published Case Reports

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Key words: tranexamic acid; thrombosis; myocardial infarction

Objective To summarize cases of acute myocardial infarction (AMI) after tranexamic acid (TXA) administration.

Methods Electronic databases were searched to identify all case reports presenting AMI after TXA. Two authors independently extracted data of patients’ manifestation, examinations, medical history, treatment and outcome.

Results Our search yielded seven case reports including seven patients. Among the seven reports, two were from USA, the other five were from India, Turkey, UK, Italy and France, respectively. Of the seven patients aged between 28- and 77-year-old who developed AMI after TXA, five patients were female and two were male. TXA were prescribed in four patients for reducing surgical bleeding, in two patients for menorrhagia and in one patient for hemoptysis. The diagnosis of AMI was made based upon patients’ symptoms, ECG, myocardium-specific enzymes, and confirmed by coronary angiography. Coronary stent were placed in four patients, and anti-platelet and anti-coagulation drugs were prescribed. No death or major cardiovascular events were reported during hospitalization and follow-up.

Conclusion These case reports suggested a possible association of TXA administration and an increased risk of AMI, even in patients with relatively low thrombotic risk.

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Antifibrinolytic agents, such as tranexamic acid (TXA) and aprotinin, have been extensively used to prevent bleeding. In a meta-analysis\(^1\) including 129 trials, there was a significant reduction in the probability of blood transfusion with the use of antifibrinolytics. The result of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) led to the suspension of aprotinin use in cardiac surgery by Food and Drug Administration (FDA) in the USA in 2007 over concerns of increased mortality.\(^2\) TXA is a synthetic derivative of 4-aminomethyl cyclohexane carboxylic acid, which binds to the lysine-binding sites on plasminogen, competitively inhibits the activation of plasminogen to plasmin, and stabilizes the clots.\(^3\) The FDA approved TXA for the treatment of heavy menstrual bleeding and as a hemostatic agent in patients with symptomatic hemophilia and von Willebrand disease. TXA is also used in the settings of cardiac surgery,\(^4\) orthopedic surgery,\(^5\) and trauma\(^6\) to minimize peri-operative blood. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial demonstrated that there was a significant reduction in all-cause mortality in trauma patients treated with TXA and death due to bleeding.\(^7\) Antifibrinolytic agents have been associated with thromboembolic events.\(^1\)-\(^3\) However, the thrombotic risks of TXA have yet to be adequately examined by prospective clinical trials and are still an area of uncertainty.\(^8\) An database maintained by the World Health Organization (WHO) recorded 56 cases of pulmonary embolism (PE), deep vein thrombosis (DVT), cerebral vein thrombosis (CVT) and retinal vein thrombosis (RVT) caused by TXA, and 9 cases of arterial thrombosis and 22 cases of cerebral embolism caused by TXA.\(^9\) In the present study, we summarized case reports of acute myocardial infarction (AMI) after the use of TXA.

**MATERIALS AND METHODS**

**Search strategy**

We included all case reports presenting AMI after TXA. Relevant case reports were identified by computerized searches of MEDLINE, Cochrane Library and EMBASE till April 2\(^{nd}\) 2019, using different combination of search words as follows:
Data abstraction

The following data were independently abstracted from the included reports to a data collection form by two authors (YTY and XY) independently: (1) first author, country, and year of publication; (2) patient gender, age, comorbidities, medical history, thrombotic risk factors and co-medications with TXA; (3) onset, manifestation, examination, diagnosis and treatment of AMI; (4) patient outcomes and follow-up. Disagreements were resolved by discussion among all authors during the process of data abstraction.

RESULTS

Database search identified seven articles of case reports,[9-15] all written in English. Among the seven reports, two were from the USA,[9,10] the other five were from India,[11] Turkey,[12] UK,[13] Italy,[14] and France,[15] respectively. Of the seven patients who developed AMI after TXA, five patients were female[9,11,13-15] and two were male.[10,12] They aged between 28- and 77-year-old, most of whom were cardiovascularly well and had no thrombotic history except one patient[10]. TXA were prescribed in four patients for reducing surgical bleeding,[9,10,12,13] in two patients for menorrhagia[11,14] and in one patient for hemoptysis.[15] Detailed information of these reports is presented in Table 1. In the first case reported by Gerstein et al.[10] from USA, a human immunodeficiency virus (HIV) positive patient undergoing elective spine fusion surgery developed an ST-elevation myocardial infarction (STEMI) and a left ventricle thrombus within 12 hours after receiving TXA. In the second reported case by Garg et al.[9] from USA, a 56-year-old hypertensive and obese female patient developed AMI after TXA being used before hip arthroplasty. In the third reported case by Gupta et al.[11] from India, a 41-year-old
female developed AMI after combined treatment of TXA for menorrhagia and Mefenamic acid for dysmenorrhoea for two years. In the fourth case reported by Günlaldi et al.\textsuperscript{[12]} from Turkey, a 49-year-old male with Hemophilia A and factor V Leiden mutation (FVLM) developed post-operative AMI after oral TXA and intravenous recombinant FVIII replacement before tooth extraction. In the fifth case reported by Sirker et al.\textsuperscript{[13]} from UK, a 28-year-old female patient with bleeding diathesis developed AMI after treatment with desmopressin and TXA before and after shoulder surgery, respectively. In the sixth reported case by Iacobellis et al.\textsuperscript{[14]} from Italy, TXA was prescribed for the management of uterine leiomyoma associated menorrhagia in a 42-year-old healthy woman who received oral contraceptive, and she developed AMI two months later. In the seventh reported case by Mekontso-Dessap et al.\textsuperscript{[15]} from France, oral TA was used for the treatment of hemoptysis secondary to pulmonary tuberculosis in a 77-year-old female patient, who developed AMI two days after TXA dose escalation.

**Table 1. Clinical characteristics of the included case reports**

| References            | Country | Sex | Age (yrs) | Risk factors of thrombosis | Past history | TXA and co-medications |
|-----------------------|---------|-----|-----------|-----------------------------|--------------|------------------------|
| Gerstein et al.\textsuperscript{[10]} | USA     | M   | 66        | deep vein thrombosis, transit ischemia attack, HIV(+) | COPD, spine surgeries | TXA (1 g iv. followed by 1 mg/kg-h infusion) during spine surgery |
| Garg et al.\textsuperscript{[9]}     | USA     | F   | 56        | hypertension, obesity, smoking | arthritis | TXA (10 mg/kg iv.) before hip anthroplasty |
| Gupta et al.\textsuperscript{[11]}   | India   | F   | 41        | hypertension                |               | TXA (0.5 g po tid \times 2 year)+mefenamic acid (0.25 g po tid \times 2 year) for menorrhagia and dysmenorrhoea |
| Günlaldi et al.\textsuperscript{[12]}| Turkey  | M   | 49        | hemophilia A, factor V Leiden mutation, intra-articular hemorrhage |               | TXA (20 mg/kg po. qd.\times 10 days) and r-FVIII (40 U/kg iv.) before |
As shown in Table 2, the diagnosis of seven cases of AMI was made based upon patients’ symptoms, ECG, myocardium-specific enzymes, and all confirmed by coronary angiography. Echocardiography was performed to confirm the diagnosis of AMI and for further evaluation of heart function in five patients. Coronary stents were placed in four patients, anti-platelet agents (aspirin, clopidogrel, eptifibatide) and anti-coagulation drugs (heparin, warfarin) were prescribed. No death or major cardiovascular events were reported during hospitalization and follow-up.
### Table 2. Diagnosis of myocardial infarction of the included case reports

| References     | Onset                    | Manifestations                        | ECG                  | Enzymes               | CA angiography | Diagnosis                      |
|----------------|--------------------------|---------------------------------------|----------------------|-----------------------|----------------|---------------------------------|
| Gerstein et al. [10] | in PACU                  | tachycardia                           | ST elevation (anterior, anterolateral leads) | TnI 4.04 ng/ml       | proximal LAD lesion, complete occlusion of diagonal branch | MI, LV thrombus |
| Garg et al. [9]     | postoperatively           | chest pain, diaphoresis, hypotension  | ST elevation (leads II, III, aVF) | TnI 0.25 ng/ml and CK 427 U/L | complete occlusion of the distal RCA | MI (inferior wall) |
| Gupta et al. [11]   | fourteen days from last time of TXA | chest pain, sweating                  | ST elevation (inferior wall and RV) | Not reported | RCA: eccentric 99% lesion of proximal RCA with thrombus | MI (inferior wall, RV) |
| Günlaldi et al. [12] | after r-FⅢ administration | chest pain, agitation, sweating        | ST elevation (leads III, II, aVF, V4) and ST depression (leads V1, V2) | LDH 392 U/L and CK-M B 170 U/L | RCA 90% stenosis, LAD 40% stenosis | MI (inferoposterolateral wall, RV) |
| Sirker et al. [13]  | three days after therapy  | chest pain (inferior)                 | ST elevation (in keeping with the acute occlusion) | Occlusion in a small distal branch of RCA, minimal wall irregularity of LAD | MI (inferior wall) |
### DISCUSSION

The association between TXA use and AMI occurrence remains unknown. Although TXA might precipitate AMI, results from clinical trials showed that TXA decreases rather than increase the risk of myocardial infarction.\[^{[16]}\] For example, The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH)-2 trial comprising 20,211 patients demonstrated that in those trauma patients who were treated with TXA within 3 hours of injury, the risk of MI was half that of the placebo ($P=0.005$).\[^{[7,17]}\] Similar to that, a meta-analysis of 129 trials involving 10,488 surgical patients demonstrated a non-significant reduction in the risk of MI in TXA-treated patients than non-TXA-treated patients ($RR=0.68$, 95% CI: 0.43-1.09, $P=0.11$).\[^{[1]}\]

Recently, the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial examined TXA involving 4,631 patients at high risk for thrombotic complications demonstrated that, TXA was associated with a lower risk of bleeding than placebo, without a higher risk of death or thrombotic complications within 30 days after surgery, and that the relative risk of MI during the same period with TXA vs. placebo

| Iacobellis et al.\[^{[14]}\] | 2 months after TXA and contraceptive | Deep negative T waves and Q wave in leads V1 to V4 | TnI 4.3 μg/ml, CK-MB 66 ng/ml, and CK 653 U/L | Ulcerated plaque on proximal LAD without narrowing | MI |
|-----------------------------|----------------------------------|------------------------------------------------|------------------------------------------|--------------------------------------------|-----|
| Mekontso-Dessap et al.\[^{[15]}\] | 2 days after dosage doubling | Chest pain | ECG resolved quickly | TnI 5 μg/ml | Middle portion of LAD focal stenosis 30% | MI |

PACU: post-anesthesia care unit; TXA: tranexamic acid; TnI: troponin I; CK: creatine kinase; LDH: lactic dehydrogenase; CA: coronary artery; LAD: left anterior descending; RCA: right coronary artery; MI: myocardial infarction; LV: left ventricle; RV: right ventricle.
was 0.84 (95%CI: 0.70-1.00, P=0.045). Results from MC-1 to Eliminate Necrosis and Damage in Coronary Artery Bypass Graft Surgery (MEND-CABG) Trial II involving 3023 CABG patients demonstrated that, TXA use was not associated with the 30-day incidence of cardiovascular death or MI, but increased the risk of myonecrosis.\textsuperscript{[18]}

Currently, TXA is contraindicated in those with known hypercoagulable disorders.\textsuperscript{[10]} HIV infection and antiretroviral therapy are both risk factors for hypercoagulability and thrombosis.\textsuperscript{[19, 20]} HIV-infected patients have a 2- to 10-fold increased risk of thrombosis as compared with the general population.\textsuperscript{[21]} In the first case,\textsuperscript{[10]} TXA administration in the context of HIV-related hypercoagulability might led to AMI. TXA is especially to be avoided in obese women and those who smoke as they can develop arterial or venous thrombosis.\textsuperscript{[11]} The 2nd case reported a 56-year-old hypertensive and obese female developed AMI after receiving TXA to minimize blood loss for hip arthroplasty.\textsuperscript{[9]} Non-steroidal anti-inflammatory drugs (NSAIDs) are very widely prescribed and there have been reports regarding adverse cardiovascular events with NSAIDs. Combined intake of TXA and NSAIDs resulted in AMI in the hypertensive, dyslipidemic premenopausal woman as presented in the 3rd case.\textsuperscript{[11]} Hemophilia A is a congenital bleeding disorder caused by F\textsubscript{VIII} deficiency. Spontaneous bleeding in patients with a F\textsubscript{VIII} activity <1% is associated with serious symptoms,\textsuperscript{[22]} which was the case in the 4th patient.\textsuperscript{[12]} However, thrombotic complications could develop in patients with hemophilia during factor replacement therapies.\textsuperscript{[23]} Additionally, factor V Leiden mutation was higher in patients with MI compared to the control group.\textsuperscript{[24]} There have been reported AMI after desmopressin in patients with prior bleeding disorders.\textsuperscript{[25]} The timing of AMI in the 5th case is suggestive of a link of MI to TXA.\textsuperscript{[13]} Oral contraceptives alter haemostatic status. The combination of pro-thrombotic TXA and estroprogestinic contraceptives treatment seems to been the cause of MI in the 6th female patient without risk factors.\textsuperscript{[14]} TXA dose escalation was deemed responsible for the AMI in the 7th patient who took the initial dose of TXA for haemoptysis uneventfully.\textsuperscript{[15]} Regardless
of the exact mechanism, it was highly likely that TXA administration contributed to the seven cases of AMI. The present study serves as an alarming that, even in patients with low thrombotic risks, TXA use may result in AMI.

**Appendix.** Database search strategies

| Search strategies                                                                 | Results |
|----------------------------------------------------------------------------------|---------|
| **MEDLINE**                                                                      |         |
| ("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields])) OR "myocardial ischemia"[MeSH Terms] OR ("myocardial"[All Fields] AND "ischemia"[All Fields]) OR "coronary artery disease"[MeSH Terms] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR "coronary artery disease"[All Fields] OR ("myocardial"[All Fields] AND "ischemia"[All Fields]) OR ("myocardial ischemia"[All Fields] OR "myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]) OR ("myocardium"[MeSH Terms] OR "myocardium"[All Fields] OR "myocardial"[All Fields]) AND ("wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "injury"[All Fields])) OR ("troponin"[MeSH Terms] OR "troponin"[All Fields]) OR ("creatine kinase"[MeSH Terms] OR ("creatine"[All Fields] AND "kinase"[All Fields]) OR "creatine kinase"[All Fields]) OR ("l-lactate dehydrogenase"[MeSH Terms] OR ("l-lactate"[All Fields] AND "dehydrogenase"[All Fields]) OR "l-lactate dehydrogenase"[All Fields]) OR ("Electrocardiograph.mp."[mp=ti, ab, tx, kw, ct, ot, sh, hw]) AND ("humans"[MeSH Terms] AND English[lang]) | 7/120    |
| **OVID**                                                                         |         |
| ((Tranexamic acid AND myocardial ischemia).mp.[mp=ti, ab, tx, kw, ct, ot, sh, hw]) OR ((Tranexamic acid AND myocardial infarction).mp.[mp=ti, ab, tx, kw, ct, ot, sh, hw]) OR ((Tranexamic acid AND myocardial injury).mp.[mp=ti, ab, tx, kw, ct, ot, sh, hw]) OR ((Tranexamic acid AND troponin).mp.[mp=ti, ab, tx, kw, ct, ot, sh, hw]) OR ((Tranexamic acid AND lactate dehydrogenase).mp.[mp=ti, ab, tx, kw, ct, ot, sh, hw]) OR ((Tranexamic acid AND Electrocardiograph.mp.[mp=ti, ab, tx, kw, ct, ot, sh, hw]) | 0/100    |
| **Cochrane**                                                                     |         |
| ("Tranexamic acid"):ti, ab, kw (Word variations have been searched) AND ("myocardial ischemia"): ti, ab, kw (Word variations have been searched) OR ("myocardial infarction"): ti, ab, kw (Word variations have been searched) OR ("myocardial injury"): ti, ab, kw (Word variations have been searched) OR ("troponin"): ti, ab, kw (Word variations have been searched) OR ("creatine kinase"): ti, ab, kw (Word variations have been searched) OR ("lactate dehydrogenase"): ti, ab, kw (Word variations have been searched) OR ("Electrocardiograph"): ti, ab, kw (Word variations have been searched)) | 0/123    |
Conflict of interest statement

The authors have no conflict of interest to disclose.

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