Critical Review Form
Therapy

PGY-4

Lindauer KE, Lo BM, Weingart GS, Karpov MV, Gartman GH, Neubauer LE, Kaplan MC. Tranexamic acid for angiotensin converting enzyme inhibitor induced angioedema: A retrospective multicenter study. Am J Emerg Med. 2024 May;79:33-37.

Objectives: **"To address this gap in literature, we conducted a retrospective chart review of patients with ACE-IIA [ACE-inhibitor-induced angioedema] who received tranexamic acid [TXA] in the ED across an integrated health system. We sought to describe the effect of tranexamic acid on patient length of stay as well as evaluate other patient-centered outcomes." (pp. 33-34)**

Methods: **This multicenter, retrospective cohort study was conducted using the electronic medical records of a 17-ED health system in Virginia between January 1, 2018 and August 31, 2021. Adult patients aged 18-89 years presenting to the ED with a diagnosis of angioedema and a prescription for an ACE-I were eligible for inclusion. Exclusion criteria were presence of urticaria alone, active prescription for an angiotensin-receptor blocker, history of hereditary angioedema, C1 esterase deficiency, presumed angioedema from another cause, history of recurrent angioedema, or incomplete medical records.**

The primary outcome evaluated was length of stay (LOS) between patients who received tranexamic acid and those who did not. Secondary outcomes included ED disposition, need for intubation, return to the ED for any cause within 7 days, death from any cause, and thrombotic events within 7 days of hospital stay. Airway risk was assessed using the Ishoo scoring system: facial rash, facial edema, lip edema (stage I), soft palate edema (stage II), lingual edema (stage III), and laryngeal edema (stage IV).

Out of 330 patients identified, 262 met inclusion criteria; of these, 73 received TXA (treatment group) and 189 did not (control group). The mean age was 59 years, 50% were male, and 70.6% were African American. Patients in the treatment group were less likely to have stage I edema (34.3% vs. 64.6%) and more likely to have stage III edema (42.5% vs. 26.5%).

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Guide	Comments
Are the results valid?	
Did experimental and control groups being the study with a similar prognosis?	
Were patients randomized?	No. This was a retrospective chart review and treatments provided were at the discretion of treating clinicians. As a result, patients in the treatment group had more severe angioedema based on the Ischoo scoring system (selection bias).

Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	N/A
Were patients analyzed in the groups to which they were randomized?	N/A. This was not a randomized controlled trial. Patients were analyzed solely based on whether or not they received TXA for the management of ACE-I induced angioedema.
Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. As noted above patients in the treatment group were more likely to have stage III edema and less likely to have stage I edema (i.e. they had more severe edema overall). Patients in the two groups were similar with respect to age, medical comorbidities (somewhat higher rate of hyperlipidemia in the control group), and ACE-I type and dose. Patients in the treatment group were less likely to be on an anticoagulant or antiplatelet agent (24.66% vs. 36.1%), and were more likely to receive IM epinephrine, FFP, and a C1-esterase inhibitor.
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	Yes. This was a retrospective chart review and hence there was no blinding. It is unlikely that performance bias on the part of patients would have affected outcomes.
Were clinicians aware of group allocation?	Yes. This was a retrospective chart review and hence there was no blinding. It is possible that performance bias on the part of clinicians would have affected outcomes.
Were outcome assessors aware of group allocation?	Yes. There is no mention of blinding of outcome assessors, which is possible in a retrospective study. There is some risk of observer bias, though the outcomes were fairly objective.
Was follow-up complete?	Likely yes. Most of the outcomes were measured during the index hospital stay and hence would have been captured for all patients. Outcomes measured up to 7 days following hospitalization could have been missed if patients went to ED's outside of the study healthcare system or if medical attention was not sought.
What are the results?	
How large was the treatment effect?	• Median LOS was longer in the treatment group compared to the controls (40.28 vs 21.08 h, $p < 0.0001$). • A multinomial logistic regression model of the subgroup of patients with only Ishoo stage 2, 3, or 4 angioedema showed that treatment with tranexamic acid did not significantly impact hospital LOS ($p = 0.247$). • More patients in the treatment group were admitted to the ICU (45.2% treatment; 15.9% controls) while the majority of patients in the control group were discharged home (46.3% treatment; 77.3% controls) ($p < 0.0001$). • A multiple linear regression model used to predict the logarithmic LOS indicated that hospital LOS was 40.1% longer in the treatment group ($p = 0.032$, 95% CI: 28.8–64.5%) compared to the controls • Patients in the treatment group had higher odds (OR = 2.59, 95% CI: 1.23–5.43) of being admitted to the ICU versus discharged home compared to patients in the control group.
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	See above
How can I apply the results to patient care?	
Were the study patients similar to my patient?	Likely yes. This study was conducted using records from a 17-hospital healthcare system in Virginia. The racial profile includes a large number of African Americans and patients had a wide array of medical

	comorbidities. It is likely that these patients would be similar to patients being seen for ACE-IIA in our institution.
Were all clinically important outcomes considered?	Mostly yes. The authors considered length of stay, ED disposition, need for intubation, mortality, thrombotic event risk, and ED return rate.
Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This study was largely limited by its retrospective nature and high risk of selection bias. Patients in the treatment group had more severe angioedema with much higher rates of lingual edema (Stage III Ishoo classification) which is likely responsible for the resulting longer length of stay and increased need for ICU admission. The authors did not attempt to use statistical tools (e.g. propensity matching or logistic regression) to control for these differences. As a result, it is not possible to use these results to evaluate the efficacy of TXA in management of ACE-IIA.

Limitations:

1. **This was a retrospective study at high risk for selection bias. The authors did not attempt to control for differences between the groups.**
    a. **Patients in the treatment group had more severe angioedema, with a large difference in those meeting stage III Ishoo classification (42.5% vs. 26.5%).**
2. **The retrospective nature of the study resulted in inconsistent and missing data capture.**
3. **The lack of blinding increases the risk of performance bias and observer bias.**
4. **Seven-day outcomes could easily have been missed if patients went to hospitals outside of the healthcare system or did not seek medical attention.**

Bottom Line:

This retrospective study comparing outcomes in patients with ACE-IIA who received TXA versus those who did not found found significantly longer hospital lengths of stay (median 40.28 vs 21.08 h, $p < 0.0001$) and higher rates of ICU admission (45.2% treatment; 15.9% controls) among patients receiving TXA. These differences are likely driven in large part by more severe angioedema seen in those patients who received TXA, among whom 42.5% had lingual involvement compared with 26.5% in the control group. It is not possible to assess the efficacy of TXA in the management of ACE-IIA given the limitations of the study.