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An Evaluation of the Use of Tranexamic Acid in the Treatment of Bradykinin-Mediated Angioedema in the Emergency Department

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Background

- Bradykinin mediated angioedema is an overarching term that includes idiopathic angioedema, angiotensin converting enzyme inhibitor (ACEi) induced angioedema and hereditary angioedema (HAE).
- This is an emergent condition that must be treated with the utmost urgency due to the fatal outcomes associated with the rapid constriction of the throat.
- Bradykinin mediated angioedema is treated differently from histamine associated angioedema due to its resistance to corticosteroids and antihistamines.
- HAE and ACEi induced angioedema are treated similarly but there is a lack of unanimity in the first line pharmacologic treatment.
- Current treatment options include fresh frozen plasma, bradykinin-2 receptor antagonists, plasma-kallikrein inhibitors and C1 esterase inhibitors.
- Tranexamic acid (TXA) has been used for moderate cases of angioedema but is not well established in the emergent setting.
- TXA has a 2270-fold lower cost compared to the preferred agent at this large multicenter hospital organization, Berinert.

Purpose

- The purpose of this study is to examine whether TXA is a viable first-line treatment option for bradykinin-mediated angioedema in the emergency department.

Objectives

- Determine whether TXA is a viable treatment option for bradykinin-mediated angioedema
- Evaluate the cost-effectiveness of TXA in comparison to Berinert
- Examine the incidence of use of TXA versus other pharmacologic agents used to treat bradykinin-mediated angioedema
- Identify the optimal or standard dose of oral TXA for patients presenting to the emergency department with bradykinin mediated angioedema

Methodology

- Institutional Review Board (IRB)-approved
- Electronic health record (EHR)-based retrospective chart review of patients admitted to any of the eight emergency departments in a large multicenter hospital organization
- Data was narrowed down by the inclusion criteria and the “SlicerDicer” tool within EPIC was utilized to extract the included study population.
- Study period: October 1, 2019 – October 1, 2020
- Inclusion criteria: patients admitted for either ACEi induced angioedema or HAE and treated with either TXA or Berinert during their emergency department visit.
- Exclusion criteria: patients <18 years of age, patients with suspected or confirmed pregnancy, those with an allergy or intolerance to TXA or Berinert, patients who were treated with any other drug besides TXA or Berinert, those with personal or religious objections to receiving blood products and finally patients with stage one angioedema.
- Primary outcomes: admission to the ICU, intubation rate and length of stay (LOS).

Patient Demographics and Clinical Outcomes

Patient Baseline Demographics

Characteristic	Tranexamic Acid (n=14)	Berinert (n=4)	Combined (n=18)	p-value
Age, in years, mean (range)	56 (39-67)	76 (65-88)	60 (39-88)	0.0116
Weight, in kilograms, mean (range)	101 (38-175)	99 (84-117)	101 (38-175)	0.9212
Gender, no. (%)				1.0000
• Male	9 (64.3)	3 (75)	12 (66.7)	
• Female	5 (35.7)	1 (25)	6 (33.3)	
Race/Ethnicity, no. (%)				0.0303
• Caucasian	8 (57.1)	4 (100)	12 (66.7)	
• African American	5 (35.7)	0 (0)	5 (27.8)	
• Native American	1 (7.1)	0 (0)	1 (5.6)	
ACEi/ARB use, no. (%)				
• ACEi	11 (78.6)	4 (100)	15 (83.3)	
• ARB	2 (14.3)	0 (0)	2 (11.1)	
Chief Complaint, no. (%)				0.5098
• Allergic Reaction	4 (28.6)	0 (0)	4 (22.2)	
• Lip Swelling	1 (7.1)	0 (0)	1 (5.6)	
• Oral Swelling	4 (28.6)	1 (25)	5 (27.8)	
• Facial Swelling	1 (7.1)	0 (0)	1 (5.6)	
• Tongue Swelling	4 (28.6)	2 (50)	6 (33.3)	
• Mouth Swelling	0 (0)	1 (25)	1 (5.6)	

Table 1. Patient Baseline Demographics

Clinical Outcomes

Outcomes	Tranexamic Acid (n=14)	Berinert (n=4)	Combined (n=18)	p-value
Admission rate (# of admissions)	7 (50)	2 (50)	18 (50)	
Admission Department, no. (%)				
• Medicine	2 (14.3)	0 (0)	2 (11.1)	
• ICU	5 (35.7)	2 (50)	7 (38.9)	1.0000
LOS, in days, mean (range)	1 (1)	2.5 (1-4)	2 (1-4)	0.6757
LOS (% ≥ 1 day)	7 (50)	2 (50)	9 (50)	1.0000
Intubation rate (# of intubations)	0 (0)	1 (25)	1 (5.6)	0.2222
Bleeding rate (# of bleeds)	0 (0)	1 (25)	1 (5.6)	0.2222
Thrombosis rate (# of thrombosis)	0 (0)	0 (0)	0 (0)	N/A
Anaphylaxis rate (# of anaphylaxis)	0 (0)	0 (0)	0 (0)	N/A
Mortality rate (# of deaths)	0 (0)	0 (0)	0 (0)	N/A

*Length of Stay in days

Table 2. Clinical Outcomes of Patients

Clinical Outcomes (continued)

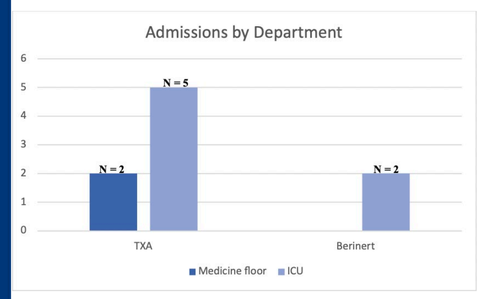

Figure 1. Admissions by Department

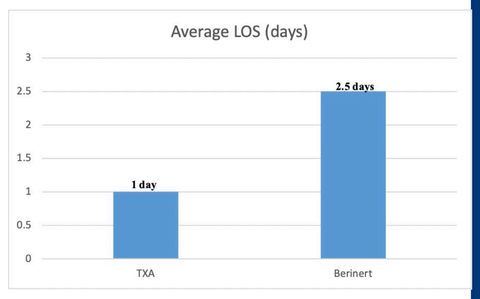

Figure 2. Average LOS (days)

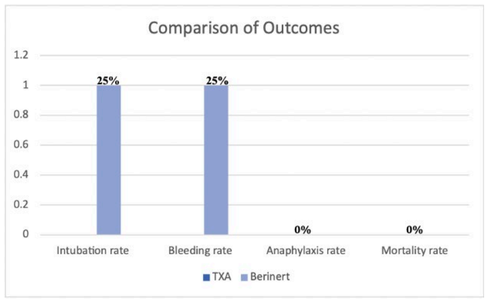

Figure 3. Comparison of clinical outcomes

Financial Comparisons

Drug	Dose	Route	Price*
Tranexamic Acid	1000 mg	IV	$6
Berinert	2000 units	IV	$13,617
Cinryze	1000 units	IV	$5,704
Ruconest	4200 units	IV	$13,674
Kalbitor	30 mg	SC	$15,889
Firazyr	30 mg	SC	$11,647

Table 3. Costs of agents used to treat bradykinin-mediated angioedema
*In accordance with primary literature, US retail pricing obtained from www.drugs.com on April 6, 2021

Discussion

Patient Population

- Average patient was a 60-year-old Caucasian male weighing 101 kg with a history of a home use of an ACEi with a chief complaint of tongue swelling.
- The mean age was 56 years (range 39-67 years) in the TXA group and 76 years (range 65-88 years) in the Berinert group.
- 94.4% of patients in total reported taking a home ACEi (83.3%) or ARB (11.1%) prior to admission.

Clinical Outcomes

- In the TXA cohort, 50% (n=7) patients were admitted to the hospital with 35.7% of patients in this cohort (n=5) admitted to the ICU. The remaining patients, 14.3% (n=2) were admitted to the medicine floor.
- The average LOS for patients treated with TXA was 1 day (range of 1 day) and there was no incidence of bleeding in this group.
- Patients in the Berinert cohort had a 25% incidence of intubation (n=1). 50% (n=2) of patients were admitted to the hospital with both patients being admitted to the ICU.
- The average LOS for patients treated with Berinert was 2.5 days (range of 1-4 days) and 25% (n=1) patient was reported to have copious amounts of blood from his mouth. There was no charting to explain the etiology of the bleed in this particular patient.
- For both cohorts, there was no incidence of mortality, anaphylaxis or thrombosis.

Financial Implications

- The average cost of 1 gram dose of TXA is $6 compared to $13,617 for Berinert. If one were to estimate an arbitrary 15 incidences of bradykinin mediated angioedema cases in a year, the average cost of TXA would be $90 compared to an estimated annual cost of $204,255 of Berinert.
- This is a 2,270-fold price difference.

Study Limitations

- Retrospective chart review
- Disproportionate sizes of cohorts
- The study did not reach the sample size required for adequate power to assess the primary outcomes of ICU admissions, intubation rate, and LOS.

Next Steps

- This small study showed the potential for utilization of intravenous TXA as a first line agent for bradykinin-mediated angioedema.
- A larger study population would need to be assessed to confirm the benefits of using intravenous tranexamic acid over a C-1 esterase inhibitor such as Berinert as a first line agent for bradykinin-mediated angioedema.
- By utilizing a more cost effective and possibly safer agent such as tranexamic acid, providers may not only improve outcomes for patients but also reduce costs for a large multicenter healthcare system.

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