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ORIGINAL ARTICLE

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 use of 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, and 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 was prescribed for four patients to reduce surgical bleeding, for two patients to treat menorrhagia and for one patient to manage hemoptysis. The diagnosis of AMI was made based upon patients' symptoms, ECG, myocardium-specific enzymes, and confirmed by coronary angiography. Coronary stents were placed in four patients, for whom 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.

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, com-

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petitively 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 administration. Relevant case reports were identified by computerized searches of MEDLINE, Cochrane Library and EMBASE till April 2nd 2019, using different combination of search words as follows: (*Tranexamic acid) AND* (*myocardial ischemia OR* (*myocardial infarction*) *OR* (*myocardial injury*) *OR troponin OR* (*creatine kinase*) *OR* (*lactate dehydrogenase*) *OR electrocardiograph*)(**Appendix**). No language restriction was used. We also used the bibliography of retrieved articles to further identify relevant studies.

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's gender, age, comorbidities, medical history, thrombotic risk factors and co-medications with TXA; (3) onset, manifestation, examination, diagnosis and treatment of AMI; (4) 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 administering 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 for four patients to reduce surgical bleeding,[9, 10, 12, 13] for two patients to control menorrhagia[11, 14] and for one to treat hemoptysis.[15]

Detailed information of these reports is presented in **Table 1**. In the first case reported by Gerstein *et al*.[10] from the 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 case reported by Garg *et al*.[9] from the USA, a 56-year-old hypertensive and obese female patient developed AMI after TXA being used before hip anthroplasty. In the third case reported 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 Günaldi *et al*.[12] from Turkey, a 49-year-old male with Hemophilia A and factor V Leiden mutation developed post-operative AMI after oral TXA and intravenous recombinant F Ⅷ replacement before tooth extraction. In the fifth case reported by Sirker *et al*.[13] from UK, a 28-year-old female patient with bleeding diathesis developed AMI after treated with desmopressin and TXA before and after shoulder surgery respectively. In the sixth case reported by Iacobellis *et al*.[14] from Italy, TXA was prescribed to manage uterine leiomyoma associated menorrhagia for a 42-year-old healthy woman who received oral contraceptive, and she developed AMI two months later. In the seventh case reported by Mekontso-Dessap *et al*.[15] from France, oral TXA 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.

As shown in **Table 2**, the diagnosis of the seven

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*.[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*.[9]	USA	F	56	hypertension, obesity, smoking	arthritis	TXA (10 mg/kg *iv.*) before hip anthroplasty
Gupta *et al*.[11]	India	F	41	hypertension	menorrhagia, dysmenorrhoea, uterus fibroid	TXA (0.5 g *po* tid ×2 year)+mefenamic acid (0.25 g *po* tid ×2 year) for menorrhagia and dysmenorrhoea
Günaldi *et al*.[12]	Turkey	M	49	hemophilia A, factor V Leiden mutation, smoking	intra-articular hemorrhage	TXA (20 mg/kg *po.* qd ×10 days) and r-F Ⅷ (40 U/kg *iv.*) before tooth extraction
Sirker *et al*.[13]	UK	F	28	hyperlipidemia, contraceptive	bleeding diathesis, nose bleeding	TXA (1 g qd ×1 week) and DDAVP *iv.* after and before shoulder surgery, respectively
Iacobellis *et al*.[14]	Italy	F	42	contraceptive	uterine leiomyoma	TXA (3 g *im.* qd) and contraceptive pill (ethinylestradiol 20 μg and gestodene 75 μg) ×2 months for menorrhagia
Mekontso-Dessap *et al*.[15]	France	F	77	hypertension	tuberculosis	TXA (0.5 g *po.* bid ×5 day then 1.0 g *po* bid ×2 days) for haemoptysis related to pulmonary tuberculosis

M: male; F: female; HIV: human immunodeficiency virus; COPD: chronic obstructive pulmonary disease; TXA: tranexamic acid; r-F Ⅷ : recombinant-factor Ⅷ ; DDAVP: desmopressin; iv: intravenously; po: peros; im: intramuscularly.

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.[9-11, 14, 15] For four patients placing coronary stents,[9-12] anti-platelet agents (aspirin,[10, 12, 13, 15] clopidogrel,[10, 15] eptifibatide[15]) and anti-coagulation drugs (heparin,[10, 12, 15] warfarin[10]) were prescribed. No death or major cardiovascular events were reported during hospitalization and follow-up.

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 increases the risk of myocardial infarction (MI).[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 4631 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 was 0.84 (95%CI: 0.70-1.00, P=0.045).[8] 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.[18]

Currently, TXA is contraindicated in those with known hypercoagulable disorders.[10] HIV infection and antiretroviral therapy are both risk factors for hypercoagulability and thrombosis.[19, 20] HIV-infected patients

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)
Günaldi *et al*.[12]	after r-F Ⅷ administration	chest pain, agitation, sweating	ST elevation (leads Ⅲ, Ⅱ, aVF, V4) and ST depression (leads V1, V2)	LDH 392U/L and CK-MB 170 U/L	RCA 90% stenosis, LAD 40% stenosis	MI (inferoposterolateral wall, RV)
Sirker *et al*.[13]	three days after therapy	chest pain	ST elevation (inferior)	elevated in keeping with the acute occlusion	Occlusion in a small distal branch of RCA, minimal wall irregularity of LAD	MI (inferior wall)
Iacobellis *et al*.[14]	two months after TXA and contraceptive	chest pain	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]	two 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; 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.

have a 2- to 10-fold increased risk of thrombosis as compared with the general population.[21] In the first case,[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.[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.[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.[11] Hemophilia A is a congenital bleeding disorder caused by F Ⅷ deficiency. Spontaneous bleeding in patients with a F Ⅷ activity <1% is associated with serious symptoms,[22] which was the case in the 4th patient.[12] However, thrombotic complications could develop in patients with hemophilia during factor replacement therapies.[23] Additionally, factor V Leiden mutation was higher in patients with MI compared to the control group.[24] There have been reported AMI after desmopressin in patients with prior bleeding disorders.[25] The timing of AMI in the 5th case is suggestive of a link of MI to TXA.[13] Oral contraceptives alter haemostatic status. The combination of pro-thrombothic TXA and estroprogestinic contraceptives treatment seems to be the cause of MI in the 6th female patient without risk factors.[14] TXA dose escalation was deemed responsible for the AMI in the 7th patient who took the initial dose of TXA for haemoptysis uneventfully.[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.

Conflict of Interests Statement

The authors have no conflict of interests to disclose.

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Appendix. Database search strategies

Search strategies	Results
MEDLINE	7/120
("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields]) AND (("myocardial ischaemia"[All Fields] OR "myocardial ischemia"[MeSH Terms] OR ("myocardial"[All Fields] AND "ischemia"[All Fields]) OR "myocardial 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 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 ("lactate"[All Fields] AND "dehydrogenase"[All Fields]) OR "lactate dehydrogenase"[All Fields]) OR ("electrocardiography"[MeSH Terms] OR "electrocardiography"[All Fields] OR "electrocardiograph"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang])	
OVID	0/100
((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 creatine kinase).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])	
Cochrane	0/123
(("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))	

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