Brief Review

Received: 2023/05/01  Revised: 2023/05/10  Accepted: 2023/05/11

DOI: https://doi.org/10.15441/ceem.23.051

Tranexamic Acid for ACE inhibitor-induced Angioedema

Running title: TXA for ACEI-induced Angioedema

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Abstract

Approximately 0.7% of patients taking Angiotensin converting enzyme inhibitors (ACEI) develop ACEI induced angioedema (ACEI-IA). With no current approved treatments for ACEI-IA, the risk of complications is concerning. Tranexamic acid (TXA) has shown the potential to prevent intubations and resolve ACEI-IA through inhibiting downstream production of bradykinin. In this review, we aim to evaluate the safety and efficacy of TXA use in ACEI-IA. We queried the PubMed database for studies involving TXA for ACEI-IA from January 2003 to January 2023. Seven studies met the study inclusion criteria, and our results demonstrate that TXA may improve angioedema symptoms and prevent intubation. In addition, its availability, low cost, and safety profile supports its use for ACEI-IA to improve symptoms and complications in an emergency setting.

Key words: ACE inhibitor induced angioedema, bradykinin mediated angioedema, Tranexamic Acid, angiotensin converting enzyme inhibitors, drug-induced angioedema.

Capsule summary: Angiotensin converting enzyme-induced angioedema is primarily bradykinin mediated with no current approved treatments. Tranexamic acid has shown promise in resolving angioedema symptoms and preventing intubations.
Introduction

Approximately 30-40% of all angioedema-related emergency medicine visits are caused by angiotensin-converting enzyme inhibitor (ACEIs) medications.[1] Populations with the highest risk of developing angiotensin-converting enzyme inhibitor-induced angioedema (ACEI-IA) are females and African Americans, who are nearly 4.5 times more likely to develop ACEI-IA.[2, 3] ACEI-IA, a potentially fatal complication of ACE inhibition, occurs in up to 0.7% of patients treated with ACE inhibitors. The incidence of ACEI-IA is the highest within the first month of initiation of therapy, accounting for nearly 1/3 of all cases.[4] However, the onset of ACEI-IA can occur any time after initiation and has been reported as late as twenty years after beginning treatment.[5] Lisinopril was the most common causative agent in 87.2% of reported ACEI-IA cases, followed by lower rates in other ACEIs such as enalapril 4.3% and benazepril 3.0%.[3, 6]

Clinical manifestations and Current treatment

The pathophysiology of angioedema involves a rapid increase in vascular permeability and subsequent submucosal edema. With ACE inhibition, the reduced kininase II mediated degradation of substance P and bradykinin causes excessive vasodilation and plasma extravasation.[4, 7] ACEI-IA attacks typically last 48-72 hours, and patients require hospital admission in most cases.[7, 8] Nearly 10% of all ACEI-IA cases require intubation within the first 6 hours of symptom onset.[9] In addition, approximately 40% of ACEI-IA patients are admitted to the intensive care unit for an average length of stay of 2.2 days.[9, 10] First-line treatment for ACEI-IA is an immediate cessation of ACEI and active airway management.

Given the prevalent use of ACEIs, there is an urgent clinical need for a rapidly effective therapeutic intervention for severe ACEI-IA. The successful use of tranexamic acid for prophylaxis of acquired angioedema was first reported in the emergency setting by Beuchene et. Al in 2018.[11] This review aims to investigate the efficacy of tranexamic acid use in the acute management of ACEI-IA.

Literature Review:
We searched the literature for TXA and ACEI-I A in the PubMed database with the following search terms: "tranexamic acid for bradykinin angioedema” and “tranexamic acid for angiotensin-converting enzyme inhibitor-induced angioedema”. The results were limited to observational studies, case reports, case series, and literature reviews published within the last 20 years and resulted in 54 eligible studies. After excluding studies evaluating tranexamic use in hereditary angioedema or non-bradykinin-mediated angioedema, there were 7 articles for full-text review. Included parameters of interest were study name, study type, sample size, primary outcomes, and results. The key findings of the search results are listed below in Table 1. Key primary endpoints of interest included the percentage of patients with resolved/improved angioedema, overall intubation rates, and treatment-related adverse effects. For studies regarding maintenance treatment, the frequency of acute angioedema attacks, treatment efficacy, and treatment safety parameters were included.

Table 1: Findings of Selected Studies for Tranexamic Acid use in ACEI Angioedema (included in separate file)
A total of seven studies that met the inclusion criteria were identified; three were retrospective, one was a case series, and three were individual case reports. All studies commented on the general efficacy of TXA for bradykinin-mediated angioedema conditions and included information regarding intubation, mortality, and adverse effects.

The two largest retrospective studies consisted of 33 patients and 16 patients each. The primary outcomes were the time to resolution of angioedema symptoms and the number of patients that required intubations. In the larger 33-patient retrospective cohort study, TXA was used as first-line therapy, with most patients (81.81%) showing significant improvement (regression of edema/dyspnea or other symptoms, not complete remission) with TXA treatment alone.[11] Additional treatment with icatibant was required in 15.2% of patients and 3.0% needed Cl esterase inhibitor (Cl-INH) concentrate due to an initial partial resolution of symptoms with TXA monotherapy, suggesting some patients needed did not have adequate resolution of symptoms.[11] In addition, approximately 40% of patients reported improvement within 1 hour of TXA administration and there were no intubations, and no side effects or fatalities occurred.[11] In the smaller 16 patient retrospective cohort study, 87.5% of the patients did not require intubations, with the other 12.5% receiving intubation prior to TXA administration. No patients reported worsening angioedema in this study, with 74% of patients experiencing partial resolution of symptoms following TXA infusion. The patients reported zero adverse effects in this study as well.[12]

A retrospective case series of 11 ACEI-IA patients treated with TXA reported the median length of hospital stay was 1.2 days. Although this series reported two intubation cases, both patients were intubated before the administration of TXA. The mortality rate in this case series was 0%, with no reported adverse effects.[13]

Another study included 35 patients, of which 25 patients received TXA during an episode of bradykinin-related angioedema. TXA was well tolerated and led to at least a partial resolution of symptoms in 92% of patients, with 48% having a complete resolution.[14] Treatment failure and treatment discontinuation due to digestive intolerance occurred in two patients, respectively. Four patients were not treated with TXA due to thromboembolic contraindications. Although this study was not specific for ACEI-IA, the similar
underlying mechanism of angioedema supports the pharmacological action of TXA in bradykinin-mediated angioedema.[13]

In addition to the retrospective studies conducted, three additional case reports have been published regarding TXA use in ACEI-IA.[15-17] There was at least partial resolution of symptoms with no adverse effects, intubations or mortality reported.[15-17] Additionally, two clinical studies reported two cases, each requiring intubation due to ACEI-IA, but these patients were both intubated before TXA initiation.[12, 13]

**Discussion:**

The mechanism of action for tranexamic acid in the treatment of ACEAI is not well understood. However, blockage of plasmin activation by tranexamic acid contributes to its fibrinolytic effect and is an important step in amplifying kallikrein (a precursor of bradykinin) activation. TXA prevents fibrin-induced inflammatory peptides and decreases the conversion of kininogen into bradykinin. C1 esterase activates plasma kallikrein and factor XIIa to allow for downstream bradykinin development.[8, 18]

Further research is needed to clarify the exact mechanisms by which it exerts its therapeutic effects in this population.

There are currently no FDA-approved medications for treating ACEI-IA, and no current guideline recommendations regarding acute ACEI-IA treatment. Traditional treatment of ACEI-IA revolves around discontinuing the offending agent and providing symptom management. Agents that are traditionally used for "on demand" treatment of hereditary angioedema (HAE) include ecallantide, icatibant, plasma-derived nano-filtered C1-INH, and recombinant C1-INH n.33 with limited studies in the acute treatment of ACE-AI. In line with the mechanism of ACEI-IA, ecallantide inhibits kallikrein, icatibant blocks Bradykinin and C1-INH inhibit the activity of C1 esterases.[19-21]

Untreated angioedema can progress to airway compromise leading to increased mortality without acute management.[22, 23] Given the findings of recent retrospective cohort studies and case reports, tranexamic acid has shown clinical utility in causing an adequate resolution of symptoms and preventing
angioedema progression to intubation. Our review suggests evidence that most patients had partial or complete resolution of symptoms following TXA treatment, with few requiring intubation.[11-17, 24] An additional clinical study evaluated TXA use as a maintenance treatment for non-histaminergic angioedema in 37 patients, of which 18 were diagnosed with HAE and 19 were diagnosed as idiopathic angioedema.[24] These patients also did not respond to anti-histaminic treatment (even at high doses) and did not have complement treatment exploration. Of the 19 patients, there were only 3 acute angioedema attacks in 6 months following TXA initiation, of which only one was severe. There were no cases of an increased number of attacks before TXA initiation. There were 6 accounts of adverse effects, of which 66.66% were digestive adverse effects and 33.33% were dizziness.[24] Although these patients were not confirmed to have ACEI-IA, the suggests the potential of TXA for non-histaminergic angioedema in non HAE confirmed cases. The higher prevalence of adverse effects can be attributed to routine prophylactic use, however in the emergency setting for ACEI-IA TXA is administered less frequently.

The dosages of intravenous TXA administered in studies varied from 500 mg to 4 g of TXA administered/event with most patients receiving 1 g IV.[11-17, 24] This is similar to the typical prophylactic dose for HAE of 1 g twice daily in adults.[25] Additionally, tranexamic acid has a favorable safety profile, with many studies reporting no adverse effects for acute TXA infusion.[12, 14] A pooled analysis of two randomized controlled trials of over 947 cycles of use in 500 women for heavy menstrual bleeding found that subjects using oral tranexamic acid at 3900 mg/day experienced at least one adverse reaction (89.7%, 208/232 vs 87.8%, 139/122) compared to placebo.[26] The most common adverse events include headache (50.4% vs 46.8%), nasal and sinus symptoms (25.4% vs 17.3%), and back pain (20.7% vs 15.1%).[26] While no thromboembolic events were reported in the articles evaluated, it is important to consider the benefit of avoiding intubation versus the potential risk of thrombotic events.

Other Therapeutic Agents
Other currently used off-label treatment options for ACEI-IA include agents commonly used for hereditary angioedema, including icatibant, ecallantide, fresh frozen plasma infusions, and C1-INH. Icatibant, a competitive bradykinin B2 receptor antagonist, is FDA-approved for the treatment of acute attacks of HAE. However, overall efficacy studies of its use in ACEI-IA are mixed.[19, 27] A potential benefit of icatibant is that it does not require hepatic or renal impairment dose adjustment.[28] Thus, there is limited data supporting icatibant-use in ACEI-IA. In addition, its relatively high cost, and limited availability make it less appealing for emergency use.[29]

Ecallantide is FDA-approved for HAE and has been used off-label for ACEI-IA with mixed efficacy data due to no statistically difference against placebo for improving discharge criteria. [20, 30] Ecallantide is a parental recombinant protein inhibitor of kallikrein thought to decrease bradykinin production to resolve angioedema. Similar to icatibant, ecallantide has a relatively high cost, and limited availability bringing into question its clinical effectiveness in medical practice.[31] Some evidence suggests ecallantide has a higher rate of hypersensitivity reactions that further complicate its use.[20]

Fresh frozen plasma (FFP) infusions have been used for ACEI-IA and are effective because they contain kininase 2 and ACE to directly breakdown bradykinin. Case series have reported the successful use of FFP in resolving angioedema symptoms. FFP may be a favorable agent in emergency use given its availability and relatively low cost, however, risks for FFP infusion including transfusion-related acute lung injury, fluid overload, and allergic reactions, pose a potential safety concern.[32] Additionally, there are some reports of worsening angioedema following FFP infusion, presumably due to initial spikes of kallikrein substrates in FPP.[20, 33] In addition there is a lack of large randomized controlled clinical trials evaluating FFP use in the acute setting of ACEI-IA.

Purified C1-INH (such as Berinert) inactivate plasma kallikrein and factor XIIa to prevent downstream bradykinin and has been used in HAE, with several case reports supporting its use in ACE-IA. C1-INH have been shown to improve symptoms within 15 minutes of administration and up to 10.1 hours for complete resolution.[8, 21] The case series reported no patients receiving C1-INH required intubation, whereas 5 required intubation in the control group. Despite several successful case reports, there are no
current clinical trials evaluating the use of C1-INH for ACEI-IA.[33] Its cost and lack of ready availability/access in the ED further limit its use.

**Summary**

Future randomized controlled trials of TXA use in ACEI-IA are needed to further support its efficacy and safety in this indication. There have been no direct comparator studies for ACEI-IA between different agents, and future studies will allow a better comparison of efficacy and adverse effects to optimize agent selection. Potential drawbacks for tranexamic use include the possibility of thrombotic events, adverse GI effects, and a lack of large-scale studies evaluating its use.

ACEI-IA remains a key unmet medical need, accounting for approximately 30-40% of angioedema emergency department visits.[1] As the ACEI class of medications is ubiquitously used for hypertension, heart failure, diabetes, and kidney disease, patients should be advised on the signs and symptoms of angioedema. Additionally, the gaining popularity of combination medications, the “polypill”, may further increase total ACEI exposure. Prompt treatment of ACEI-IA is needed to prevent intubation and improve clinical outcomes.

In this literature review, we highlight the valuable role of TXA in ACEI-IA in reducing intubation rates and improving angioedema symptoms. Notably, there were no deaths reported, and four patients requiring intubation in the evaluated studies were all intubated prior to TXA administration. TXA use may be advantageous due to ready acute availability, lower cost, and a low prevalence of adverse effects compared to other currently used off-label medications for ACEI-IA.
References


Table 1: Findings of Selected Studies for Tranexamic Acid use in ACEI Angioedema

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Sample size</th>
<th>TXA Dosing</th>
<th>Clinical outcomes of interest</th>
<th>Primary Efficacy Outcomes</th>
<th>Safety</th>
</tr>
</thead>
</table>
| Beauchene, et. al [11]| Retrospective chart analysis | 33          | 1-4 gram IV or PO once | - Efficacy  
- Intubations  
- Mortality  
- Adverse effects | 27/33 had improvement TXA monotherapy, 6/33 partial improvement, 0 fatalities, 0 intubations | No adverse effects reported                                    |
| Hasara et.al [12]     | Retrospective cohort study | 16          | 1 gram IV once; one patient 100 mg IV once | - Intubation  
- Mortality  
- Adverse effects | 14/16 patients didn’t require intubation, 0 fatalities | No Adverse effects reported                                    |
| Manzano, et.al [13]   | Retrospective case series | 11          | 1 gram IV once | - Length of stay  
- Intubation  
- Mortality  
- Adverse effects | Mean length of stay 1.2 day, 2/11 required intubation, 0% mortality | No adverse effects reported                                    |
<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Type</th>
<th>Participants</th>
<th>Dose</th>
<th>Efficacy</th>
<th>Adverse Effects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du-Thanh, et.al [14]</td>
<td>Retrospective study</td>
<td>35</td>
<td>1 gram PO once, 3-gram daily maintenance</td>
<td>- Efficacy - Adverse effects</td>
<td>23/25 decrease of duration/intensity of episode, 1 treatment failure, 4 contraindicated (thromboembolic) 1 d/c GI intolerance</td>
<td></td>
</tr>
<tr>
<td>Wang, et.al [15]</td>
<td>Case Report</td>
<td>1</td>
<td>1 gram IV once</td>
<td>- Efficacy - Adverse effects</td>
<td>Patient’s symptoms resolved</td>
<td>No adverse effects reported</td>
</tr>
<tr>
<td>Grewal, et.al [16]</td>
<td>Case Report</td>
<td>1</td>
<td>Not listed</td>
<td>- Efficacy - Adverse effects</td>
<td>Patient’s symptoms resolved</td>
<td>No adverse effects reported</td>
</tr>
<tr>
<td>Stoldt, et.al [17]</td>
<td>Case Report</td>
<td>1</td>
<td>1 gram IV once</td>
<td>- Efficacy - Adverse effects</td>
<td>Patient’s symptoms resolved</td>
<td>No adverse effects reported</td>
</tr>
</tbody>
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IV: intravenous, PO: by mouth, GI: gastrointestinal, TXA: tranexamic acid