

# Safety of tissue plasminogen activator factor in an acute stroke patient with two unruptured cerebral aneurysms

Ali M. Sonbaa, MBBS, Alaa F. Khayat, MBBS, Mohammed A. Almekhlafi, MSc, FRCPC.

## ABSTRACT

يعد مرض أم الدم المخية ومرض السكتة الدماغية من الأمراض الخطيرة واجتماعهما سوياً يزيد من الخطورة والتعقيد، وتنص عدة دراسات على أن نسبة (6.6%-9.3%) من مرضى السكتة الدماغية لديهم أم دم مخية غير منفجرة. وبالتالي هل منشط مولد البلازمين النسيجي مأمون الاستخدام في علاج مرضى السكتة الدماغية الحادة الذين لديهم أم الدم المخية الغير منفجرة؟ نورد تقريراً عن حالة مريض سكتة دماغية إقفارية حادة حُقت بمنشط مولد البلازمين النسيجي وريدياً بآمان. هذا المريض يبلغ من العمر 58 عاماً أصيب بسكتة دماغية إقفارية حادة، قُدم إلى قسم الطوارئ بعد مُضي ساعتان من ظهور أعراض السكتة، وتلقى العلاج باستخدام منشط مولد البلازمين النسيجي، ثم أظهرت الفحوصات اللاحقة وجود أم دم مخيتين غير منفجرتين اكتشفاً عرضياً. نستنتج من ذلك أنه على الرغم من أن بعض الدراسات تُعد منشط مولد البلازمين النسيجي محظوراً لمن لديه أم دم مخية إلا أن حالتنا أظهرت مأمونية منشط مولد البلازمين النسيجي لهؤلاء المرضى.

It is estimated that 6.6%-9.3% of stroke patients have unruptured cerebral aneurysms. The safety of recombinant tissue plasminogen activator (r-tPA) for stroke patients with these aneurysms is uncertain. We report the case of a 58-year old male presented with an acute ischemic stroke within 2 hours of symptom onset and was treated with r-tPA. Further investigation showed that the patient had 2 unruptured cerebral aneurysms. He recovered completely from the stroke and was discharged home in a few days with no deficits. Although cerebral aneurysms are considered a relative contraindication for r-tPA, our case provides evidence that it can be safely administered to these patients.

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*From the Division of Neurology, Department of Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.*

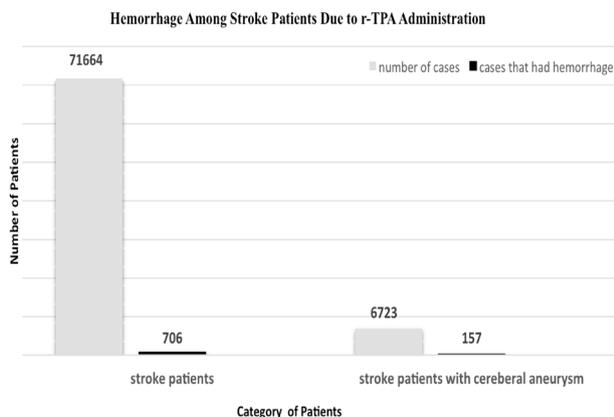
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*Address correspondence and reprint request to: Dr. Ali M. Sonbaa, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia. E-mail: alysonbaa@gmail.com  
ORCID ID: orcid.org/0000-0002-3003-1356*

The use of thrombolytic agents in treating stroke patients with incidental cerebral aneurysms is controversial. The number of stroke patients described as having unruptured intracranial aneurysms ranges from 6.6-9.3%.<sup>1</sup> Reports and studies suggest that thrombolytic agents such as recombinant tissue plasminogen activator (r-tPA) are safe in these patients.<sup>2,3</sup> Based on the available literature, the historical risk estimation for aneurysmal bleeding after receiving intravenous thrombolytics for acute ischemic stroke with cerebral aneurysm is approximately 5.7% (Figure 1).<sup>4</sup> Most of the studies focused on the treatment methods and outcomes, but not on the presence of aneurysmal risk factors such as hypertension, smoking, or a family history of aneurysm or subarachnoid hemorrhage.<sup>1,5,6</sup> In addition to chronic diseases, these factors can play a role in aneurysmal rupture and hemorrhage after using r-tPA. Our objective is to report the case of an acute ischemic stroke patient who safely received intravenous r-tPA and was later found to have 2 incidental cerebral aneurysms, demonstrating the safety of r-tPA among these patients. We also aim to review the literature to explore the safety of r-tPA and how clinicians can estimate the risk of an aneurysmal rupture hemorrhage.

**Case Report. Patient information.** A 58-year old Eritrean African black man was known to be hypertensive

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**Figure 1** - The total number of stroke patients who had hemorrhages after administration of r-tPA, including those who had cerebral aneurysms.

**Table 1** - Analysis of previous case reports.

Age	Co-morbidities	NIHSS	Rx	Hemorrhage	Conclusion
78	HTN, DM, hyperthyroidism & angina	17	Aspirin	No	Uncertain based on reviewed literature
56		21	r-tPA	Yes	
66			Heparin	yes	Recommend cautious usage of r-tPA
51				yes	
66		10		No	
71	Smoking, HTN & peripheral artery disease	15	r-tPA	Yes	not safe
37	Smoking, HTN	2		No	
79	HTN	1		No	safe
71		11		No	

HTN - Hypertension, r-tPA - recombinant tissue plasminogen activator, NIHSS - NIH Stroke Scale, DM - Diabetes mellitus



**Figure 2** - CT angiography scans of patient's brain performed after starting the r-tPA A) Computed tomography (CT) angiography of a distal branch occlusion of the middle cerebral artery; B) CT angiography of a 2-mm middle cerebral artery bifurcation aneurysm; C) CT angiography of a 5-mm pericallosal aneurysm.

**Table 2** - Analysis of previous systemic studies.

No. cases	Rx	Hemorrhage	Conclusion
116	Urokinase (17) r-tPA (66) Mechanical (32)	16 (4 from each category)	Uncertain based on reviewed literature
3	r-tPA	1	
5620		50	Related to risk factors
201		3	Related to aneurysm size
112426	71370	698	Recommend cautious usage of r-tPA
105		0	Safe
22		3	

r-tPA - recombinant tissue plasminogen activator

and dyslipidemic and had undergone a coronary artery stenting 3 weeks prior to his presentation. He presented to the Emergency Department complaining of weakness and aphasia.

**Clinical findings.** The patient had significant sudden onset weakness for the past 2 hours on the right side of his body, more so in his face and arm than in his leg. He had expressive aphasia but was able to follow simple commands. He was rated an 11 on the National Institute of Health Stroke Scale.

**Diagnostic assessment.** An emergency computed tomography (CT) scan was performed which showed no evidence of hemorrhage or other acute changes.

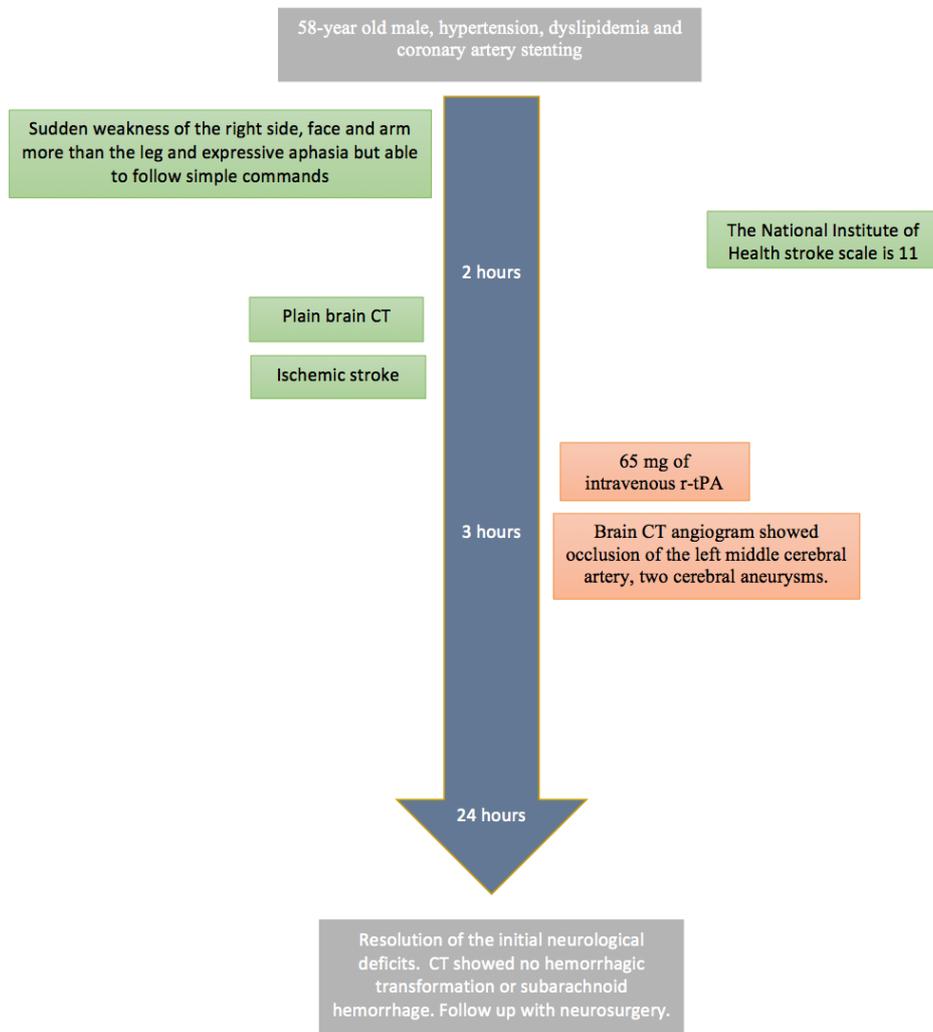
**Therapeutic intervention.** After discussing with the patient's family and receiving consent, 65 mg of

intravenous r-tPA was administered at the beginning, 3 hours after the time of onset. After starting the r-tPA, the patient was rushed for a CT angiogram that showed a distal branch occlusion of the left middle cerebral artery (Figure 2A). In addition, there were 2 cerebral aneurysms: one 5-mm pericallosal aneurysm (Figure 2B) and one 2-mm middle-cerebral artery bifurcation aneurysm (Figure 2C). Because these were believed to be incidentally discovered, r-tPA was continued and the patient was admitted to the intensive care unit.

**Follow-up and outcomes.** The neurological examination on the next day showed complete resolution of the initial deficits, with no complaints by the patient of headache or other neurological symptoms. A 24-h CT scan of the head showed no hemorrhagic

transformation or subarachnoid hemorrhage. He was discharged home on Day 3 in a normal state with an elective plan for follow-up.

**Discussion.** Because it affects the outcome, time is extremely sensitive in the management of acute ischemic stroke patients. The most feared complication of administering r-tPA is intracranial hemorrhage, which is estimated to occur in 0.3%-6.4% of cases.<sup>5,7,8</sup> In the majority of cases, the benefits of therapy outweigh the risks when given within 4.5 hours of onset or last-seen well time. However, there are circumstances in which r-tPA use poses a significant risk and is thus contraindicated. These include the presence of an intracranial hemorrhage or large subacute stroke and



**Figure 3** - Case report timeline.

uncontrolled hypertension at the time of presentation that is not responding to intravenous blood pressure-lowering agents. However, there are perceived absolute contraindications that have not actually been proven with data.<sup>9</sup> One of these is the presence of incidental unruptured brain aneurysms.

There is a good body of literature reporting on the safety of r-tPA in patients with incidental brain aneurysms. However, there are variations among the case reports (Table 1) and analytic reviews (Table 2) such as the thrombolytic agent, aneurysm size and site, and the existence of co-morbidities and risk factors of intracerebral hemorrhage that is related to thrombolysis. These risk factors include hypertension, smoking, alcohol consumption, a family history of aneurysm or subarachnoid hemorrhage, advanced age of the patient, thrombolytic dosage, hyperfibrinogenemia, increased prothrombin time, thrombocytopenia, hyperglycemia, and delayed treatment.<sup>1,5,6</sup>

Thrombolytic therapy may provoke aneurysm rupture by one of the following mechanisms: (1) increasing turbulence within the sac though hemodynamic changes or (2) increasing the flow within the aneurysm by dissolving a clot in the aneurysm dome.<sup>5</sup> Yet, the use of r-tPA is an effective method for acute ischemic stroke treatment.<sup>5</sup> Some of the r-tPA-related hemorrhages in patients with brain aneurysms were at the site of infarction but not due to aneurysmal rupture.<sup>4</sup> A careful evaluation of the aneurysm's size and site must be made to assess the risk of rupture. In addition, other medical conditions can be associated with an increased risk of rupture that are independent of the presenting stroke or r-tPA usage.<sup>1</sup> The presence of co-morbidities plays a major role in aneurysmal rupture, first because they have an impact on the pathological vascular changes, and second, in the absence of stroke, the co-morbidities will be under consideration while evaluating the aneurysm for its risk of rupturing. Most of the reported cases with a ruptured aneurysm or hemorrhagic event had a co-existing chronic medical condition. Aneurysms can only be diagnosed by a CT angiogram, and the majority of stroke patients in Kingdom of Saudi Arabia do not receive them. Despite that, subarachnoid hemorrhage after r-tPA administration is very rare, which means that r-tPA is safe in these patients.

In conclusion, According to the available evidence, treating acute ischemic stroke patients with incidental unruptured aneurysms by r-tPA appears to be safe. A careful CT-scan assessment of stroke patients and an evaluation of the risk of aneurysmal rupture is important when CT angiography reveals brain aneurysms in the acute-stroke setting as in our case that is summarized in a timeline (Figure 3).

## References

1. Haji F, van Adel B, Avery M, Megyesi J, Young GB. Intracranial aneurysm rupture following intravenous thrombolysis for stroke. *Can J Neurol Sci* 2014; 41: 95-98.
2. Mittal MK, Seet RC, Zhang Y, Brown RD Jr, Rabinstein AA. Safety of intravenous thrombolysis in acute ischemic stroke patients with saccular intracranial aneurysms. *J Stroke Cerebrovasc Dis* 2013; 22: 639-643.
3. Edwards NJ, Kamel H, Josephson SA. The safety of intravenous thrombolysis for ischemic stroke in patients with pre-existing cerebral aneurysms: a case series and review of the literature. *Stroke* 2012; 43: 412-416.
4. Wang HF, Chan CW, Chan HH, Hung HC. Asymptomatic cerebral aneurysm in stroke patients eligible for intravenous thrombolytic therapy. *Acta Neurol Taiwan* 2013; 22: 43-48.
5. Lagares A, Gómez PA, Lobato RD, Alén JF, Campollo J, Benito-León J. Cerebral aneurysm rupture after r-TPA thrombolysis for acute myocardial infarction. *Surg Neurol* 1999; 52: 623-626.
6. D'Olhaberriague L, Joshi N, Chaturvedi S, Mitsias P, Coplin W, Lewandowski CA, et al. Tissue plasminogen activator for acute ischemic stroke in patients with unruptured cerebral aneurysms. *J Stroke Cerebrovasc Dis* 2000; 9: 181-184.
7. Rammos SK, Neils DM, Fraser K, Klopfenstein JD. Anterior communicating artery aneurysm rupture after intravenous thrombolysis for acute middle cerebral artery thromboembolism: case report. *Neurosurgery* 2012; 70: E1603-E1607.
8. Kane I, Sandercock P, Thomas B. Can patients with unruptured intracranial aneurysms be treated with thrombolysis? *Cerebrovasc Dis* 2005; 20: 51-52.
9. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, et al. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2016; 47: 581-641.