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Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke.

Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, Broderick JP, Chen X, Chen G, Sharma VK, Kim JS, Thang NH, Cao Y, Parsons MW, Levi C, Huang Y, Olavarría VV, Demchuk AM, Bath PM, Donnan GA, Martins S, Pontes-Neto OM, Silva F, Ricci S, Roffe C, Pandian J, Billot L, Woodward M, Li Q, Wang X, Wang J, Chalmers J; ENCHANTED Investigators and Coordinators.

Abstract

BACKGROUND:
Thrombolytic therapy for acute ischemic stroke with a lower-than-standard dose of intravenous alteplase may improve recovery along with a reduced risk of intracerebral hemorrhage.

METHODS:
Using a 2-by-2 quasi-factorial open-label design, we randomly assigned 3310 patients who were eligible for thrombolytic therapy (median age, 67 years; 63% Asian) to low-dose intravenous alteplase (0.6 mg per kilogram of body weight) or the standard dose (0.9 mg per kilogram); patients underwent randomization within 4.5 hours after the onset of stroke. The primary objective was to determine whether the low dose would be noninferior to the standard dose with respect to the primary outcome of death or disability at 90 days, which was defined by scores of 2 to 6 on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]). Secondary objectives were to determine whether the low dose would be superior to the standard dose with respect to centrally adjudicated symptomatic intracerebral hemorrhage and whether the low dose would be noninferior in an ordinal analysis of modified Rankin scale scores (testing for an improvement in the distribution of scores). The trial included 935 patients who were also randomly assigned to intensive or guideline-recommended blood-pressure control.

RESULTS:
The primary outcome occurred in 855 of 1607 participants (53.2%) in the low-dose group and in 817 of 1599 participants (51.1%) in the standard-dose group (odds ratio, 1.09; 95% confidence interval [CI], 0.95 to 1.25; the upper boundary exceeded the noninferiority margin of 1.14; P=0.51 for noninferiority). Low-dose alteplase was noninferior in the ordinal analysis of modified Rankin scale scores (unadjusted common odds ratio, 1.00; 95% CI, 0.89 to 1.13; P=0.04 for noninferiority). Major symptomatic intracerebral hemorrhage occurred in 1.0% of the participants in the low-dose group and in 2.1% of the participants in the standard-dose group (P=0.01); fatal events occurred within 7 days in 0.5% and 1.5%, respectively (P=0.01). Mortality at 90 days did not differ significantly between the two groups (8.5% and 10.3%, respectively; P=0.07).

CONCLUSIONS:
This trial involving predominantly Asian patients with acute ischemic stroke did not show the noninferiority of low-dose alteplase to standard-dose alteplase with respect to death and disability at 90 days. There were significantly fewer symptomatic intracerebral hemorrhages with low-dose alteplase. (Funded by the National Health and Medical Research Council of Australia and others; ENCHANTED ClinicalTrials.gov number, NCT01422616.).