Frequency, determinants, and effects of early seizures after thrombolysis for acute ischemic stroke

The ENCHANTED trial

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Abstract

Background: Seizures after ischemic stroke have not been well-studied. We aim to determine the frequency, determinants, and significance of early seizures after thrombolysis for acute ischemic stroke.

Methods: Data are from the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED), an international, multicenter, randomized controlled trial where patients with acute ischemic stroke were randomized to low-dose (0.6 mg/kg) or standard-dose (0.9 mg/kg) IV alteplase. The protocol prespecified prospective data collection on in-hospital seizures over 7 days postrandomization. Logistic regression models were used to determine variables associated with seizures and their significance on poor outcomes of death or disability (modified Rankin scale scores 3–6), symptomatic intracerebral hemorrhage (sICH), and European Quality of Life 5-Dimensions questionnaire (EQ-5D) over 90 days.

Results: Data were available for 3,139 acute ischemic stroke participants, of whom 42 (1.3%) had seizures at a median 22.7 hours after the onset of symptoms. Baseline variables associated with seizures were male sex (odds ratio [OR] 2.19, 95% confidence interval [CI] 1.07–4.50), severe neurologic impairment (NIH Stroke Scale score ≥10; OR 2.16, 95% CI 1.06–4.40), and fever (OR 4.55, 95% CI 2.37–8.71). Seizures independently predicted poor recovery: death or major disability (OR 2.88, 95% CI 1.28–6.47), unfavorable ordinal shift of mRS scores (OR 1.94, 95% CI 1.10–3.39), and lower than median EQ-5D health utility index score (OR 3.50, 95% CI 1.37–8.91). There...
was no association of seizures with sICH in adjusted analysis. **Conclusions:** In thrombolysis-treated patients with acute ischemic stroke, seizures are uncommon, occur early, and predict poor recovery. Clinicaltrials.gov identifier: NCT01422616. *Neural Clin Pract* 2017;7:324–332

Seizures occur in 2%–18% of stroke patients, but the frequency may vary according to various factors: the type, location, and severity of stroke; complications such as delirium, hyponatremia, pneumonia, and fever; time period of observation; and by sex, age, and use of thrombolysis. Although seizures that occur early after the onset of acute ischemic stroke represent only a small proportion of poststroke seizures, they appear to have adverse effects on recovery by increasing risks of death. However, the strength of association is inconsistent, with some studies reporting an increase in mortality after adjustment for confounding variables, while other studies have shown no association with mortality at 6 months poststroke. Findings are also contradictory concerning the association between seizures and symptomatic intracerebral hemorrhage (sICH) after acute ischemic stroke. We sought to provide a reliable assessment of the frequency, determinants, and effects of early seizures among thrombolysis-treated ischemic stroke patients who participated in the large-scale Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED).

**METHODS**

**Overview**

ENCHANTED was an international, multicenter, prospective, open-label, quasifactorial, randomized controlled trial with blinded outcome evaluation, as outlined in detail elsewhere. A total of 3,310 patients with acute ischemic stroke who fulfilled standard eligibility criteria for thrombolytic treatment (median age, 67 years; 63% Asian) participated in the alteplase dose arm of the trial. They were randomly assigned to receive low-dose (0.6 mg per kilogram of body weight) or standard-dose (0.9 mg per kilogram) IV alteplase within 4.5 hours after onset of symptoms.

**Standard protocol approvals, registrations, and patient consents**

The trial protocol was approved by appropriate regulatory authorities and ethics committees at participating centers, and written informed consent was obtained from patients or, where appropriate, approved surrogates. The study is registered at ClinicalTrials.gov (NCT01422616).

**Measures**

Data on seizures (i.e., onset time, syndrome type, and number; use of antiepilepsy treatment) during 7 days (or to death or at hospital discharge, if sooner) was prespecified to be collected as part of the study protocol. Seizures were observed by trial investigators (mainly neurologists) and classified according to International League Against Epilepsy criteria. Baseline severity of neurologic impairment was measured using the NIH Stroke Scale (NIHSS; scores range from 0 to 42, higher scores indicate greater severity). Management details (i.e., fever occurrence, time from stroke onset to alteplase treatment, and stroke unit and intensive care unit admission) were collected to 7 days after randomization. The primary endpoint of functional outcome was assessed on the modified Rankin Scale (mRS) at 90 days, by trained researchers who were blind to the treatment assignment and management. The mRS is a global 7-level measure of functioning in which scores of 0–2 indicate a good outcome with no/minor neurologic symptoms or slight disability, 3–5 indicate major disability with grades of dependency, and 6 indicates death. A secondary outcome was sICH, defined according to various standard criteria (appendix e-1 at Neurology.org/cp), with the key measure being from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-
We sought to provide a reliable assessment of the frequency, determinants, and effects of early seizures among thrombolysis-treated ischemic stroke patients.

MOST). Health-related quality of life was measured using the European Quality of Life group 5-Dimension self-report questionnaire (EQ-5D), where scores range from −0.594 (worse than death) to 1 (optimal health).

Statistical analysis
Complete case analysis was used. Univariate comparisons of characteristics between participants with and without seizures were conducted using \( \chi^2 \) test for categorical variables and 2-sample \( t \) test for continuous variables. Other than age, only variables having an association (\( p < 0.2 \)) with seizures were considered for inclusion in multivariate models. Multivariate logistic regression was used to identify independent predictors of seizures with stepwise removal of nonsignificant covariates identified using the Wald test until all the remaining variables were statistically significant (\( p < 0.05 \)). The association between seizures and clinical outcomes was identified through multivariate logistic regression with adjustment for minimization and key prognostic covariates. Data were reported with odds ratios (OR) and 95% confidence intervals (CI). All analyses were undertaken using SAS Enterprise version 7.1 (SAS Institute, Cary, NC).

RESULTS
Of the 3,310 participants in the alteplase dose arm of ENCHANTED, 3,139 had a final diagnosis of ischemic stroke and information on seizures (figure).

Seizures occurred in 42 participants (1.3%): simple partial in 16 (38%), complex partial in 11 (26%), partial with secondary generalization in 2 (5%), primary generalized without an observable focal onset in 11 (26%), and undetermined type in 2 (5%). Antiepilepsy drugs were
used in in 37 (88%). Most (27 [64%]) patients had a single seizure (interquartile range [IQR] 1–2). A total of 22 (52%) patients had seizures within 24 hours, including 3 at the time of presentation. The median time from stroke onset to first seizure was 22.7 (IQR 3.5–48.3) hours.

Table 1 shows that patients with seizures had more severe neurologic deficit than others (median NIHSS scores 14 vs 8), premorbid symptoms (mRS score of 1), signs of early cerebral ischemia, nonlacunar type pathology, fever, intensive care unit admission, and prior use of aspirin or other antiplatelet agent. Multivariable analysis indicates the following baseline or management characteristics were independently associated with early seizures: being male (OR 2.19, 95% CI 1.07–4.50), greater neurologic impairment (NIHSS ≥10; OR 2.16, 95% CI 1.06–4.40), and fever (OR 4.55, 95% CI 2.37–8.71).

Death or major disability (mRS 3–6) occurred in 31 of 41 participants (76%) with seizures compared with 1,118 of 3,035 participants (37%) without seizures (p < 0.001) (table 2). After adjustment, seizures remained an independent predictor of poor outcome: death or major disability (OR 2.88, 95% CI 1.28–6.47) and major disability alone (OR 2.45, 95% CI 1.06–5.67), but not with death (OR 1.23, 95% CI 0.53–2.83). Moreover, adjusted ordinal analysis showed that seizures were associated with an unfavorable ordinal shift on the mRS (OR 1.94, 95% CI 1.10–3.39).

For the other outcomes, sICH tended to be more frequent in those with seizures, but this was not significant in multivariable analysis (table e-1). However, after adjustment, participants with seizures were more likely to have lower EQ-5D scores (OR 3.50, 95% CI 1.37–8.91) (table e-1).

DISCUSSION

Early seizures are uncommon in patients who receive lytic treatment for acute ischemic stroke and are associated with being male, more severe neurologic deficit (NIHSS score ≥10), and fever in the first 7 days. Yet seizures are a serious complication of this illness/management, as they independently predict an adverse functional outcome and poor quality of life.

Despite our dataset being derived from a clinical trial that tended to include patients with relatively mild severity of ischemic stroke who were managed according to standardized protocols, the frequency of seizures in our study is consistent with other studies reporting occurrences of 2.5% (10/400) and 1.2% (28/2,327) in the first 7 days after the onset of symptoms, where all or some of the patients were treated with IV alteplase. In the longer term, however, the frequency approaches 10% in a broader range of patients. The most common seizure type in our cohort—simple or complex partial—is also consistent with other studies and likely relates to the underlying focal ischemic lesion.

The greater frequency of postischemic stroke seizures in men was also noted in a Chinese study, and gives some support for a protective effect of estrogen, although most female participants in our study were postmenopausal. Low testosterone has been shown to enhance ictal activity. As shown in previous studies, stroke severity, whether measured clinically or by the size and location of lesion, is related to seizures. The relevance of fever to seizures could be related to infection or inflammation after ischemic stroke; further studies are required to investigate the role of comorbid stress or tissue necrosis in triggering seizures. Thrombolytic treatment can increase the risk of hemorrhagic transformation of cerebral
<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall (n = 3,139)</th>
<th>Occurrence of seizure</th>
<th>p Value</th>
<th>Adjusted OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>67 ± 13</td>
<td>66 ± 15</td>
<td>67 ± 13</td>
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<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>1,960 (62)</td>
<td>32 (76)</td>
<td>1,928 (62)</td>
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<td>2.19 (1.07-4.50)</td>
</tr>
<tr>
<td>Non-Asian race</td>
<td>1,141 (36)</td>
<td>19 (45)</td>
<td>1,122 (36)</td>
<td>0.228</td>
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<tr>
<td>Baseline NIHSS ≥10</td>
<td>1,391 (44)</td>
<td>30 (71)</td>
<td>1,361 (44)</td>
<td>&lt;0.001</td>
<td>2.16 (1.06-4.40)</td>
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<tr>
<td>Premorbid stroke risk factors</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,987 (63)</td>
<td>27 (64)</td>
<td>1,960 (63)</td>
<td>0.894</td>
<td></td>
</tr>
<tr>
<td>Previous any stroke</td>
<td>554 (18)</td>
<td>11 (26)</td>
<td>543 (18)</td>
<td>0.144</td>
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</tr>
<tr>
<td>Coronary artery disease</td>
<td>455 (15)</td>
<td>8 (19)</td>
<td>447 (14)</td>
<td>0.399</td>
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</tr>
<tr>
<td>Other heart disease (e.g., heart failure)</td>
<td>227 (7)</td>
<td>6 (14)</td>
<td>221 (7)</td>
<td>0.076</td>
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<tr>
<td>Atrial fibrillation</td>
<td>458 (15)</td>
<td>8 (19)</td>
<td>450 (15)</td>
<td>0.410</td>
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<tr>
<td>Diabetes mellitus</td>
<td>618 (20)</td>
<td>5 (12)</td>
<td>613 (20)</td>
<td>0.202</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>528 (17)</td>
<td>9 (21)</td>
<td>519 (17)</td>
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<td>Current cigarette use</td>
<td>737 (23)</td>
<td>7 (17)</td>
<td>730 (24)</td>
<td>0.293</td>
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<tr>
<td>Premorbid mRS score of 1</td>
<td>582 (19)</td>
<td>13 (31)</td>
<td>569 (18)</td>
<td>0.037</td>
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</tr>
<tr>
<td>Use of statin or other lipid-lowering agent</td>
<td>583 (19)</td>
<td>12 (29)</td>
<td>571 (18)</td>
<td>0.094</td>
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</tr>
<tr>
<td>Use of aspirin or other antiplatelet agent</td>
<td>720 (23)</td>
<td>15 (36)</td>
<td>705 (23)</td>
<td>0.048</td>
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<tr>
<td>Warfarin anticoagulation</td>
<td>80 (3)</td>
<td>2 (5)</td>
<td>78 (3)</td>
<td>0.360</td>
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<tr>
<td>Final diagnosis at time of hospital discharge</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Large artery occlusion</td>
<td>1,270 (40)</td>
<td>17 (40)</td>
<td>1,253 (40)</td>
<td>0.998</td>
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<td>Small vessel lacunar disease</td>
<td>673 (21)</td>
<td>2 (5)</td>
<td>671 (22)</td>
<td>0.008</td>
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<tr>
<td>Cardioembolism</td>
<td>641 (20)</td>
<td>9 (21)</td>
<td>632 (20)</td>
<td>0.870</td>
<td></td>
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<tr>
<td>Multiple lesions reported on final diagnosis</td>
<td>509 (16)</td>
<td>11 (26)</td>
<td>498 (16)</td>
<td>0.079</td>
<td></td>
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<tr>
<td>Brain imaging features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early cerebral ischemia on brain imaging</td>
<td>749 (24)</td>
<td>16 (38)</td>
<td>733 (24)</td>
<td>0.029</td>
<td></td>
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<tr>
<td>Proximal vessel occlusion on CTA or MRA</td>
<td>494 (16)</td>
<td>8 (19)</td>
<td>486 (16)</td>
<td>0.480</td>
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<tr>
<td>Normal serum sodium (135-145 mmol/L)</td>
<td>2,732 (87)</td>
<td>36 (86)</td>
<td>2,696 (87)</td>
<td>0.798</td>
<td></td>
</tr>
<tr>
<td>Normal serum potassium (3.5-5.0 mEq/L)</td>
<td>2,585 (82)</td>
<td>34 (81)</td>
<td>2,551 (82)</td>
<td>0.811</td>
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<tr>
<td>Fever occurrence</td>
<td>612 (19)</td>
<td>24 (57)</td>
<td>588 (19)</td>
<td>&lt;0.001</td>
<td>4.55 (2.37-8.71)</td>
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<tr>
<td>Time from stroke onset to alteplase, min</td>
<td>170</td>
<td>162</td>
<td>170</td>
<td>0.488</td>
<td></td>
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<tr>
<td>Median</td>
<td>126-219</td>
<td>128-210</td>
<td>126-219</td>
<td>0.488</td>
<td></td>
</tr>
</tbody>
</table>

Continued
but there are conflicting animal and human data regarding the risk of seizures after thrombolysis. 

Our data add to the literature that dose (i.e., low vs standard) of alteplase treatment did not appear to have a major effect on the risk of early seizures in acute ischemic stroke.

### Table 1  Continued

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall (n = 3,139)</th>
<th>Yes (n = 42)</th>
<th>No (n = 3,097)</th>
<th>p Value</th>
<th>Adjusted OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received low-dose alteplase</td>
<td>1,563 (50)</td>
<td>19 (45)</td>
<td>1,557 (50)</td>
<td>0.517</td>
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<tr>
<td>Stroke unit admission</td>
<td>1,903 (61)</td>
<td>25 (60)</td>
<td>1,878 (61)</td>
<td>0.877</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit admission</td>
<td>758 (24)</td>
<td>18 (43)</td>
<td>740 (24)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; CTA = CT angiography; IQR = interquartile range; MRA = magnetic resonance angiography; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio.

p Values are for comparisons between seizure and nonseizure groups. Variables with p < 0.2 and age were considered for adjustment.

*Race was self-reported.

bScores range from 0 to 42, with higher scores indicating more severe neurologic deficit. There is a significant difference between seizure and nonseizure groups, median scores 14 (IQR 8–20) and 8 (IQR 5–14), respectively.

cPremorbid risk factors based on self-report, except atrial fibrillation from findings on ECG at presentation.

dScores range from 0 (no symptoms) to 6 (death).

eDiagnoses determined by clinician investigators.

fThis finding was determined by clinician investigators.

gTimes range from 73 to 268 minutes (1.2–4.5 hours) in the seizure group and 11–1,678 minutes (0.2–28.0 hours) in the nonseizure group.

infarction, but there are conflicting animal and human data regarding the risk of seizures after thrombolysis. 

Our data add to the literature that dose (i.e., low vs standard) of alteplase treatment did not appear to have a major effect on the risk of early seizures in acute ischemic stroke.
Contrary to the finding of another study,1 we were unable to show a definite association between seizures and mortality. This may be due to the ENCHANTED patients having better premorbid health (previously independent), and being less likely to die within 24 hours than a broader group of patients with acute ischemic stroke. There is an indication that early seizures increased the propensity for disability as the association with 90-day disability outcomes was consistent across the various approaches to analyze the mRS scores and the overall and individual components (data not shown) of the EQ-5D, independent of the severity of neurologic impairment at presentation. Any association between seizures and sICH could relate to increased tissue excitability within the ischemic penumbra,9 or increased intracranial pressure,7 but we could not find a clear association between these outcomes in multivariable analysis, although the numbers were small.

Strengths of this study include the broad range of well-characterized patients who were recruited from different health care settings with prospective, detailed, and complete data on early seizures. However, there are several limitations: this was a selected clinical trial population and we lack data on the location (cortical involvement or not) and extent of cerebral ischemia at this time, both of which have been associated with seizures.5,7,22,27 Further, we are unable to assess the influence of a history of epilepsy or the use of antiepilepsy agents, although these have not been found to predict the incidence of poststroke seizures.17 Furthermore, we do not have data on the use of specific antiepilepsy agents, their dosage, or duration of treatment. We note a deficiency in the literature on the efficacy of antiepilepsy agents in the prevention or control of seizures or of their influence on stroke recovery. Finally, we do not have any EEG data to confirm the reported diagnoses or to identify subclinical seizures. Of note, stroke severity predicts electrical seizures identified on continuous EEG.28 Most previous studies did not employ EEG, while most of those that did report the use of EEG have not presented any data on the findings in relation to early seizures.2,10,17,18 However, in one study, EEGs were obtained in 10 out of 29 patients with seizures, showing mild nonspecific changes in 3, focal slowing in 6, and paroxysmal features in 1 (generalized status epilepticus).7

Although seizure is an uncommon complication of acute ischemic stroke in patients treated with IV alteplase, it has adverse effects upon recovery. Early recognition of those at high risk and effective management of comorbid factors such as fever may improve outcomes.

REFERENCES


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AUTHOR CONTRIBUTIONS
Y. Xu: statistical analysis, interpretation of data, first draft, and revision of the manuscript. M.L. Hackett: interpretation of data, supervision, and revision of the manuscript. J. Chalmers: design/conceptualization of the study, interpretation of data, supervision, and revision of the manuscript. R.I. Lindley: revision of the manuscript. X. Wang: check of statistical analysis and interpretation of data. Q. Li: check of statistical analysis and interpretation of data. T. Robinson: design/conceptualization of the study and revision of the manuscript. H. Arima: design/conceptualization of the study and revision of the manuscript. P.M. Lavados: design/conceptualization of the study and revision of the manuscript. C.S. Anderson: design/conceptualization of the study, interpretation of data, supervision, and revision of the manuscript.

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DISCLOSURE

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