Management of Postthrombolysis Hemorrhagic and Orolingual Angioedema Complications

The Neurohospitalist
2015, Vol. 5(3) 133-141
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DOI: 10.1177/1941874415587680
nhos.sagepub.com

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Abstract

Intravenous recombinant tissue plasminogen activator was first approved for the treatment of acute ischemic stroke in the United States in 1996. Thrombolytic therapy has been proven to be effective in acute ischemic stroke treatment and shown to improve long-term functional outcomes. Its use is associated with an increased risk of symptomatic intracerebral hemorrhage as well as orolingual angioedema. Our goal is to outline the management strategies for these postthrombolysis complications.

Keywords

stroke, cerebrovascular disorders, intracranial hemorrhages, neurohospitalist, clinical specialty

Introduction

In 1996, recombinant tissue-type plasminogen activator (r-tPA; alteplase) was first approved by the US Food and Drug Administration (FDA) for treatment of acute ischemic stroke within 3 hours of symptom onset.¹ The American Stroke Association has since advised extending the intravenous (IV) r-tPA treatment window to 4.5 hours in select patients, based on the results of the European Cooperative Acute Stroke Study (ECASS) III study.^{2,3} Since up to 50% of patients never gain functional independence after ischemic stroke,⁴ interventions aimed at recovery of function are therefore crucial. Intravenous thrombolytic therapy remains the mainstay of evidence-based acute ischemic stroke therapy and is not only efficacious but also cost effective.⁵ Unfortunately, despite FDA approval of IV r-tPA, its use in the United States is limited to 2% to 5% of all acute ischemic strokes, mostly due to delayed presentation to emergency departments.⁶⁻⁸ Additionally, concern over potential symptomatic intracerebral hemorrhage (SICH) is the factor most likely to deter emergency physicians from using r-tPA in patients with acute stroke.⁹ Although there are several thrombolysis-related complications, intracerebral hemorrhage (ICH) causes the most significant morbidity and mortality (Figure 1).^{8,10} When compared to spontaneous ICH, postthrombolysis ICHs tend to be larger, more often multifocal, have less perihematomal edema, and contain a blood fluid level.^{11,12} A less frequent but potentially life-threatening complication is orolingual angioedema. Although it usually presents transiently as a self-limited swelling of the lips and tongue, at times it can progress rapidly with severe swelling necessitating emergent intubation

or cricothyrotomy.^{13,14} Neurohospitalists should be aware of these potential complications after thrombolysis and their practical management and treatment.

Symptomatic ICH After Thrombolysis

The risk of SICH is roughly 6% in patients with stroke treated with IV r-tPA.¹⁵ In the National Institute of Neurological Disorders and Stroke (NINDS) trials, SICH occurred in 6.4% of patients treated with r-tPA within 3 hours of symptom onset versus 0.6% of placebo-treated patients.¹ In the ECASS III trial, SICH occurred in 2.4% of patients treated with r-tPA in the extended 3- to 4.5-hour window versus 0.2% of the placebo-treated patients.² A meta-analysis of 15 open-label studies including 2639 patients with acute ischemic stroke treated with IV r-tPA reported the rate of SICH at 5.2%.¹⁶ Additionally, in a pooled analysis of 6 randomized placebo-controlled trials of IV r-tPA for acute stroke, the rate of SICH was 5.9% in those treated with IV r-tPA versus 1.1% in the placebo group.¹⁷ The risk of SICH after intra-arterial (IA) thrombolysis with or without IV r-tPA is approximately 10%.^{8,18,19}

Differences exist in the criteria used to define SICH following IV thrombolysis in clinical trials, cohort studies, and

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Figure 1. Thrombolysis-related intracerebral hemorrhage (ICH). Intraparenchymal hemorrhage in the right temporal lobe with surrounding edema and mass effect resulting in both subfalcine and transtentorial herniation.

stroke registries.²⁰ For example, in the NINDS trials, SICH was defined as “any CT-documented hemorrhage that was temporally related to deterioration in the patients clinical condition in the judgment of the clinical investigator,” with the hemorrhage occurring within 36 hours of treatment.¹ In the ECASS III trial, SICH was defined as computed tomography (CT) or magnetic resonance imaging-documented hemorrhage associated with clinical deterioration, defined as an increase in the National Institute of Health Stroke Scale (NIHSS) score of 4 points or more and was determined to be the cause of the neurological deterioration or if the hemorrhage resulted in death.² Since there is a high frequency of clinically irrelevant cerebral hemorrhage after thrombolysis, the investigators of the Prolyse for Acute Cerebral Thromboembolism (PROACT II) study, ECASS, and the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) proposed that a 4-point increase in the NIHSS score was unlikely to be caused by examiner fluctuations and likely to be clinically relevant.^{1,21-24} In contrast, the investigators of Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) differentiated between “minor” symptomatic hemorrhage and “major” symptomatic hemorrhage, with the latter classified as patients with a ≥ 4 -point increase in their NIHSS.²⁵ Finally, it is important to emphasize that there is no definitive consensus as to what time period constitutes a clinically relevant SICH attributable to thrombolysis.²⁰ In the NINDS, SITS-MOST, and DEFUSE trials, SICH were considered attributable to thrombolysis when they occurred within 36 hours of receiving r-tPA,

whereas in the ECASS II trial, investigators used a time period of 7 days.^{1,23-25}

Risk Factors for SICH and Pathophysiology

There are several patient characteristics that are thought to increase the probability of developing SICH after thrombolysis. Some studies have suggested that advanced age may increase the risk of postthrombolysis SICH.^{8,15,26} In the NINDS trial, patients older than 80 years of age were 2.87 times more likely to experience an SICH within 36 hours of IV tPA compared to younger patients.^{1,27} However, in the Canadian Alteplase for Stroke Effectiveness Study, the rate of SICH was not higher in patients older than 80 years.²⁸ We must remember advanced age is associated with worse outcomes and higher numbers of comorbidities regardless of thrombolysis-related complications, and traditionally most trials have excluded patients older than the age of 80. Stroke severity has been identified as an independent risk factor for SICH after IV or IA thrombolysis.^{8,10,15,24} In pooled multi-variable analysis from the Stroke-Acute Ischemic NXY Treatment (SAINT) I and SAINT II trials, SICH was increased in patients with early ischemic changes in CT, as defined by an Alberta Stroke Programme Early CT Score of ≤ 7 (odds ratio 5.63; $P = .006$).²⁹ Additionally, many studies suggest that hyperglycemia on admission and history of diabetes increases the risk of thrombolysis-associated SICH.^{8,15} In PROACT II, 36% of patients with hyperglycemia treated with IA r-tPA had an ICH, with similar rates in the NINDS trial.^{18,27} A subsequent study by Demchuk et al confirmed serum glucose and diabetes were predictors of ICH in patients treated with r-tPA, with baseline serum glucose the only independent predictor of both SICH and all hemorrhage and serum glucose >11.1 mmol/L associated with a 25% SICH rate.³⁰ The majority of patients presenting with acute ischemic stroke have elevated blood pressure, and this places them at risk of ICH postthrombolysis.^{15,24,31} There is a higher rate of SICH postthrombolysis in patients presenting with uncontrolled hypertension compared to those without uncontrolled hypertension, 26% versus 12%, with elevated systolic blood pressure (SBP) in the first 24 hours posttreatment further associated with increased risk of SICH.^{32,33} There is also suggestion that dual antiplatelet therapy places patients at a higher risk of SICH than those patients on single therapy or no antiplatelet therapy, but data are inconclusive and even in the studies with higher rates of SICH, there does not appear to be an effect on outcome.^{8,29,34} There are limited data to suggest that renal impairment is associated with a higher risk of SICH after administration of IV r-tPA, but larger prospective studies are needed to determine whether or not this observation is true³⁵ (Table 1).

The underlying mechanism by which rt-PA leads to ICH is complex. It was initially thought to be due to the breakdown of vessel walls caused by free radical production upon reperfusion,³⁶ in addition to the effects of fibrinogen depletion and

Table 1. Risk Factors for SICH After Thrombolysis.^{8,15,33}

CT hypodensity (early ischemic changes >1/3 of MCA territory)
Elevated serum glucose or history of diabetes mellitus
Symptom severity
Time to treatment
High systolic blood pressure
Low platelets
Advanced age

Abbreviations: CT, computed tomography; MCA, middle cerebral artery; SICH, symptomatic intracerebral hemorrhage.

platelet dysfunction due to circulating fibrin degradation products.³⁷ More recently, it has been discovered that r-tPA may also be associated with disruption of the blood–brain barrier, as it has pleiotrophic effects on signaling cascades inducing expression of matrix metalloproteinase, which is responsible for the breakdown of the extracellular matrix and subsequent vascular permeability.³⁷ Animal models have discovered that by inhibiting activation of metalloproteinase or oxygen free radical formation, the incidence of SICH is decreased, thus further supporting this underlying mechanism of action.³⁸

Thrombolysis-related ICH usually occurs at the site of ischemic brain tissue though can present at a distant, unrelated site (Figure 2). Remote postthrombolysis cerebral hemorrhages can be solitary or multiple and by definition appear in brain regions without visible ischemic damage.³⁹ Traditionally, the risk of remote cerebral hemorrhage postthrombolysis has been reported as occurring in approximately 1.3% to 3.7% of patients.^{24,27,39,40} However, the recent Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) study, which included 45 079 patients treated with IV r-tPA, discovered that remote parenchymal hematomas made up one-third of all parenchymal hematomas after IV thrombolysis.³⁹ Patients with remote hematomas postthrombolysis were more likely to be female, with a higher median age, and have a history of previous nonrecent stroke (>3 months) compared to patients with local/intraischemic parenchymal hemorrhage. They were also less likely to have severe strokes, early infarct signs, and hyperdense cerebral artery signs (HCAS) on baseline CT head, which were all characteristics more commonly found in patients with local/intraischemic hemorrhage. Additionally, patients with remote hemorrhages had a lower frequency of atrial fibrillation (AF) and diabetes compared to patients with local/intraischemic hemorrhage (despite being older and having a history of previous strokes) but similar rates of other vascular risk factors. Small-vessel disease was rarely found in either hemorrhage type. This raises the possibility that the risk factor profile differs between the different types of SICH seen postthrombolysis, with local/intraischemic hemorrhage more often seen in association with large-vessel occlusion (higher NIHSS, AF, and HCAS) and remote hemorrhages associated with previous stroke and older age, that is, markers of previous cerebrovascular pathology. We must consider the possibility of underlying cerebral amyloid angiopathy (CAA) as

another mechanism of remote hemorrhage in postthrombolysis patients, as these patients were more often female and older in SITS-ISTR, similar to postmortem studies of spontaneous CAA-related ICH in which patients with CAA were also more likely older and female.^{39,41,42}

Randomized clinical trials have shown that r-tPA dosed at 0.9 mg/kg with a maximum dose of 90 mg is not only safe but also effective.¹ There are some who propose the use of lower doses of r-tPA in populations at higher risk of ICH, such as East Asian populations, as a way to decrease the risk of bleeding.^{43,44} For example in Japan, 0.6 mg/kg of r-tPA is the only approved dose since 2005 for acute stroke presenting within 3 hours of symptom onset, based on the results of the Japan Alteplase Clinical Trial (J-ACT)⁴⁵ and supported by J-ACT2 and the Japan post-Marketing Alteplase Registration Study (JMARS).^{46,47} Additionally, the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) Study Group found the dose of 0.9 mg/kg of r-tPA to be suboptimal in Chinese patients with higher rates of SICH and found that in patients aged 71 to 80, a lower dose of 0.6 mg/kg was associated with better outcome.⁴⁴ These findings have not been confirmed through randomized controlled trials. The practice of administering lower doses of r-tPA for select high-risk patients is not followed in the United States.

Management of SICH After r-tPA

Unfortunately, standardized guidelines for managing thrombolytic-associated hemorrhages do not currently exist, likely because of a lack of published original research exploring the most appropriate management of this complication. In the absence of evidence-based guidelines, many academic institutions have developed their own protocols for managing postthrombolysis hemorrhage, and these include the use of fresh frozen plasma (FFP), cryoprecipitate, vitamin K, platelets, and aminocaproic acid.^{48,49} Given the optimal approach to management of thrombolysis-associated SICH is not clear, we provide the NINDS trial protocol¹ as a guide with modifications incorporated from Khatri et al⁵⁰ and Goldszmidt and Caplan⁵¹ (Table 2).

Most SICH hemorrhages will occur within the first 24 hours after receiving IV r-tPA, with the bulk of fatal hemorrhages occurring within the first 12 hours.²⁷ Because of this, close monitoring of the patient with acute stroke in an intensive care unit or dedicated stroke unit is imperative status post-thrombolysis, with special attention paid to signs of clinical deterioration, decreasing mental status, new headache, acute hypertension, nausea, or vomiting. If a clinician suspects the possibility of a postthrombolysis SICH, then any remaining IV r-tPA should be held immediately until an ICH is excluded. Once the thrombolysis infusion has been discontinued and it is determined that the patient is stable enough to be transported for imaging, an emergent noncontrast CT head should be obtained. Concurrently, the clinician should rule out other causes of neurological deterioration such as hemodynamic

Figure 2. Intraparenchymal brain stem (A) and left lateral intraventricular hemorrhage (B) in a patient presenting with a right anterior cerebral artery acute ischemic stroke receiving intravenous recombinant tissue-type plasminogen activator (IV r-tPA).

Table 2. Protocol for Management of Postthrombolysis Intracerebral Hemorrhage.^{1,48-50}

Suspect ICH (new headache, nausea, vomiting, etc)

- ☐ Discontinue r-tPA infusion
- ☐ STAT blood draw: PT, PTT, platelet count, fibrinogen, type & cross
- ☐ STAT noncontrast CT head

Hemorrhage confirmed?

- ☐ Administer 6-8 units of cryoprecipitate, followed by 6-8 units platelets
- ☐ Consult neurosurgeon & alert to ICH
- ☐ Consult hematologist & alert to current coagulation status
- ☐ Administer ϵ -aminocaproic acid 4-5 gm IV over 1 hour, followed by 1 gm PO or IV hourly until bleeding is controlled
- ☐ Fibrinogen levels should be rechecked every Q 4 hours & cryoprecipitate transfused PRN to maintain fibrinogen levels > 150 mg/dL
- ☐ Blood pressure monitoring Q 15 minutes
- ☐ Periodic blood work (CBC, PT/PTT) to re-assess coagulation status & need for blood transfusion
- ☐ Consider repeat CT head to assess for ICH growth
- ☐ Consensus decision regarding surgical and/or medical therapy

Abbreviations: ICH, intracerebral hemorrhage; r-tPA, recombinant tissue-type plasminogen activator; STAT, at once; PT, prothrombin time; PTT, partial thromboplastin time; IV, intravenous; PO, orally; Q, every; PRN, as needed; CBC, complete blood count.

instability, seizure, and infection and urgently obtain laboratory studies including prothrombin time (PT), partial thromboplastin time (PTT), platelet count, fibrinogen levels, and type and cross.^{48,50} If a serious or life-threatening hemorrhage is confirmed, then attempts should be made to mitigate the hemorrhage.⁴⁸ Urgent treatment includes the transfusion of cryoprecipitate (6-8 units) followed by platelets (6-8 units) in order to rapidly correct the fibrinolytic state produced by r-tPA.^{50,52} The on-call neurosurgeon should be alerted to the ICH, and a hematologist should also be consulted in order to weigh-in on the patient's coagulation status. Fibrinogen levels should be rechecked every 4 hours and cryoprecipitate transfused as needed to maintain fibrinogen levels >150 mg/dL.⁵¹ There should be periodic complete blood counts as well as

PT/PTT measurements with blood transfusions administered if necessary. The patient should continue to be cared for in an ICU or neurointensive care unit with vital signs and neurochecks every 15 minutes during the acute setting. The intensivist should implement intracranial pressure monitoring and intubation when appropriate.⁸ A repeat CT head should be considered to assess for ICH growth and clinical status followed closely.

In the "Modified National Institute of Neurological Disorders and Stroke Management Protocol for Intracranial Hemorrhage" developed by Khatri et al,⁵⁰ treatment with ϵ -aminocaproic acid was not included as part of the protocol. Goldszmidt and Caplan⁵¹ propose the addition of ϵ -aminocaproic acid to both the cryoprecipitate and the platelet infusions

and suggests a dose of 4 to 5 g IV over 1 hour followed by 1 g orally or IV every hour until the bleeding is controlled. ϵ -Aminocaproic acid inhibits fibrinolysis by preventing the conversion of plasminogen to plasmin and increases fibrinogen levels that are reduced in patients with SICH.⁵³ Tranexamic acid is a newer analog of ϵ -aminocaproic acid.⁵⁴ Much of our current knowledge on the efficacy and safety of both ϵ -aminocaproic acid and tranexamic acid comes from studies involving patients with aneurysmal subarachnoid hemorrhage. In many of these trials, there was a reduction in the rebleeding rate in those patients treated with tranexamic acid or ϵ -aminocaproic acid, but this was offset by an increased risk of thrombotic complications, cerebral ischemia, and hydrocephalus.⁵⁴ In a small, open-label study involving 14 patients with spontaneous ICH, 5 of which were treated with ϵ -aminocaproic acid, ϵ -aminocaproic acid had no effect on preventing hematoma expansion, and there were no thrombotic complications reported.⁵⁵ In a case report published in 2012, tranexamic acid monotherapy was successful in stabilizing a thrombolysis-associated SICH in a Jehovah's Witness patient with stroke who refused blood products.⁵⁶ Although there continues to be concern regarding the potential increased risk of thrombotic events with these 2 antifibrinolytic agents, a meta-analysis of randomized and observational studies assessing the risk of antifibrinolytics in cardiac surgery suggests that both tranexamic acid and ϵ -aminocaproic acid are safer than aprotinin.⁵⁷ The usefulness of other agents including prothrombin complex concentrate (PCC), fibrinogen, fresh frozen plasma (FFP), and recombinant factor VII in postthrombolysis ICH is unknown.^{8,53} Since FFP activates the coagulation cascade, potentially driving fibrin formation, it can theoretically counter the effect of r-tPA, which increases plasmin activity. However, FFP must be administered slowly and in large volumes to prevent transfusion-related reactions and fluid overload. The need for large volumes of FFP increases the time it takes for reversal of the underlying coagulopathy in a patient with ongoing SICH. For example, in warfarin-related ICH, it can take a median of 30 hours for FFP to return the international normalized ratio to normal limits, and although the mechanism of coagulopathy differs in thrombolysis-associated ICH, the length of time needed for reversal is similar, with concern for continued hematoma expansion before correction of the coagulopathy can occur.^{53,58} Prothrombin complex concentrate (PCC) offers a quick way to activate both the intrinsic and the extrinsic pathways of the coagulation cascade, leading to the downstream conversion of fibrinogen into fibrin, but because r-tPA reduces fibrinogen levels, coadministration of fibrinogen to patients receiving PCC may be necessary. Importantly, the use of PCC in patients with recent ischemic stroke is associated with a low risk (approximately 1%) of thrombotic events.^{53,59}

Although guidelines exist for blood pressure and surgical management of spontaneous ICH, they are lacking for postthrombolysis ICH. Given the lack of data in postthrombolysis ICH, we think it is reasonable to follow current guidelines for

Table 3. Suggested Management of Elevated Blood Pressure in Postthrombolysis ICH.^a

If SBP > 200 mm Hg or MAP > 150 mm Hg, consider aggressive reduction in BP with continuous IV infusion
If SBP > 180 mm Hg or MAP > 130 mm Hg and there is concern for elevated ICP, then initiate ICP monitoring and reduce BP using intermittent or continuous IV antihypertensives, while cautiously maintaining CPP above 60 mm Hg
If SBP > 180 mm Hg or MAP > 130 mm Hg, but there is no indication of increased ICP, then a modest reduction in BP may be considered (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) as long as BP is monitored every 15 minutes

Abbreviations: SBP, systolic blood pressure; MAP, mean arterial pressure; BP, blood pressure; ICP, intracerebral pressure; CPP, cerebral perfusion pressure.

^aAdapted from Morgenstern et al.⁶⁰

spontaneous ICH, which suggest a target blood pressure of 160/90 mm Hg and that the acute lowering of SBP to 140 mm Hg in patients presenting with a SBP of 150 to 220 mm Hg is probably safe⁶⁰ (Table 3). The decision about whether to surgically remove a spontaneous ICH remains controversial, and the benefit of surgery uncertain with 2 exceptions: (1) patients with cerebellar hemorrhage who are deteriorating neurologically and/or who have brain stem compression and (2) patients with a lobar hemorrhage within 1 cm of the surface and measuring >30 mL.⁶⁰ The Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial looked at the association between neurosurgical evacuation and clinical outcomes in patients with myocardial infarction suffering from a thrombolysis-associated ICH. The GUSTO-I trial showed a trend toward higher functional status and significantly higher 30-day survival in patients who underwent neurosurgical evacuation of their hemorrhage.⁶¹ It is crucial to remember that surgical intervention should only ever be considered after adequate reversal of the fibrinolytic effects of r-tPA.^{8,52}

A question that commonly arises in clinical practice is: "For how long after r-tPA administration is it reasonable to attempt to reverse the lytic effects if SICH occurs?" Although r-tPA is short acting with rapid clearance, its effects on the coagulation profile (prolonged PT/PTT and reduced fibrinogen levels) may last 24 hours or more postinfusion.⁵³ With standardized guidelines on management of postthrombolysis hemorrhage lacking, we propose a window of 24 hours for lytic reversal in SICH, as most SICH will occur within this time frame, and this window is consistent with time monitored in the ICU, follow-up CT head, duration of coagulation abnormalities, and initiation of antiplatelet therapy. However, as NINDS, SITS-MOST, and DEFUSE all define hemorrhages attributable to thrombolysis as occurring within 36 hours, one could argue that a 36-hour window for lytic reversal is also appropriate, especially when considering the likelihood of poor prognosis and high mortality.^{1,24,25}

Table 4. Management of Orolingual Angioedema After IV r-tPA.^{48,50}

Begin examining the tongue 20 minutes before the IV r-tPA infusion is complete & repeat several times until 20 minutes after r-tPA infusion
Look for any signs of unilateral or bilateral tongue enlargement
If angioedema is suspected immediately
☐ Discontinue r-tPA infusion
☐ Administer diphenhydramine (Benadryl) 50 mg IV
☐ Administer ranitidine 50 mg IV or famotidine 20 mg IV
If tongue continues to enlarge after the above steps have been completed then
☐ Administer methylprednisolone (Solu-Medrol) 80 to 100 mg IV
If there is any further increase in angioedema
☐ Administer epinephrine 0.1% 0.3 mL SQ or by nebulizer 0.5 mL
☐ Consult ENT/anesthesiology or the appropriate in-house service STAT for possible emergency cricotomy/tracheostomy or fiberoptic nasotracheal intubation if oral intubation fails
If the tongue is large, but oral intubation is possible → perform orotracheal intubation STAT
If tongue is too large for orotracheal intubation → perform fiberoptic nasotracheal intubation
If severe stridor with impending airway obstruction → perform tracheostomy

Abbreviations: r-tPA, recombinant tissue-type plasminogen activator; SQ, subcutaneous; ENT, ears, nose, and throat; STAT, at once; IV, intravenous; ICH, intracerebral hemorrhage.

Thrombolysis and Angioedema

Orolingual angioedema after thrombolysis is an even less common complication than SICH, but since it is also potentially life threatening, it is important to recognize it quickly and have a treatment algorithm in place. It is estimated that orolingual angioedema occurs in approximately 1.3% to 5% of patients with stroke receiving IV r-tPA.^{13,62,63} It usually presents as a transient, self-limited swelling of the tongue and lips but can potentially cause airway obstruction and respiratory compromise requiring emergent intubation or cricothyrotomy.^{13,64} The exact mechanism of action underlying the development of orolingual angioedema has not been elucidated.⁶⁵ We know that patients taking angiotensin-converting enzyme (ACE) inhibitors are at increased risk of developing this rare complication, but it has also been reported in patients not taking these medications.^{13,63,65} It appears that the incidence of r-tPA-related orolingual angioedema is higher in caucasians than in Asians, and the use of ACE inhibitors prior to stroke also significantly increases the risk of orolingual angioedema in Asians.⁶⁶ Orolingual angioedema following thrombolysis can be bilateral or unilateral, and if it is unilateral, it is usually contralateral to the affected hemisphere.^{8,13,67} Hill et al found that the risk of developing orolingual angioedema was associated with (1) prior use of ACE inhibitors (relative risk [RR] 13.6; 95% confidence interval [CI]: 3.0-62.7) and (2) ischemic strokes involving the insular and frontal cortex (RR 9.1; 95% CI: 1.4-30.0).⁶³ A recent meta-analysis including 19 articles on orolingual angioedema after r-tPA administration concluded that orolingual angioedema occurs in patients of all ages with no gender predilection. It also found that the majority of patients in the analysis had orolingual angioedema, which was asymmetrical and ipsilateral to the side of hemiparesis.⁶⁵

Although there are no guidelines suggesting a specific treatment protocol for the management of orolingual angioedema associated with r-tPA, we encourage the use of a

protocol developed at the University of Cincinnati⁵⁰ (Table 4). Since orolingual angioedema can appear quickly and unexpectedly after thrombolysis, we recommend close monitoring and examination of the patient with stroke, especially toward the end of the r-tPA infusion, as this is when it is more likely to occur. If there are any signs of unilateral or bilateral tongue or lip swelling, immediately discontinue the remaining r-tPA infusion if it is still running. Promptly, administer diphenhydramine (Benadryl) 50 mg IV, followed by either ranitidine 50 mg IV or famotidine 20 mg IV. If reassessment of the patient reveals that the tongue is continuing to enlarge even after the administration of diphenhydramine and ranitidine or famotidine IV, then proceed to administer methylprednisolone (Solu-Medrol) 80 to 100 mg IV. If the orolingual angioedema has not halted at this point, then there should be urgent administration of epinephrine 0.1% 0.3 mL subcutaneous or by nebulizer 0.5 mL, while a STAT consult is requested of the on-call ears, nose, and throat (ENT)/otolaryngologist or anesthesiologist or appropriate in-house service for possible emergency cricotomy/tracheostomy or fiberoptic nasotracheal intubation if oral intubation is unsuccessful. There are obviously many potential scenarios that can occur, such as the tongue being too enlarged for orotracheal intubation or severe stridor with impending airway obstruction possibly requiring a tracheostomy, and these should be managed by the appropriate specialist.⁵⁰ The decision regarding whether or not intubation should be considered and the appropriate timing is a challenging one and should be made by a qualified specialist. Oftentimes, the decision is guided by several factors such as the anatomical location of the edema, the speed of edema progression, the early involvement of a skilled intubator, and whether or not the patient is in respiratory distress. Finally, a short course of maintenance, corticosteroids, and antihistamines should be considered for those patients who are intubated or for those patients with extensive edema not responding to the initial doses of medications.¹³

Conclusion

Intravenous r-tPA for acute ischemic stroke not only improves outcomes but is also relatively safe. Feared complications include SICH and orolingual angioedema. Although both of these complications are uncommon, they are potentially life threatening and thus require special attention. Although there are no established treatment guidelines for the management of postthrombolysis SICH or postthrombolysis orolingual angioedema, we have outlined some potential treatment algorithms based on empirical data and from the extrapolation of data from other related scenarios. These can serve as a guide until there is more definitive data from clinical trials.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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