Research article

Onset of Orolingual Angioedema After Treatment of Acute Brain Ischemia with Alteplase Depends on the Site of Brain Ischemia: A Meta-analysis

Josef Yayan

Department of Internal Medicine, University Hospital of Saarland, Homburg, Saarland, Germany

Abstract

Background: Alteplase is used to treat acute ischemic stroke. However, it has several documented adverse effects, including the development of orolingual angioedema (OA). Although, OA is a rare side-effect, it is thought to be life-threatening and is difficult to treat. Until date, little is known about this condition and a better understanding of OA may contribute to improve the morbidity and mortality amongst patients that develop this condition. **Materials and Methods:** Using the PubMed and Medknow databases, we searched for peer reviewed published articles on OA after alteplase administration in 1950-2012. We gathered demographic data and investigated the relationship between the location of OA, neurological symptoms and the site of cerebral ischemia. In addition, we studied the effects of hypertensive premedication on OA development. We identified 19 published manuscripts that fulfilled our search criteria. These manuscripts reported 41 cases of OA after alteplase administration. **Results:** We found that this condition is associated with cerebral ischemia ($P < 0.012$) and that 65.9% ($n = 27$) of patients who developed OA had a hypertensive drug as a premedication. **Conclusions:** Although OA is a rare side-effect of alteplase, it can occur depending upon the localization of acute cerebral ischemia.

Keywords: Acute ischemic stroke, Angiotensin-converting enzyme inhibitors, Ischemic stroke, Life-threatening, Orolingual angioedema, Recombinant tissue plasminogen activator, Tongue swelling

Address for correspondence: Dr. Josef Yayan, Department of Internal Medicine, University Hospital of Saarland, Kirrberger Straße, D-66421 Homburg, Saarland, Germany. E-mail: josef.yayan@hotmail.com

Introduction

Cerebrovascular diseases are the second most common cause of death and dementia in adulthood and the leading cause of disability in industrialized countries.[1] Acute ischemic stroke results in a sudden loss of brain function due to reduced blood flow to the brain that is caused by vascular blockage.[1] Patients with atherosclerosis are particularly vulnerable to develop cerebral ischemia, as high blood pressure, a condition that often coexists with cerebrovascular disease, can detach clots that form on the surface of atherosclerotic plaques what can lead to cerebral vascular closure.[1] For this reason, reperfusion therapy with the use of anti-coagulants and antifibrinolytics has been at the forefront of therapy for acute ischemic stroke for the past several decades.[2-6]

Since 1996, the US Food and Drug Administration has only approved recombinant tissue plasminogen activator (rt-PA) for the treatment of acute ischemic stroke.[7,8] This approval followed the results of a large-scale trial conducted by the National Institute of Neurological Disorders and Stroke (NINDS).[7,8] This study showed that bolus intravenous (IV) rt-PA given within 3 h of the onset of stroke results in a significant decrease in the risk of brain hemorrhage.[7,8] However, this therapeutic approach remains controversial because it is associated with serious adverse events, including symptomatic intracerebral hemorrhage and orolingual angioedema (OA). Although intracranial hemorrhage was not found in patients enrolled in the NINDS investigation, clinical studies have reported intracranial hemorrhage in 2-9% of patients treated with rt-PA.[9,10]

Access this article online

Quick Response Code:

Website: www.najms.org

DOI: 10.4103/1947-2714.120794

OA has been reported in isolated cases.[11-28] This complication can be life-threatening, but the mortality rate associated with OA is not yet known.[12-17] OA occurs within minutes after the injection of rt-PA in patients who experience this side-effect and it is characterized by swelling of the tongue and upper lip. In severe cases, it can cause airway obstruction and breathing problems.[12-17] The physiological mechanisms of actions underlying the development of OA have not yet been elucidated. Previous studies have reported that the development of OA after the administration of the rt-PA agent, is associated with the use of angiotensin-converting enzyme (ACE) inhibitors.[13,14,17] Close observation for and early identification of OA is likely to limit the mortality associated with this condition.

However, no systematic review of data regarding possible causes of OA due to alteplase administration exists within the literature. Thus, the aim of our study was to review the available literature on OA after alteplase treatment and then to use the acquired demographic information to clarify the causes of rt-PA-mediated OA. We examined also blood pressure medications as a possible cause for the development of OA.

Methods

We systematically reviewed the literature available on the PubMed and Medknow databases. We searched for the terms "OA" plus "alteplase" in articles published from 1950 to 2012. Only original articles written in English were included in this study. We included both case reports and original research manuscripts. The publications were classified by year of publication, authorship and country. Some articles were excluded because of irrelevant content.

In our analyses, we included cases from studies if patients had ischemic stroke and developed OA within minutes after receiving an alteplase injection. We also ensured that in all cases, IV alteplase (0.9 mg/kg) was administered within the suggested period of 3 h from the onset of neurological symptoms of acute ischemic stroke. The severity of ischemic stroke was assessed with the National Institutes of Health Stroke Survey (NIHSS) scoring system, a 11-item stroke examination utilized to determine the neurological effect of acute cerebral infarction on consciousness, language, neglect, test of visual field, eye movement, motor strength, ataxia, dysarthria and loss of sensation. Ratings for each item are scored with three to five grades, with a grade of zero representing normality. Several studies have used the NIHSS to evaluate the efficacy of clinical therapy in stroke recovery.

Patients were classified according to age, gender and the following clinical neurological symptoms of stroke: Hemiparesis, polarity of facial paralysis, dysphasia and dysphagia. All patients underwent cranial computerized tomography (CT) to identify the site of cerebral ischemia indicated when acute stroke was suspected.

Clinical investigations of OA have reported the period between alteplase injection and the first signs of edema, as well as the duration of edema and the areas of the tongue affected. Hemiparesis was noted as ipsilateral, symmetrical or asymmetrical. We considered the terms: (1) "swelling of the tongue" as a reference to symmetrical swelling of the entire tongue, (2) "the same side as hemiparesis" as a reference to ipsilateral swelling and (3) "on the opposite side of hemiparesis" as a reference to asymmetrical swelling. We considered the term hemiparesis to refer to a weakness of function resulting from stroke. As a measure of adverse effect severity, we documented the number of patients that required life-support.

We also investigated whether patients receiving ACE or angiotensin II inhibitors for hypertension were at greater risk of developing OA after receiving alteplase than those who did not receive these antihypertensive drugs. We also compared the risk associated with gender and administration of ACE or angiotensin II inhibitors with the development of OA.

Statistical analysis

Multiple regression analysis was used to investigate the relationship between OA and the specific characteristics of ischemic stroke. We used one-way analysis of variance to compare the localization of cerebral ischemia in the brain to hemiparesis. Then, we determined the relative risk (RR) for OA by gender with antihypertensive pharmacotherapy. A value of $P < 0.05$ was considered to be significant.

Results

We identified 37 publications in the PubMed database and 1 publication in the Medknow database from 1950 to 2012 that corresponding with our search criteria. For our review, we selected 19 of these publications (16 case reports and 3 case series) that reporting about OA in acute ischemic stroke patients after treatment with alteplase. The publications originated from the United States of America (6), Canada (4), Germany (4), India (1), Japan (1), Switzerland (1), Taiwan (1) and Turkey (1) and they were published between 1977 and 2012. In these publications, 41 cases of OA after alteplase administration were described; 15 cases (36.6%) were male and 26 (63.4%) were female. The mean age was 69.25 years [Table 1].

The average NIHSS scores reported in these studies was 13.91 ± 5.75. Four of the publications reported the incidence of OA as varying between 1.70% and 5.88%. Reanimation of the airway obstruction because of OA was performed in only 1 (2.4%) of the 41 reported cases. Of patients, 24 (58.5%) were taking an ACE inhibitor as a medication prior to thrombolysis, 3 (7.3%) were taking angiotensin II inhibitors and 14 (34.1%) were not taking prior medication (n = 41). Of those taking ACE inhibitors, 12 were men while 13 were women. The RR for OA was not statistically increased for those who took an ACE inhibitor as a prior medication (RR = 1.4667, 95% confidence interval (CI): 0.8978-2.396, P = 0.1261). The RR of OA for women taking angiotensin II inhibitors (3/26) was 4.1481 (95% CI: 0.2287-75.2386, P = 0.3360). In one case (2.4%) of the total of 41 patients in this study, the development of OA caused fatal ventricular tachycardia. Treatments for OA included antihistamine (20), corticosteroids (15) and epinephrine (2). We found no association between the neurological symptoms of hemiparesis and the position of the OA [ipsilateral, P = 0.074; symmetrical, P = 0.79; asymmetrical; P = 0.79, Table 2]. However, we found a statistically significant association between the site of acute ischemia (as mapped by CT) and the position of the OA on the tongue [ipsilateral, P = 0.012; symmetrical, P = 0.012; asymmetrical, P = 0.009; Table 2]. A statistically significant association was also found between the site of acute ischemia and tracheotomy following symmetrical OA (P = 0.016) and asymmetrical OA [P = 0.03, Table 2]. The 41 patients included in the study had a 97.6% chance of surviving an episode of OA (95% CI: 92.78-102.39).

Discussion

Globally, alteplase is used as a therapy for acute ischemic stroke and it is considered a safe and effective treatment choice for thromboembolic vascular occlusions.[3-10] During treatment with alteplase, life-threatening adverse events, such as brain hemorrhage and other bleeding

Table 1: Demographic characteristics of patients

Study origin	Number of patients	Age (mean±SD) (range)	Gender (male:female)	Cases of ischemic events in these studies (%)	Cases of orolingual angioedema (n=41) (%)
USA	5	71.8±11.45 (58-89)	2:3		12.2
Germany	15	67.79±13.75 (47-92)	6:9	17 (4.07)	36.6
Canada	15	75.67±1.53 (74-77)	6:9	281 (67.22)	36.6
Japan	1	75	0:1		2.4
Switzerland	2	66	1:1	120 (28.71)	4.9
Taiwan	1	82	0:1		2.4
Turkey	1	65	0:1		2.4
India	1	50	0:1		2.4
Total	41	69.25±11.62 (47-92)	15:26	418 (100)	100

SD: Standard deviation

Table 2: Clinical and radiologic stroke symptoms of patients with orolingual angioedema

Ischemic stroke condition	Number of cases	Tongue location			Delay in time onset (min) (mean±SD)	Duration (min) (mean±SD)	Intubation/ tracheostomy
		I	S	AS			
Neurological disorder							
Hemiparesis right	16	10	1	0	43.57±19.73	840±848.53	2/1
Hemiparesis left	15	3	3	7	47±42.2	1920±831.38	1/2
Facial paralysis right	3	1	1	0	70±14.14		1/1
Facial paralysis left	4	1	0	2	47.5±45.96	2160±1018.23	1/2
Dysphasia	9	2	2	1	43.33±23.59	1520±1321.82	2/3
Dysphagia	1	0	1	0	80±0.0		1/1
Total	48	17	8	10	48.48±27.65	1632±985	8/10
Cerebral infarction							
Middle cerebral artery	18	11	3	3	52.5±38.96	240±0.0	1/1
Insula infarction	3	0	0	1	35±8.66		1
Brainstem infarction	1	0	0	1			
Thalamic infarction	1	0	1	0			
Multiple cerebral infarction	1	1	0	0			
Total	24	12	4	5	46.67±32.31	1720±1011.61	2/1

Location of tongue location in relation to hemiparesis, I: ipsilateral; S: Symmetrical; AS: Asymmetrical; SD: Standard deviation

complications, can occur.[4-6,8-10] OA is a rare, but serious complication of rt-PA treatment in patients with ischemic stroke.[13-15] Little information about this particular side-effect of rt-PA treatment is available and the currently available information comes from developed countries.[11-19] In addition, information regarding patients who might be at risk of developing OA is sparse. Until date, most of the available information has been reported from case reports and a few original articles.[11-28]

Our results show that age has no effect on the incidence of OA. The neurological symptoms of patients included in this review were not specific to the left or the right side of the body and the severities of ischemic stroke were not correlated with the development of OA. The literature that we reviewed reported that OA usually occurred within the first 2 h after the initiation of thrombolysis. Symmetrical swelling of the tongue seems to result in the highest risk for complications, although not all studies provided a description of the exact position of the angioedema. Although previous studies often described infarction of the middle cerebral artery in patients who developed OA, we found that acute ischemia in the brain played a significant role in the development of OA. Premedication that includes ACE inhibitors is considered as a potential risk for the development of OA after treatment with alteplase.[14-17] For instance, Hill *et al*.[13] treated 176 patients with IV tissue PA for acute ischemic stroke and nine of them developed OA (5.1%; 95% CI: 2.3-9.5).[13] In Hill *et al*., OA was usually mild, transient and contra-lateral to the site of ischemia[13] and the risk for the development of OA was associated with (1) the use of ACE inhibitors as a prior medication (RR 13.6; 95% CI: 3.0-62.7) and (2) CT evidence of ischemia in the insular and frontal cortex (RR 9.1; 95% CI: 1.4-30.0).[13] A previous study also reported that OA was often ipsilateral to the side of hemiparesis.[15] Interestingly, in the majority of patients with OA identified in our review, the position of swelling was ipsilateral to that of hemiparesis or it was asymmetrical.

Patients taking ACE inhibitors have a high risk of developing OA after alteplase treatment.[13,14,17] Most of the patients in our study were taking ACE inhibitors as premedication and we found that in these patients, gender did not statistically affect the risk of developing OA. Although previous studies reported the development of OA in patients treated with ACE inhibitors, most of the men included in our review were taking this antihypertensive medication for the treatment of high blood pressure.[18] Patients treated with angiotensin II inhibitors were also reported to develop OA after treatment with alteplase.[28] In our review, women who were treated with angiotensin II inhibitors did not have a statistically increased risk for the development of angioedema. Two different *in vitro* studies reported that rt-PA could be associated with angioedema, as it initiates a plasmin-mediated release of bradykinin.[29,30]

Conclusions

The results of our study show that OA after treatment with alteplase can occur in patients of all ages and in both genders. Previous studies reported that it was primarily women who were affected by OA. This study confirmed that OA could occur within a few minutes of alteplase administration. The position of OA is often associated with the site of acute cerebral ischemia. More than half of patients in our study were given ACE inhibitors as prior medication, but patients not treated with antihypertensive drugs also developed OA after alteplase administration. The symmetric swelling of the tongue as a result of OA complicates the required use of life-saving techniques such as intubation and tracheotomy.

References

1. Soler EP, Ruiz VC. Epidemiology and risk factors of cerebral ischemia and ischemic heart diseases: Similarities and differences. Curr Cardiol Rev 2010;6:138-49.
2. Sussman BJ, Fitch TS. Thrombolysis with fibrinolysin in cerebral arterial occlusion. J Am Med Assoc 1958;167:1705-9.
3. Meyer JS, Gilroy J, Barnhart MI, Johnson JF. Therapeutic thrombolysis in cerebral thromboembolism. Double-blind evaluation of intravenous plasmin therapy in carotid and middle cerebral arterial occlusion. Neurology 1963;13:927-37.
4. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, *et al*. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol 1992;32:78-86.
5. Brott TG, Haley EC Jr, Levy DE, Barsan W, Broderick J, Sheppard GL, *et al*. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 1992;23:632-40.
6. Haley EC Jr, Levy DE, Brott TG, Sheppard GL, Wong MC, Kongable GL, *et al*. Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91-180 minutes from onset. Stroke 1992;23:641-5.
7. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, *et al*. Early stroke treatment associated with better outcome: The NINDS rt-PA stroke study. Neurology 2000;55:1649-55.
8. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333:1581-7.
9. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, *et al*. Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (SITS-MOST): An observational study. Lancet 2007;369:275-82.
10. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, *et al*. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian acute stroke study investigators. Lancet 1998;352:1245-51.
11. Hill MD, Barber PA, Takahashi J, Demchuk AM, Feasby TE,

Buchan AM. Anaphylactoid reactions and angioedema during alteplase treatment of acute ischemic stroke. CMAJ 2000;162:1281-4.
12. Ottomeyer C, Sick C, Hennerici MG, Szabo K. Orolingual angioedema under systemic thrombolysis with rt-PA: An underestimated side effect. Nervenarzt 2009;80:459-63.
13. Hill MD, Lye T, Moss H, Barber PA, Demchuk AM, Newcommon NJ, *et al*. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. Neurology 2003;60:1525-7.
14. Okada Y, Shibazaki K, Sakai K, Kobayashi K, Iguchi Y, Kimura K. Orolingual angioedema as complication after rt-PA in stroke patient treated with ACE inhibitor. Rinsho Shinkeigaku 2008;48:278-80.
15. Fugate JE, Kalimullah EA, Wijdicks EF. Angioedema after tPA: What neurointensivists should know. Neurocrit Care 2012;16:440-3.
16. Yayan J. Lingual angioedema with macroglossia during the treatment of acute ischemic stroke with alteplase. Int J Gen Med 2012;5:183-6.
17. Rafii MS, Koenig M, Ziai WC. Orolingual angioedema associated with ACE inhibitor use after rtPA treatment of acute stroke. Neurology 2005;65:1906.
18. Papamitsakis NI, Kuyl J, Lutsep HL, Clark WM. Benign angioedema after thrombolysis for acute stroke. J Stroke Cerebrovasc Dis 2000;9:79-81.
19. Maertins M, Wold R, Swider M. Angioedema after administration of tPA for ischemic stroke: Case report. Air Med J 2011;30:276-8.
20. Khurana D, Sharma M, Prabhakar S. Hemi orolingual angioedema. Ann Indian Acad Neurol 2008;11:199.
21. Ekmekçi P, Bengisun ZK, Kazbek BK, Akmansu H, Beriat GK, Süer AH. Oropharyngeal angioneurotic edema due to recombinant tissue plasminogen activator following massive pulmonary thromboembolism. Int Immunopharmacol 2011;11:1384-5.
22. Laubinger R, Guthke K, Erdmann U, Klein U. Angioneurotic orolingual edema associated with the use of rt-PA following a stroke. Anaesthesist 2007;56:1024-7.
23. Krmpotic KR, Fernandes CM. Anaphylactoid reaction to recombinant tissue plasminogen activator. Eur J Emerg Med 2007;14:60-1.
24. Engelter ST, Fluri F, Buitrago-Téllez C, Marsch S, Steck AJ, Rüegg S, *et al*. Life-threatening orolingual angioedema during thrombolysis in acute ischemic stroke. J Neurol 2005;252:1167-70.
25. Rudolf J, Grond M, Schmülling S, Neveling M, Heiss W. Orolingual angioneurotic edema following therapy of acute ischemic stroke with alteplase. Neurology 2000;55:599-600.
26. Jahnke HK. An 89-year-old woman with angioedema during t-PA infusion for acute ischemic stroke. J Emerg Nurs 2003;29:142-4.
27. Pancioli A, Brott T, Donaldson V, Miller R. Asymmetric angioneurotic edema associated with thrombolysis for acute stroke. Ann Emerg Med 1997;30:227-9.
28. Tan CH, Tang SC, Lin RJ, Jeng JS. Neurological picture. Orolingual angio-oedema after alteplase therapy in a stroke patient concurrently using angiotensin II receptor blocker. J Neurol Neurosurg Psychiatry 2010;81:1079.
29. Molinaro G, Gervais N, Adam A. Biochemical basis of angioedema associated with recombinant tissue plasminogen activator treatment: An *in vitro* experimental approach. Stroke 2002;33:1712-6.
30. Kaplan AP, Joseph K, Silverberg M. Pathways for bradykinin formation and inflammatory disease. J Allergy Clin Immunol 2002;109:195-209.

How to cite this article: Yayan J. Onset of orolingual angioedema after treatment of acute brain ischemia with alteplase depends on the site of brain Ischemia: A meta-analysis. North Am J Med Sci 2013;5:589-93.

Source of Support: Nil. **Conflict of Interest:** None declared.