

Use of recombinant factor VIIa in symptomatic intracerebral hemorrhage following intravenous thrombolysis

Shadi Yaghi, Aya Haggiagi,
Ayesha Sherzai, Randolph S. Marshall,
Sachin Agarwal

Department of Neurology, Columbia
University Medical Center, New York, NY,
USA

Abstract

Symptomatic intracerebral hemorrhage (sICH) occurs in up to 7% of stroke patients treated with thrombolytic therapy. There are limited data on the effectiveness of the reversal agents used for intravenous tissue plasminogen activator related intracranial bleeds. We report a patient with sICH following intravenous thrombolysis whose intracerebral hemorrhage continued to expand despite treatment with platelets and cryoprecipitate, needing recombinant factor VIIa use for stabilization before surgical evacuation. Factor VIIa along with routine reversal agents following intravenous thrombolysis related sICH may further enhance clot stability and reduce the risk of hematoma expansion. It could be a bridge to definitive surgical management in those patients.

Introduction

Intravenous thrombolytic therapy when given within 4.5 h from symptom onset remains the mainstay of treatment for ischemic stroke patients. While intravenous tissue plasminogen activator (IV tPA) has been shown to be effective in improving outcome,^{1,2} the most feared complication is symptomatic intracerebral hemorrhage (sICH), which occurs in up to 7 percent of patients and significantly increases mortality and morbidity.³ Standard management of post thrombolysis intracerebral hemorrhage includes replacement of coagulation factors with cryoprecipitate and platelets, as suggested by the American Heart Association, which is based on small case series and expert opinion and the efficacy of such treatment is unknown.⁴ Thus there exists heterogeneity in clinical practice with respect to the strategies implemented in the management of sICH. The lack of consensus on how to manage sICH as well as continued poor outcomes despite treatment should

create a driving force in the stroke community to investigate effectiveness and rapidity of other potential treatment options.

Case Report

We report a 68-year old right handed Hispanic woman with a history of diabetes mellitus type II, hypertension, hyperlipidemia, and two prior strokes with residual right hemiparesis, who presented with sudden onset vertigo, slurred speech, and blurred vision. The first stroke was a left putamen intracerebral hemorrhage with minimal residual right hemiparesis that occurred over 20 years prior to admission. The second stroke was a cryptogenic stroke that occurred around 5 years prior to admission for which she was outside the time window of thrombolytic therapy and was maintained on aspirin 81 mg daily. Her initial exam showed dysarthria, left sided sensory loss, skew deviation with upgaze vertical nystagmus, mild right hemiparesis, and an NIHSS score of 4. Initial head computed tomography (CT) (Figure 1A) showed evidence of prior strokes and no acute hemorrhage. Since she had a new fixed and potentially disabling neurological deficit and she was within the 4.5 h window, decision was made to administer thrombolytic therapy. She received IV tPA 2.5 h

Correspondence: Shadi Yaghi, 710 W. 168th Street, New York, NY, 10032 USA.
Tel.: 212.305.6940.
E-mail: shadiyaghi@yahoo.com

Key words: Intracerebral hemorrhage; ischemic stroke; thrombolysis; factor VIIa; outcome; expansion.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 1 February 2015.
Revision received: 12 March 2015.
Accepted for publication: 16 April 2015.

This work is licensed under a Creative Commons Attribution NonCommercial 3.0 License (CC BY-NC 3.0).

©Copyright S. Yaghi et al., 2015
Licensee PAGEPress, Italy
Clinics and Practice 2015; 5:756
doi:10.4081/cp.2015.756

from symptom onset. An hour after the IV tPA infusion was complete, she complained of an acute severe headache without a change in neurological exam and repeat CT head showed right temporal ICH with a subdural component (Figure 1B). She received 20 units of cryoprecipitate and 6 units of platelets within 60 min.

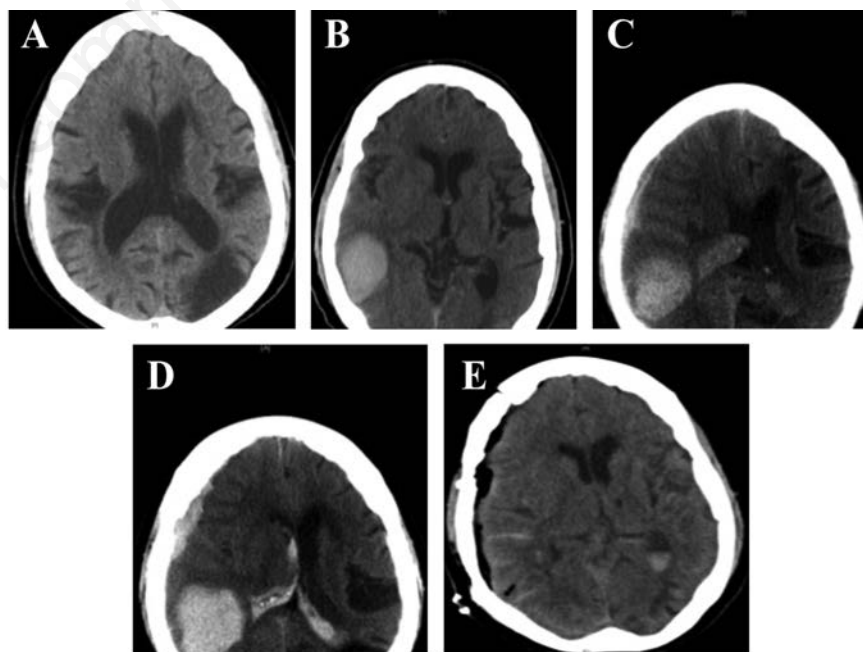


Figure 1. A) Admission computed tomography (CT) scan showing old infarcts and no hemorrhage. B) First CT scan showing right temporal intracerebral hemorrhage (ICH) with subdural hemorrhage. C) CT scan showing expansion of ICH with intraventricular hemorrhage. D) CT scan showing further expansion of hematoma despite the standard treatment. E) Post-operative CT.

Two hours after the completion of this treatment, she became somnolent and had new left hemiparesis. CT head was repeated that showed ICH expansion and new intraventricular hemorrhage (Figure 1C). In the next 3 h, her exam continued to deteriorate, became stuporous and stopped following commands. Head CT at that point showed further expansion of ICH and intraventricular hemorrhage (Figure 1D). The decision was made to administer recombinant factor VIIa (50 mcg/kg) and she was subsequently taken to the operating room with successful clot evacuation. Postoperatively, her exam slowly improved and she was back to her baseline neurological exam on post-operative day 3 (Figure 1E).

Discussion

Alteplase converts plasminogen to plasmin, which in turn converts fibrin into the fibrin split products causing thrombolysis. It also causes a reduction in fibrinogen the degree of which is associated with sICH.⁵ Using cryoprecipitate (factor VIII and fibrinogen), in post thrombolysis sICH increases fibrinogen levels, enhances fibrin formation and may potentially stabilize the clot thus reducing the risk of further hemorrhage. However, a study from Get with the Guidelines data showed that around 40 percent of patients with post thrombolysis sICH have continued bleeding despite cryoprecipitate treatment.⁶ The lack of efficacy may be due to delays in diagnosis and treatment, insufficient dosing of cryoprecipitate to replenish fibrinogen, or lack of augmentation with rapid acting factors that help convert fibrinogen into fibrin.

Conclusions

To our knowledge, this is the first case reporting the use of recombinant factor VIIa along with cryoprecipitate and platelets in the treatment of symptomatic ICH following intravenous thrombolysis. Activated factor VIIa has been studied in spontaneous intracerebral hemorrhage and has been shown to reduce hematoma growth with no effect on mortality and morbidity however.⁷ Activated factor VIIa, which has a relatively quick time of onset and is an extrinsic and intrinsic pathway activator, may further enhance clot stability and potentially reduce the risk of hematoma expansion, which is likely what happened with our patient. Although recombinant factor VIIa carries a risk of thrombosis and is relatively expensive, its use in this patient population may potentially alter the course of the disease and improve outcome. Randomized studies may be considered to compare the outcome of patients with post thrombolysis sICH when rapid reversal agents such as recombinant factor VIIa or prothrombin complex concentrate are added to the standard treatment or given in isolation.

References

1. Hacke W, Kaste M, Bluhmki E, et al. ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.
2. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-7.
3. Sloan MA, Sila CA, Mahaffey KW, et al. Prediction of 30-day mortality among patients with thrombolysis-related intracranial hemorrhage. *Circulation* 1998;98:1376-82.
4. Broderick J, Connolly S, Feldmann E, et al. American Heart Association; American Stroke Association Stroke Council; High Blood Pressure Research Council; Quality of Care and Outcomes in Research Interdisciplinary Working Group. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke* 2007;38:2001-23.
5. Trouillas P, Derex L, Philippeau F, et al. Early fibrinogen degradation coagulopathy is predictive of parenchymal hematomas in cerebral rt-PA thrombolysis: a study of 157 cases. *Stroke* 2004;35:1323-8.
6. Goldstein JN, Marrero M, Masrur S, et al. Management of thrombolysis-associated symptomatic intracerebral hemorrhage. *Arch Neurol* 2010;67:965-9.
7. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008;358:2127.