High-Dose Tranexamic Acid Is Associated with Nonischemic Clinical Seizures in Cardiac Surgical Patients

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BACKGROUND: In 2 separate centers, we observed a notable increase in the incidence of postoperative convulsive seizures from 1.3% to 3.8% in patients having undergone major cardiac surgical procedures. These events were temporally coincident with the initial use of high-dose tranexamic acid (TXA) therapy after withdrawal of aprotinin from general clinical usage. The purpose of this review was to perform a retrospective analysis to examine whether there was a relation between TXA usage and seizures after cardiac surgery.

METHODS: An in-depth chart review was undertaken in all 24 patients who developed perioperative seizures. Electroencephalographic activity was recorded in 11 of these patients, and all patients had a formal neurological evaluation and brain imaging studies.

RESULTS: Twenty-one of the 24 patients did not have evidence of new cerebral ischemic injury, but seizures were likely due to ischemic brain injury in 3 patients. All patients with seizures did not have permanent neurological abnormalities. All 24 patients with seizures received high doses of TXA intraoperatively ranging from 61 to 259 mg/kg, had a mean age of 69.9 years, and 21 of 24 had undergone open chamber rather than coronary bypass procedures. All but one patient were managed using cardiopulmonary bypass. No evidence of brain ischemic, metabolic, or hyperthermia-induced causes for their seizures was apparent.

CONCLUSION: Our results suggest that use of high-dose TXA in older patients in conjunction with cardiopulmonary bypass and open-chamber cardiac surgery is associated with clinical seizures in susceptible patients.

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Bleeding and the subsequent need for blood transfusion is a major contributor to postoperative mortality and morbidity in cardiac surgery.[1,2] Antifibrinolytic therapy has become a mainstay in complex cardiac surgical procedures to decrease bleeding and minimize transfusion requirements. The recent Society of Cardiovascular Anesthesia and Society of Thoracic Surgery transfusion guidelines specifically recommended the use of antifibrinolytic therapy, namely, ϵ-aminocaproic acid (EACA), tranexamic acid (TXA), or aprotinin, for patients at increased risk of bleeding during cardiac surgery.[3] However, increasing concern regarding the adverse effects of aprotinin[4] has led to its worldwide withdrawal.[5] Furthermore, in some countries including Canada and New Zealand, EACA is not available for clinical use.[6,7] Given the demonstrated efficacy of antifibrinolytic therapy[8] and the increased morbidity and mortality associated with postoperative hemorrhage and allogeneic blood transfusion,[9,10] many clinicians have chosen to use TXA to minimize the risk of hemorrhage in cardiac surgical patients.

In several dose-ranging studies, TXA doses of up to 100 mg/kg have been recommended.[11] However, a significant increase in clinical seizures in the early postoperative period was noted in 2 institutions after introduction of routine TXA infusions for high-risk cardiac surgical patients. The purpose of this investigation was to perform a retrospective review to examine whether there was a relation between the use of TXA and seizures after cardiac surgery.

METHODS

After withdrawal of aprotinin from clinical use, both Papworth Hospital in Cambridge, United Kingdom, and London Health Sciences Center (LHSC) in

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Table 1. Demographic and Procedural Characteristics in Patients Having Seizures

Age (yr)	Height (cm)	BSA	Procedure	Type	CT finding	TXA (mg/kg)	Renal dysfunction	Gender
71	187	2.02	Redo arch replacement	GM	Negative	137	No	Male
66	163	1.85	AVR, MVR	GM	Old infarct	128	Yes	Male
80	172	1.70	PTE	GM	Negative	202	No	Female
67	153	1.64	PTE	GM	Negative	127	Yes	Female
72	150	1.46	PTE	GM	Old infarct	142	No	Female
67	160	1.85	AVR, AA replacement	GM	Negative	137	No	Female
37	158	1.47	HTX	Myocloni	Negative	102	Yes	Female
64	172	1.58	AVR	GM	Negative	222	Yes	Male
42	185	2.04	PTE	GM	Negative	98	Yes	Male
75	182	2.19	CAB/AVR/MVR	GM	Negative	71	No	Male
66	162	1.59	CAB/AVR	GM	Old infarct	178	No	Female
77	165	1.87	AVR/CAB	GM	Negative	259	Yes	Male
87	164	1.93	OPCAB	GM	Negative	61	Yes	Female
62	188	2.26	CAB	GM	Infarct	148		Male
76	157	1.63	MVR/TVR	GM	Old infarct	237	Yes	Female
86	158	1.79	CAB	Myocloni	Infarct	139	Yes	Male
69	150	1.63	ASD	GM	Negative	164	No	Female
69	175	1.95	AVR/CAB	GM	Negative	117	No	Male
81	157	1.83	AVR	GM	Negative	181	No	Female
75	170	1.76	AVR/MR	GM	Negative	151	No	Male
76	183	2.60	AVR/MVR	GM	Subdural	110	Yes	Male
67	180	2.11	AVR/MVR	Myocloni	Negative	191	Yes	Male
82	163	1.84	MVR/CAB	Myocloni	Negative	213	Yes	Male
79	183	2.00	Arch	GM	Infarct	125	No	Male

Type refers to initial presentation of seizures; TXA refers to tranexamic acid dosage; renal dysfunction refers to elevation of creatinine above institutional normal range.

BSA = body surface area; AVR = aortic valve replacement; AA = ascending aorta; Arch = aortic arch surgery; TVR = tricuspid valve repair or replacement; MVR = mitral valve repair or replacement; CAB = coronary artery bypass; OPCAB = off-pump coronary artery bypass; HTX = heart transplant; PTE = pulmonary thrombectomy; CT = computerized tomography; GM = grand mal seizure; Myocloni = myoclonic motor activity; Negative = no ischemic brain injury; Infarct = new ischemic injury.

London, Ontario, implemented the continuous intraoperative use of TXA in patients at high risk for bleeding undergoing cardiac surgery. This commenced in mid-November 2007 at LHSC and in January 2008 at Papworth. Our clinical observation was drawn from a series of 24 patients at both institutions in whom generalized convulsive seizures were observed in the postoperative period in the absence of significant new ischemic lesions on brain imaging identified over a 5-month (LHSC) and an 11-month (Papworth) period after the initial commencement of this strategy.

In an attempt to determine the etiology of the seizure activity, a comprehensive review of medical records was undertaken in all 24 patients. All patients who experienced seizures had head computerized tomography or magnetic resonance imaging performed. Furthermore, at LHSC, a subset of 11 patients had an electroencephalogram recorded.

RESULTS

Six hundred sixty-nine patients were treated with TXA at both institutions (Papworth 149 patients, LHSC 520 patients) during the time period of this review. The usual initial loading dose was 100 mg/kg at LHSC and 20 to 50 mg/kg at Papworth. The infusion rate varied between 10 and 25 $mg \cdot kg^{-1} \cdot h^{-1}$. Because of the novelty of the protocol and the differing nature and duration of the surgical procedures, there was considerable variation in the total dose of TXA ranging from 61 to 259 mg/kg at LHSC and 71 to 258 mg/kg at the Papworth Hospital.

Patient characteristics and procedure details are shown in Table 1. Factors potentially predisposing to seizure activity were not present in any patients. A large proportion had operations requiring opening of cardiac chambers. Seizures occurred on average 4.7 hours postoperatively. In a number of these patients, onset of seizure activity was coincident with weaning of the sedation dose of propofol before tracheal extubation. Two patients had focal seizures, one of which became generalized, whereas the others had generalized convulsions. In the patients in whom electroencephalograms were obtained, spikes or generalized seizures were demonstrated in 7, focal spikes in 1, multifocal spikes in 4, and generalized in 2. Of the 24 identified patients, 3 showed evidence of recent small areas of cerebral infarction on brain imaging, which were not thought to contribute to their seizures. There was no evidence of ischemic injury in 21 patients. All reported patients made an uneventful neurological recovery without subsequent deficits or recurring seizures.

Papworth Hospital had an increase in cases of clinical seizures from 19 in the 11 months preceding the introduction of TXA to 30 cases in the 11 months after its introduction. This reflects an unchanged incidence of seizures with positive brain imaging findings and an additional 11 patients with negative imaging studies.

Since this review, dosing guidelines have been modified to a lower dose of TXA (30 mg/kg load, 15 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion, and 2 mg/kg in the cardiopulmonary bypass priming solution) consistent with doses used in the BART (Blood Conservation Using Antifibrinolytics in a Randomized Trial) study.[4] Since this dosing change, the incidence of postoperative seizures has returned to the previous baseline of 0 to 2 per month.

DISCUSSION

Reports of the incidence of seizures after adult cardiac surgery are remarkably rare. In their large multicenter observational study, Roach et al.[12] reported seizures in approximately 0.4% of cardiac surgical patients. Before the introduction of TXA, the clinical seizure incidence at LHSC was 1.3% (unpublished data), increasing to 3.8% during the period reported here.

In neither the 770 TXA-treated patients reported in the BART study[4] nor the 822 TXA-treated patients reported in an international survey[13] was the incidence of perioperative seizures reported. Although this absence could reflect a relative lack of data sensitivity, it may more likely indicate that the frequency of seizures was low because of the lower dosage of TXA used in these population. Recently, however, 2 large series of patients undergoing cardiac surgery have linked the use of TXA with postoperative seizures.[14,15]

In a nonselective, prospective study of cardiac surgical patients, a significantly higher incidence of seizures was found in patients receiving TXA versus aprotinin (4.6% vs 1.2%, $P < 0.001$). However, the authors did not analyze for incidence of ischemic or nonischemic seizures in this population.[14] Also of note is the recent abstract reported by Jerath in which 15.4% of 39 adult cardiac surgical patients having received median doses of TXA of 109 mg/kg experienced postoperative seizures compared with 4.8% of 103 patients receiving median TXA doses of 67 mg/kg.[16] Several case reports describe seizure activity from TXA when inadvertently injected into the spinal and subarachnoid spaces.[17–20]

Possible mechanisms of TXA-induced seizures include direct cerebral ischemia secondary to decreases in regional or global cerebral blood flow[21–23] and blockage of inhibitory cortical γ-aminobutyric acid (GABA)-A receptors.[24] Because GABA-A receptors govern opening of neuronal chloride channels resulting in neuronal hyperpolarization and reduced excitability, blockage by TXA results in lowering of the depolarization threshold and enhanced excitotoxicity.[24] TXA has been shown to cause hyperexcitability and convulsions when applied directly onto central nervous system tissue.[25]

Plasma TXA levels after a dose of 100 mg/kg, similar to that given to our patients with seizures, can exceed 4000 μmol/L (600 mg/L).[26] Extrapolating from animal studies[27] and from cerebrospinal fluid (CSF) concentrations of TXA measured in patients with subarachnoid hemorrhage,[28] this may produce CSF concentrations approximating 100 to 200 mg/L. There is evidence for a dose-related toxicity. In a dose-ranging study of topical TXA applied cortically in a rat model, concentrations of topical hemostatic agent containing TXA 0.5, 5, or 47.5 mg/mL produced seizures in progressively more animals, which were of greater severity and duration with increasing TXA dosage.[29]

Of relevance to the series reported here, cardiac surgery leads to an inflammatory response as well as generation of cerebral emboli, all of which may contribute to altered blood-brain barrier permeability[30] and possibly a larger TXA concentration in the CSF and brain compartment than reported in vitro.

Whether another lysine analog antifibrinolytic, EACA, may share the same epileptogenic propensity if administered in a high enough dose remains unclear.[31] Regardless, our series should caution physicians from using large doses of TXA during cardiac surgery because of our observation of a link of this dose with clinical seizures.

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