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Early Tranexamic Acid Administration After Traumatic Brain Injury Is Associated With Reduced Syndecan-1 and Angiopoietin-2 in Patients With Traumatic Intracranial Hemorrhage

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Abstract

Objective: To evaluate the effect of early tranexamic acid (TXA) administration on circulating markers of endotheliopathy.

Setting: Twenty trauma centers in the United States and Canada.

Participants: Patients with moderate-to-severe traumatic brain injury (TBI) (MS-TBI) and intracranial hemorrhage who were not in shock (systolic blood pressure ≥90 mm Hg).

Design: TXA (2 g) or placebo administered prior to hospital arrival, less than 2 hours postinjury. Blood samples and head computed tomographic scan collected upon arrival. Plasma markers measured using Luminex analyte platform. Differences in median marker levels evaluated using *t* tests performed on log-transformed variables. Comparison groups were TXA versus placebo and less than 45 minutes versus 45 minutes or more from time of injury to treatment administration.

Main Measures: Plasma levels of angiopoietin-1, angiopoietin-2, syndecan-1, thrombomodulin, thrombospondin-2, intercellular adhesion molecule 1, vascular adhesion molecule 1.

Results: Demographics and Injury Severity Score were similar between the placebo ($n = 129$) and TXA ($n = 158$) groups. Levels of syndecan-1 were lower in the TXA group (median [interquartile range or IQR] = 254.6 pg/mL [200.7–322.0] vs 272.4 pg/mL [219.7–373.1], $P = .05$. Patients who received TXA less than 45 minutes postinjury had significantly lower levels of angiopoietin-2 (median [IQR] = 144.3 pg/mL [94.0–174.3] vs 154.6 pg/mL [110.4–209.8], $P = .05$). No differences were observed in remaining markers.

Conclusions: TXA may inhibit early upregulation of syndecan-1 and angiopoietin-2 in patients with MS-TBI, suggesting attenuation of protease-mediated vascular glycocalyx breakdown. The

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findings of this exploratory analysis should be considered preliminary and require confirmation in future studies.

Keywords

angiopoietin-2; brain injuries; cell adhesion molecules; craniocerebral trauma; endothelium; extracellular matrix proteins; glycocalyx; intracranial hemorrhages; syndecan-1; tranexamic acid; traumatic

Traumatic brain injury (TBI) is a leading cause of death (50 000 per year) and disability (13.5 million) in the United States, with an estimated 2.8 million individuals seeking medical treatment of TBI per year.[1] Current treatment strategies for TBI are limited, focusing primarily on reactive management of initial symptoms and sequelae.[2] However, a number of recent clinical trials have demonstrated improved outcomes with early administration of tranexamic acid (TXA), a potent procoagulant that inhibits enzymatic clot breakdown.[3–5] While mortality reduction associated with TXA has been attributed to reduction of hemorrhage progression, this explanation fails to account for the fact that this effect is only observed after early administration (<3 hours postinjury).[3,6–8]

In vitro studies have suggested a potential alternative mechanism underpinning this time-dependent effect, demonstrating a reduction in markers of endothelial injury with early administration of TXA.[9,10] In TBI, early upregulation of injury-response cascades results in endotheliopathy, which has been associated with increased vascular permeability and posttraumatic hypocoagulability.[9,11] It has been suggested that early administration of TXA attenuates vascular glycocalyx breakdown through protease inhibition, thus preserving endothelial integrity and mitigating subsequent coagulopathy.[9] On the basis of these observations, we hypothesized that patients with moderate-to-severe TBI (MS-TBI) with intracranial hemorrhage (ICH) who received TXA within 2 hours postinjury would have a circulating endothelial marker profile consistent with greater preservation of endothelial integrity than patients who received placebo. This profile includes increased levels of circulating angiopoietin-1 (ang-1) and lower levels of angiopoietin-2 (ang-2), syndecan-1, thrombospondin-2 (TSP-2), thrombomodulin, intercellular adhesion molecule 1 (ICAM-1), and vascular adhesion molecule 1 (VCAM-1). Furthermore, we hypothesized that a greater degree of endothelial preservation would be observed in patients who received TXA early (<45 minutes postinjury) than in those who received TXA late (≥45 minutes postinjury).

METHODS

Study design

We analyzed plasma samples from a subset of patients in the phase II double-blind, multicenter randomized controlled trial, “Prehospital Tranexamic Acid Use for Traumatic Brain Injury.” This subset included patients in the 2-g TXA or placebo arms of the parent trial with evidence of ICH on initial head computed tomographic (CT) scan and available blood samples.

Parent study design

The parent trial enrolled patients with MS-TBI defined as a Glasgow Coma Scale score of 3 to 12 who were not in shock (systolic blood pressure ≥90 mm Hg) for comparison of the efficacy and safety of early prehospital TXA versus placebo. Additional criteria for enrollment in the parent study can be found in the US National Institutes of Health database (ClinicalTrials.gov NCT01990768).

Subjects were recruited by 20 trauma centers at 12 regional sites in the United States and Canada between May 2015 and March 2017. Subjects with an estimated time from injury to hospital arrival less than 2 hours were enrolled in the prehospital setting. The treatment arm was determined according to randomized, double-blinded assignment. Patients in the TXA group received an initial prehospital bolus dose of 2 g of TXA administered in the prehospital setting, followed by a 250-mL infusion of 0.9% sodium chloride administered over 8 hours after hospital arrival. Patients in the placebo group received bolus and infusion doses of 0.9% sodium chloride. In both groups, administration of the prehospital bolus dose was initiated within 2 hours of injury. Upon hospital arrival, whole blood samples were collected and a head CT scan was performed to evaluate for ICH.

Endothelial marker measurement

Plasma from whole blood samples was separated via centrifugation and stored in a central repository at Oregon Health & Science University. Plasma concentrations of markers of endothelial function (ang-1, ang-2, ICAM-1, VCAM-1, TSP-2, thrombomodulin, and syndecan-1) were determined by multiplex immunoassay analysis (R&D Systems, Minneapolis, Minnesota) using the Luminex xMAP analytical system (xMAP technology, Austin, Texas).

Statistical analysis

Clinical variables were compared using Wilcoxon rank-sum tests for nonparametric continuous data and χ^2 or Fisher's exact tests for categorical data. Differences in median marker levels were assessed in the TXA and placebo groups using t tests performed on log-transformed variables. Additional comparison was performed in subpopulations of patients who received treatment assignment less than 45 minutes postinjury (early) and 45 minutes or more postinjury (late). The 45-minute cutoff was selected to maintain a relatively even distribution between early and late populations while remaining as close as possible to the 60-minute time point used in a previous in vitro study of the effect of TXA on endothelial dysfunction.[9] Significance was set at $P \leq .05$.

RESULTS

Population

A total of 285 patients from the parent trial with ICH and 0-hour blood samples (129/373 in the placebo arm and 156/345 in the 2-g TXA arm) were included in this analysis. The median time from injury to blood sample collection was 90 minutes (interquartile range [IQR] = 63–125.5), and this interval was not significantly different in the placebo and 2-g TXA groups (median [IQR] = 91 minutes [61.5–124.5] vs 91 minutes [64.3–125.8], P

= .37). Baseline characteristics of included patients and those excluded on the basis of lack of available blood samples are shown in Table 1. No significant differences in baseline characteristics, Injury Severity Score, or head Abbreviated Injury Score were observed between the TXA and placebo groups (see Table 2).

2-g TXA versus placebo

Median baseline levels of syndecan-1 were lower in patients who received TXA than in those in the placebo group (254.6 pg/mL [IQR = 200.9–324.0] vs 272.4 pg/mL [IQR = 219.7–373.1], $P = .05$). No significant differences were observed in median baseline levels of ang-1, ang-2, TSP-2, thrombomodulin, ICAM-1, or VCAM-1 (see Table 3).

Timing of treatment administration

Patients who received TXA early had significantly lower levels of ang-2 at baseline than those who received TXA late (median [IQR] = 142.6 pg/mL [94.0–171.8] vs 155.4 pg/mL [111.3–211.3], $P = .05$) (see Table 4). No significant differences were observed on the basis of timing of administration among patients in the placebo group (see Table 5).

DISCUSSION

In this study, we examined the effect of early TXA administration on 7 circulating markers of endothelial dysfunction in patients with MS-TBI and ICH. These markers were selected on the basis of previous evidence demonstrating their utility as indicators of vascular glycocalyx breakdown and endothelial permeability.

Endothelial dysfunction in TBI is initiated by tissue damage and release of inflammatory mediators, which catalyze a self-perpetuating cycle of vascular endothelial breakdown and clotting factor consumption. Furthermore, activation of inflammatory and sympathoadrenal cascades in the setting of TBI upregulates extracellular sheddases such as A disintegrin, metalloproteinase-17 (ADAM-17), and matrix metalloproteinase-9 (MMP-9), which catalyze glycocalyx breakdown.[9,11] Enzymatic disruption of this network results in the release of endothelial markers, among which syndecan-1, thrombomodulin, ICAM-1, and VCAM-1 are some of the most well-characterized.[12,13] These processes collectively contribute to the development of increased blood-brain barrier permeability, which has been proposed as a mechanism underlying the delayed development of ICH and cerebral edema in TBI.[12]

Markers of endotheliopathy

Markers associated with endothelial dysfunction include endothelial surface proteoglycan syndecan-1, leukocyte-endothelial cell ligands ICAM-1 and VCAM-1, endothelial cell receptor thrombomodulin, glycocalyx ligand TSP-2, and angiopoietin-1 and −2, which are involved in regulation of endothelial growth and permeability. On the basis of previous studies noting directional changes in these markers, we proposed that endothelial preservation would be reflected by increased levels of ang-1 and decreased levels of ang-2, syndecan-1, TSP-2, thrombomodulin, ICAM-1, and VCAM-1.

While each of these markers have been independently associated with endothelial disruption, the relationships between them have not been fully defined and it remains unclear which is the most robust. However, syndecan-1, the predominant endothelial surface proteoglycan, has been most widely studied. Elevated levels of syndecan-1 have been repeatedly associated with coagulopathy and mortality in patients with TBI.[14–16] Upon endothelial disruption, the leukocyte-endothelial cell ligands ICAM-1 and VCAM-1 are released into systemic circulation, corresponding with a detectable increase in circulating levels as early as 15 minutes post-TBI.[16–19] Levels of soluble thrombomodulin increase through a process of neutrophil-mediated cleavage that is upregulated in patients with TBI. Thrombomodulin levels have been shown to correlate with increased levels of syndecan-1 in the context of endothelial dysfunction.[11,12,20,21] The glycocalyx ligand TSP-2 inhibits angiogenesis and contributes to repair of the blood-brain barrier after injury.[22–25] Cerebral expression of TSP-2 is upregulated in models of ICH and delayed cerebral reperfusion, while an increase in circulating TSP-2 has been observed after ischemic stroke.[24,26–28]

The angiopoietins were selected because of their role as endothelial growth factors involved in the regulation of vascular permeability, inflammatory cascades, and angiogenesis.[29] Under noninflammatory conditions, ang-1 promotes vascular interendothelial cell junction stability and inhibits upregulation of ang-2.[30] In a proinflammatory state, ang-2 predominates, promoting glycocalyx degradation and increasing endothelial permeability through destabilization of intercellular interactions.[31] Angiopoietin upregulation has been demonstrated in experimental models of TBI,[32,33] and disturbances in the ang-1/ang-2 equilibrium have been demonstrated in other causes of cerebral injury.[34,35] These studies provided the foundation for our hypothesis that early TXA administration would inhibit this disequilibrium through attenuation of the endotheliopathic cascade, leading to relatively higher levels of protective ang-1 and lower levels of the destabilizing ang-2.

TXA in endotheliopathy

TXA is a potent antifibrinolytic that acts via inhibition of plasmin-fibrin binding and enzymatic clot breakdown. With recent clinical evidence of TBI mortality reduction with the early administration of TXA, there has been increased interest in characterizing the mechanism associated with this observation.[6–8] Elucidating the time-dependent nature of TXA's effects is critical for the development of enhanced treatment protocols and targeted therapies for mitigating secondary injury in TBI.

Our observation of decreased levels of syndecan-1 among patients with MS-TBI receiving TXA early postinjury is consistent with previous in vitro findings. Diebel et al[9] found that TXA administered less than 60 minutes postreperfusion mitigated endothelial disruption as evidenced by decreased markers of glycocalyx degradation (syndecan-1, hyaluronic acid, tumor necrosis factor-α). Furthermore, the authors observed inhibition of endothelial sheddases with administration of TXA, suggesting a potential mechanistic explanation for the early mortality benefit of TXA in TBI.[9] In another study, intraluminal TXA administration inhibited murine sheddase activity, reducing gut and lung histopathologic injury, inflammation, and systemic shedding of gut and lung syndecan-1 in the setting of hemorrhagic shock.[10] Although we did not directly measure protease activity, our

observation of decreased syndecan-1 is consistent with these in vitro observations, supporting the hypothesis that TXA reduces enzymatic cleavage of syndecan-1 through serine protease inhibition.

Contrary to the observed decrease in levels of syndecan-1 with administration of TXA in this study, a recently published clinical trial examining biomarkers of endothelial dysfunction in 91 trauma patients (not TBI-specific) found no significant differences in levels of syndecan-1 in patients who received TXA within 1 hour of injury.[36] These researchers also found no difference in thrombomodulin levels with TXA administration, consistent with our findings. They did note, however, that elevated levels of both syndecan-1 and thrombomodulin were associated with a greater incidence of multiorgan dysfunction syndrome.

Higher levels of syndecan-1 have also been associated with isolated severe TBI and nonsignificant differences in thrombomodulin compared with uninjured controls.[15] While we did not limit our population to isolated TBI, this is consistent with our observations in this population of patients with primarily moderate and severe TBI.

Although the effect of TXA on plasma levels of ang-2 in TBI has not been previously described, the association between ang-2 and glycocalyx degradation has been demonstrated in other models of cerebral injury.[34,35] Our observation of lower ang-2 levels among patients who received TXA less than 45 minutes postinjury provides potential support for the proposed mechanism of endothelial preservation. Although we did not observe a significant difference when comparing syndecan-1 ($P = .09$) and ang-1 ($P = .08$) in patients who received early (<45 minutes) versus late (≥45 minutes) TXA, the observed trend warrants further investigation. While TXA may have no effect on levels of these and other markers of endotheliopathy, it is also possible that our narrow timing range and small sample size may have limited our ability to detect important differences. Alternatively, TXA may selectively impact syndecan-1 and ang-2 upregulation through a limited mechanism of endothelial preservation.

There are several limitations to this work. While we do report significant findings, adjustment for multiple comparisons was not performed. These results should therefore be confirmed in an adequately powered study designed for this purpose. Furthermore, this was an exploratory study using data from a parent trial not designed to evaluate these outcomes. As such, this analysis should be viewed as a hypothesis-generating preliminary study. In addition, the 45-minute cutoff used to define early versus late treatment administration may not be the optimal time point for detecting effect differences, as previous evidence has demonstrated a mortality benefit with TXA administration up to 3 hours postinjury.

Our observation of alterations in levels of syndecan-1 and ang-2 with early TXA administration suggests a potential role for TXA in modulation of endotheliopathy. However, because of the limitations of this hypothesis-generating study, these findings should be considered preliminary. Further investigation is required to clarify the relationship between TXA and endothelial disruption in patients with TBI.

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TABLE 1

Descriptive statistics in patients with and without available blood samples according to the treatment group (placebo or TXA)[a]

	Placebo					TXA				
	No sample		Blood sample			No sample		Blood sample		
Variable	*n*	Median [IQR] or %	*n*	Median [IQR] or %	*P*	*n*	Median [IQR] or %	*n*	Median [IQR] or %	*P*
Age	39	43 [27–60]	129	35 [25–54]	.27	38	58 [24–69]	156	41 [27–56]	.04
Male gender	27	69%	107	83%	.07	27	71%	117	75%	.68
ISS	39	29 [20–34]	129	21 [17–30]	.01	37	26 [20–31]	155	25 [17–31]	.72
Head AIS	39	4 [3–5]	129	4 [3–5]	.13	38	4 [3–5]	156	4 [3–5]	.72
Penetrating injury	6	15%	8	6%	.09	…	…	…	…	…

Abbreviations: AIS, Abbreviated Injury Score; IQR, interquartile range; ISS, Injury Severity Score; TXA, tranexamic acid.

[a]No comparison was made for penetrating injury in the TXA group due to a lack of patients in the no-sample population.

TABLE 2

Descriptive statistics according to the treatment group in patients receiving placebo versus TXA

	Placebo		TXA		
Variable	***n***	**Median [IQR] or %**	***n***	**Median [IQR] or %**	***P***
Age	129	35 [25–54]	156	41 [27–56]	.34
Male gender	107	83%	117	75%	.10
ISS	129	21 [17–30]	155	25 [17–31]	.31
Head AIS	129	4 [3–5]	156	4 [3–5]	.74
Penetrating injury	8	6%	4	3%	.15

Abbreviations: AIS, Abbreviated Injury Score; IQR, interquartile range; ISS, Injury Severity Score; TXA, tranexamic acid.

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TABLE 3

Median baseline marker levels in patients who received placebo versus TXA

	Placebo		TXA		
Marker	***n***	**Median [IQR]**	***n***	**Median [IQR]**	***P***
Syndecan-1	129	272.4 [219.7–373.1]	156	254.6 [200.9–324.0]	.05
ICAM-1	128	42 879.8 [31 552.3–66 088.9]	155	43 491.3 [32 198.0–58 107.6]	.45
VCAM-1	129	61 206.0 [47 652.8–90 083.6]	156	63 739.9 [49 402.7–87 275.7]	.36
Thrombomodulin	129	598.9 [514.1–760.5]	156	594.2 [505.4–714.6]	.14
Thrombospondin-2	129	2 055.7 [1 537.9–2 787.1]	156	1 975.9 [1456.0–2642.5]	.22
Angiopoietin-1	129	477.7 [303.9–876.2]	155	482.8 [289.1–695.3]	.23
Angiopoietin-2	129	144.2 [103.3–196.0]	156	150.4 [106.6–190.0]	.66

Abbreviations: ICAM-1, intercellular adhesion molecule 1; IQR, interquartile range; TXA, tranexamic acid; VCAM-1, vascular cell adhesion protein 1.

TABLE 4

Median baseline marker levels in patients who received TXA early (<45 minutes) versus late (≥45 minutes) relative to time of injury

	Early (<45 min)		Late (≥45 min)		
Marker	***n***	**Median [IQR]**	***n***	**Median [IQR]**	***P***
Syndecan-1	77	234.4 [200.1–293.3]	79	270.1 [201.1–358.0]	.09
ICAM-1	76	40 492.4 [30 446.2–56 903.7]	79	46 502.6 [32 971.5–63 558.4]	.16
VCAM-1	77	63 801.8 [49 866.8–86 826.1]	79	63 678.0 [49 133.7–87 963.5]	.70
Thrombomodulin	77	583.5 [478.4–707.8]	79	605.7 [520.7–723.3]	.42
Thrombospondin-2	77	1 954.9 [1 363.0–2 820.8]	79	1 991.4 [1 516.9–2 596.0]	.46
Angiopoietin-1	77	371.5 [266.7–690.9]	78	532.6 [346.2–768.6]	.08
Angiopoietin-2	77	142.6 [94.0–171.8]	79	155.4 [111.3–211.3]	.05

Abbreviations: ICAM-1, intercellular adhesion molecule 1; IQR, interquartile range; TXA, tranexamic acid; VCAM-1, vascular cell adhesion protein 1.

TABLE 5

Median baseline marker levels in patients who received placebo early (<45 minutes) versus late (≥45 minutes) relative to time of injury

	Early (<45 min)		Late (≥45 min)		
Marker	***n***	**Median [IQR]**	***n***	**Median [IQR]**	***P***
Syndecan-1	65	286.5 [218.8–380.6]	64	268.9 [220.5–373.9]	.99
ICAM-1	65	45 469.5 [30 363.0–65 899.7]	63	41 819.3 [31 514.0–66 355.4]	.84
VCAM-1	65	59 537.5 [50 480.7–84 164.1]	64	68 190.4 [44 785.9–94 065.8]	.81
Thrombomodulin	65	586.1 [518.0–727.4]	64	611.0 [512.2–784.7]	.91
Thrombospondin-2	65	2 055.7 [1 585.3–2 678.8]	64	2 042.2 [1 462.3–2 875.7]	.98
Angiopoietin-1	65	484.5 [281.2–857.4]	64	473.7 [318.3–938.2]	.67
Angiopoietin-2	65	143.3 [105.1–200.7]	64	145.8 [94.2–193.4]	.48

Abbreviations: ICAM-1, intercellular adhesion molecule 1; IQR, interquartile range; VCAM-1, vascular cell adhesion protein 1.