Letter to the Editor

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Age and Stroke Severity: Hazards for Intravenous Thrombolysis?

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Dear Editor,

Acute ischemic stroke (AIS) is a major cause of death and disability worldwide and may have a devastating impact on the quality of life [1]. Most strokes are due to blockage of an artery in the brain by a blood clot that begins in the heart or neck arteries [2].

Almost 20 years ago, alteplase (recombinant tissue plasminogen activator, rt-PA), a manufactured thrombolytic drug derived from naturally occurring enzymes that dissolve thrombus as part of the natural clotting cascade, was first shown to improve functional outcome after AIS [3]. It could reduce brain damage from a stroke by restoring the blood flow if given rapidly enough after an AIS. Moreover, intravenous thrombolysis is the current recommended therapy for acute ischemic stroke [4]. Previous systematic reviews and guidelines revealed that thrombolysis with alteplase is beneficial when administered to some patients within 4.5 h after the onset of ischemic stroke [5, 6]. However, uncertainties remain about the benefit and risk of intravenous thrombolysis (rt-PA), to older patients or to patients with very severe strokes [7].

Interestingly, a new meta-analysis of individual patient data from randomized trials – published in *The Lancet* – provided clear answers to these uncertainties [7]. The authors' analysis is different from previous pooled analyses [8] of alteplase trials by including patients from the International Stroke Trial (IST-3), which almost doubled the number of patients available. Even more importantly, they included more than 1,700 patients aged 80 years or older (alteplase is restricted to patients younger than 80 years in some European countries [9]).

The results of the meta-analysis are persuasive. Additionally, the proportional benefits were similar for patients aged older than 80 years compared with younger patients, and for patients with minor (NIH Stroke Scale, NIHSS, score ≤4) or very severe (NIHSS score ≥22) strokes compared with other patients, although minor or very severe stroke is no common operational diagnosis. However, the effects on disability-free survival of rt-PA administration between 4.5 and 6 h after stroke onset remain uncertain, and caution is warranted in this time window. Similar outcomes have been found in the latest study [10].

Recently, in the European Stroke Organisation Conference 2015, Mazya et al. [10] reported that very severe stroke (defined as an NIHSS score >25) should not be a contraindication for rt-PA, and these patients should be treated rapidly and not differently from patients with strokes of lesser severity.

To examine whether the use of rt-PA was more dangerous in patients with very severe strokes (NIHSS score >25) compared with patients with moderately severe strokes (NIHSS score 15–25), they conducted the Safe Implementation of Treatments in Stroke (SITS) study to determine the differences among these two groups of patients and to further identify the relationship between intracerebral hemorrhage and stroke severity. The SITS registry included data on 60,000 stroke patients who had received thrombolysis since 2002. Of these, 868 (1.5%) had a stroke with an NIHSS score >25 and 19,995 (35%) had an NIHSS score of 15–25. They found that the symptomatic intracerebral hemorrhage risk appeared lower in the very severe stroke group compared with the moderately severe group when defined by the SITS-MOST criteria (a type 2 parenchymal hemorrhage with deterioration in NIHSS score of >4 points or death). But when defined by European Cooperative Acute Stroke Study/NINDs criteria, the risk trended slightly higher in the very severe group. Moreover, they also observed that a very severe stroke was not independently associated with symptomatic hemorrhage after adjusting the baseline variables between the two groups using logistic regression analysis. They also noted that patients appeared similar in terms of sex, blood pressure, weight, rt-PA dose, comorbidities, risk factors and other medications. Therefore, the authors concluded that these patients with very severe stroke were not very different from those with moderately severe stroke, the pathophysiology and demographics may be fairly similar.

In conclusion, based on the current evidence, patients should not be excluded from intravenous thrombolysis only based on the criterion of older age >80 years or very severe strokes (NIHSS >22 or 25).

References

1 Mukherjee D, Patil CG: Epidemiology and the global burden of stroke. World Neurosurg 2011;76:S85–S90.
2 Wardlaw JM, Murray V, Berge E, et al: Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 2014;7:CD000213.
3 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;333:1581–1587.
4 European Stroke Organisation Executive Committee: Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457–507.

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5 Lees KR, Bluhmki E, von Kummer R, et al: Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375:1695–1703.
6 Kernan WN, Ovbiagele B, Black HR, et al: Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160–2236.
7 Emberson J, Lees KR, Lyden P, et al: Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929–1935.
8 Sandercock P, Wardlaw JM, Lindley RI, et al: The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the Third International Stroke Trial IST-3): a randomised controlled trial. Lancet 2012;379:2352–2363.
9 Summary of product characteristics (Actilyse). http://www.medicines.org.uk/EMC/medicine/308/SPC/Actlyse (accessed May 9, 2015).
10 Mazya M, Lees KR, Collas D, et al: Intravenous thrombolysis in very severe ischemic strokes. Results from the SITS International Stroke Thrombolysis Register (SITS-ISTR). ESOC-0411 – 2015; abstract 228.