Adverse Effect of Early Epileptic Seizures in Patients Receiving Endovascular Therapy for Acute Stroke

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Background and Purpose—The aim of this study was to analyze epileptic seizures and their impact on outcome in patients with stroke treated with endovascular therapy.

Methods—From December 1992 to December 2010 we managed 805 patients with stroke with endovascular therapy. Epileptic seizures, bleeding complications, and 3-month outcomes were recorded prospectively. Outcomes of patients with early seizures (within 24 hours of stroke onset) and patients with late seizures (>24 hours after stroke) were compared with outcomes of seizure-free patients using uni- and multivariable statistics.

Results—Forty-four of 805 patients (5.5%) had seizures between stroke onset and 3-month follow-up, 26 patients early and 18 late. Outcome of patients with late seizures and seizure-free patients was similar (P=0.144 and 0.807). Patients with early seizures had higher baseline National Institutes of Health Stroke Scale (P=0.023) and were younger (P=0.021) than seizure-free patients. Their mortality rate was 50% compared with 22.3% of the seizure-free patients (P=0.003), and less patients reached a favorable outcome (modified Rankin Scale 0–2): 15.4% and 46.8%, respectively (P=0.001). Early seizures independently predicted an unfavorable outcome (P=0.014; OR, 4.749; 95% CI, 0.376–3.914) and increased mortality (P=0.001; OR, 5.861; 95% CI, 0.770–2.947) in multiregression analysis. Patients with early seizures had a 1.6-fold higher risk for unfavorable outcome and a 2.2-fold higher risk for death compared with seizure-free patients.

Conclusions—Seizures within 24 hours of stroke onset were associated with worse outcome in patients with stroke undergoing endovascular therapy. Our findings confirm a need for trials for prophylactic anticonvulsive treatment in patients receiving endovascular therapy for acute stroke. (Stroke. 2012;43:00-00.)

Key Words: epilepsy ■ intra-arterial thrombolysis ■ outcome ■ seizure

Ischemic and hemorrhagic strokes are risk factors for single seizures and epilepsy that occur in 2.2% to 10.5% after acute ischemic strokes. Continuous electroencephalographic recordings in the acute phase after stroke found focal epileptiform abnormalities even in up to 17% of the patients. The time from stroke onset to the first seizure is known to be critical for development of epilepsy, although the time to distinguish early and late seizures varies from 24 hours to 2 weeks in different studies. Early seizures constitute a risk of 17% to 35% for later epilepsy and late seizures, a risk of 65% to 90%. Results of outcome of stroke after seizures are conflicting. Some authors found a worsening effect on outcome and increased mortality, whereas others did not. In randomized trials of intravenous and intra-arterial (IAT) thrombolytic therapy of ischemic strokes, seizures after stroke onset were exclusion criteria. Many clinicians and guidelines still consider seizures as a contraindication for thrombolysis, because seizure-related loss of neurological functions can mimic stroke. However, modern multimodal imaging can differentiate strokes from seizure-related effects, and thus patients with stroke with seizures have become increasingly candidates for thrombolysis. Although the natural course of strokes with seizures has been addressed in earlier studies, the impact of seizures on outcome after intravenous thrombolytic therapy or IAT has hardly been explored yet. We found only 1 report on outcome of 3 patients with seizures who received intravenous thrombolytic therapy.

The aim of this study was to analyze the influence of early and late epileptic seizures on outcome of patients with acute ischemic stroke treated with IAT.

Patients and Methods

Patients

In 1992 we started endovascular treatment of patients with acute ischemic stroke. Some aspects of these patients have been reported previously.

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A neurologist examined all patients immediately after admission in the emergency room. The neurological deficit was scored using the National Institutes of Health Stroke Scale (NIHSS) and demographic and clinical data were recorded (age, gender, premedication, time of symptom onset, coronary artery disease, atrial fibrillation, hypertension, diabetes, current cigarette smoking, hypercholesterolemia, history of transient ischemic attack or ischemic stroke, family history of transient ischemic attack and stroke). IAT was performed with the consent of the patient or his or her family immediately after CT or MRI if: (1) a diagnosis of ischemic stroke was established; (2) baseline NIHSS score was ≥4 points or isolated aphasia or isolated hemianopia was present or in case of recurrent...
neurological deficits with a persistent major vessel occlusion; (3) hemorrhage on cranial CT or MRI was excluded; (4) vessel occlusion correlated with the neurological deficit; (5) symptom duration was not >24 hours; and (6) no individual clinical or premorbid conditions or laboratory findings advised against thrombolysis. IAT was usually not performed if the spin-echo T2-weighted images revealed significant hypertensive signal changes or if the CT showed extensive early signs of stroke. Digital subtraction angiography was performed through a transfemoral approach using a biplane, high-resolution angiography system and all patients underwent complete 4-vessel cerebral angiography. The site of the artery occlusion was categorized. Collaterals were classified as none; poor, if minimal leptomeningeal anastomoses were visualized and no or minimal filling of the occluded vessel territory was seen; and good, if leptomeningeal anastomoses filled the occluded vessel territory by more than half. The interventional neuroradiologist and neurologist decided on the use of urokinase, mechanical intervention, both, or bridging therapy. At the end of angiography, recanalization was classified according to Thrombolysis In Myocardial Infarction grades: 0 no, 1, minimal; 2, partial and 3, complete recanalization.

A CT or MRI scan was obtained usually after 24 hours and never >72 hours after treatment or in any case of clinical deterioration. Symptomatic and asymptomatic intracerebral hemorrhage (ICH) was graded according to the Prolyse in Acute Cerebral Thromboembolism (PROACT) II Study. Etiology of the stroke was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria using ancillary investigations as necessary and secondary preventive treatment was given according to current evidence and European guidelines. Clinical outcome was assessed 3 months after the stroke using the modified Rankin Scale.

NIHSS and modified Rankin Scale were assessed by the treating neurologists and stroke study nurses helped with modified Rankin Scale assessments at phone follow-up. The follow-up rate was 97.9% (788 of 805). A total of 76.6% (604 of 788) of patients returned to the hospital for follow-up or their information such as death was obtained from the hospital records and in 23.4% (184 of 788) patients telephone follow-up was performed.

The occurrence of epileptic seizures, the seizure type, and the time of occurrence were recorded from symptom onset until the 3-month follow-up. Information was obtained from the patient, from persons who observed the seizure, or from both. In basilar artery occlusions, patients sometimes show extension spasm at symptom onset as a result of brain stem ischemia, which are not considered to reflect seizure activity in the cortex. Consequently, seizures in basilar artery occlusion were only assumed if further signs like unequivocal clonic movements, tongue bite, or incontinence were observed. Seizures occurring within 24 hours after stroke onset were classified as early seizures and seizures occurring thereafter up to 3 months as late seizures. Data were collected prospectively, but the analysis was performed retrospectively.

**Statistical Analysis**

Statistical analysis was performed using SPSS 18 (SPSS Inc., Chicago, IL). Categorical variables were compared with $\chi^2$ and Fisher exact test as appropriate and continuous variables with Mann-Whitney test. Outcome was dichotomized into favorable (modified Rankin Scale 0–2) and poor clinical outcome (modified Rankin Scale 3–6). Recanalization was dichotomized into poor (Thrombolysis In Myocardial Infarction 0–1) and good (Thrombolysis In Myocardial Infarction 2–3) recanalization. Bonferroni adjustment was made for univariate tests.

Forward stepwise logistic regression analysis including all variables with $P<0.2$ in univariate analysis (considering the following factors: age, gender, time to thrombolysis, NIHSS score on admission, atrial fibrillation, vessel dissection, diabetes, smoking, hypertension, hypercholesterolemia, coronary artery disease, history of stroke or transient ischemic attack, smoking, family history of stroke, stroke etiology, occlusion localization, degree of collaterals, recanalization after IAT, dose of urokinase, early seizures, late seizures, symptomatic and asymptomatic ICH after IAT) was used to determine the predictors of clinical outcome and survival. The parameters of the final models were estimated with bootstrapping (1000 samples). A probability value of $<0.05$ was considered significant. The predictors of early seizures were determined with the same variables in multivariable regression analysis except the 2 variables early and late seizures.

**Results**

From December 1992 to December 2010 we prospectively acquired data of 805 patients with acute ischemic stroke who received endovascular treatment at our center. In 44 (5.5%) patients, a seizure was recorded between stroke onset and the 3-month follow-up, 26 (3.2%) with early-onset and 18 (2.2%) with late-onset of the seizures. None of these patients were known for epilepsy.

The baseline characteristics, treatment, and outcome of patients with and without seizures are given in Table 1 and more detailed information on patients with early seizures in Table 2 and 3.

The 18 late-onset seizures occurred between Days 1 and 7 in 5 patients, between Days 8 and 21 in 5, and between Day 22 and 3 months follow-up in 8. Patients with late-onset seizures did not differ significantly in baseline characteristics or outcome compared with the seizure-free patients after Bonferroni adjustment.

Early seizures occurred in 26 patients and the frequency of early seizures did not change significantly during the treatment period from 1992 to 2010. Sixteen of the 26 early seizures occurred before angiography, 7 of them at stroke onset. The seizures occurred in 5 patients during angiography (3 during urokinase infusion, 2 shortly after infusion) and in another 5 patients after angiography until 24 hours after stroke.

### Table 2. Seizure Occurrence-Dependent Characterization of Patients With Early Seizures

<table>
<thead>
<tr>
<th></th>
<th>Before Angiography</th>
<th>During or After Angiography</th>
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<tbody>
<tr>
<td><strong>Seizure type</strong></td>
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<tr>
<td>Simple focal</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Generalized</td>
<td>11</td>
<td>5</td>
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<tr>
<td><strong>Oclusion location</strong></td>
<td></td>
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<tr>
<td>ICA</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>MCA/ACA</td>
<td>6/1</td>
<td>7/0</td>
</tr>
<tr>
<td>BAO</td>
<td>4</td>
<td>1</td>
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<tr>
<td><strong>Early CT/MRI signs</strong></td>
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<tr>
<td>Asymptomatic ICH</td>
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<tr>
<td>Symptomatic ICH</td>
<td>1/6</td>
<td>2/10</td>
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<tr>
<td>Asymptomatic ICH</td>
<td>5/6</td>
<td>4/10</td>
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<tr>
<td>TIMI 2–3 recanalization</td>
<td>9/6</td>
<td>8/10</td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>3/6</td>
<td>1/10</td>
</tr>
<tr>
<td>Survival</td>
<td>9/6</td>
<td>4/10</td>
</tr>
</tbody>
</table>

No. of patients and percent.

ICA indicates internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; BAO, basilar artery occlusion; NIHSS, National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; TIMI, Thrombolysis In Myocardial Infarction; mRS, modified Rankin Scale.
The characteristics of patients with early seizures before angiography and those during or after angiography are noted in Table 2. In 13 of the 16 patients with seizures before angiography, CT or MRI ruled out a hemorrhage after the admission (P=0.023) and were younger (P=0.021; OR, 0.969; 95% CI, 0.945–0.994) independently predicted early seizures.

In multivariable analysis, the following independent predictors of an unfavorable outcome were found: early seizures (P=0.014; OR, 4.749; 95% CI, 0.376–3.914), older age (P=0.001; OR, 1.043; 95% CI, 0.029–0.060), higher baseline NIHSS (P=0.001; OR, 1.153; 95% CI, 0.108–0.190), symptomatic ICH (P=0.001; OR, 42.852; 95% CI, 2.359–21.603), diabetes mellitus (P=0.001; OR, 2.770; 95% CI, 0.505–1.543), worse recanalization (P=0.001; OR, 3.785; 95% CI, 0.975–1.785), longer time from symptom onset to IAT (P=0.013; OR, 1.002; 95% CI, 0.000–0.004), and occlusion site as a categorical variable (P=0.001; categories: internal carotid artery, internal carotid artery T, middle cerebral artery, anterior cerebral artery, basilar artery occlusion) with worst outcomes in internal carotid and basilar artery occlusions. Independent predictors of increased mortality were identified: early seizures (P=0.001; OR, 5.861; 95% CI, 0.0770–2.947), older age (P=0.001; OR, 1.069; 95% CI, 0.046–0.092), higher baseline NIHSS (P=0.001; OR, 1.079; 95% CI, 0.051–0.111), worse collaterals (P=0.001; OR, 1.714; 95% CI, 0.885 to 0.259), symptomatic ICH (P=0.001; OR, 12.823; 95% CI, 1.825–3.560), worse recanalization (P=0.01; OR, 1.754; 95% CI, 0.104–0.991), and occlusion site as a categorical variable (P=0.001). In the regression analysis, excluding patients with basilar artery occlusion, early seizures remained an independent predictor.

In multivariable regression analysis, asymptomatic ICH (P=0.019; OR, 2.763; 95% CI, 1.185–6.442), a higher NIHSS on admission (P=0.041; OR, 1.050; 95% CI, 1.001–1.01), and younger age (P=0.021; OR, 0.969; 95% CI, 0.945–0.994) independently predicted early seizures.

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of unfavorable outcome ($P=0.029$; OR, 4.516; 95% CI, 0.084–4.038) and increased mortality ($P=0.001$; OR, 7.239; 95% CI, 0.721–3.523).

**Discussion**

The main finding of this study is that early seizures independently predict mortality and unfavorable outcome in patients with stroke treated with IAT. Early-onset seizures carry a 1.6-fold risk for unfavorable outcome and a 2.2-fold risk for death.

Among 805 patients, early seizures were noted in 26 (3.2%). This result is similar to previous reports with seizure rates ranging from 2.2% to 6.5%.1

The baseline characteristics and outcome of patients with late seizures did not differ from the seizure-free patients ($P>0.025$ with Bonferroni adjustment).

Several studies investigated whether seizures after stroke change the natural course and outcome, but only in 3 studies multivariable regression analysis was performed. Arboix et al3 analyzed 452 patients and Vernino et al4 444 patients. They found early seizures to act as an independent predictor of death. Szafarski et al5 found a higher mortality rate in patients with seizures, but seizures were not an independent predictor of mortality at 30 days. This study of 5324 strokes included 720 patients with hemorrhagic strokes and results for ischemic strokes were not reported separately. Other smaller studies did not find early seizures to influence outcome.6,8 Differing definitions of early seizures might explain these conflicting results. The cutoff time point seems to be critical because early and late seizures are triggered by different mechanisms and therefore represent different entities.21,22 Definitions of early seizures range from occurrence within 24 hours to 14 days after stroke onset, whereas the usual cutoff time is 7 to 14 days in epilepsy research.23 We chose a 24-hour cutoff time in our study because of pathophysiological deliberations considering the penumbral tissue in acute ischemic stroke and because the first peak of poststroke seizures occurs within 24 hours.24,25

To date there is only 1 report on early seizures and outcome after thrombolysis for ischemic stroke. Rodan et al9 described 3 patients who experienced early seizure during tissue-type plasminogen activator infusion. The seizures heralded dramatic recovery, and a seizure mechanism with cortical re- or hyperperfusion or both due to recanalization of an intracranial artery was discussed. In contrast to this case report, 50% of our patients with early seizures and IAT died compared with 22.3% without seizures ($P=0.003$), and only 15.4% of patients with early seizures compared with 46.8% without seizures reached a favorable outcome ($P=0.001$; Figure).

In multivariable regression analysis, early seizures independently predicted an unfavorable outcome ($P=0.014$; OR, 4.749; 95% CI, 0.376–3.914) and increased ($P=0.001$; OR, 5.861; 95% CI, 0.770–2.947). This negative effect on outcome remained consistent also when omitting patients with basilar artery occlusions from the analysis, which represent a group with less certain seizure diagnosis and potential “seizure mimics.” Consequently, the detrimental effect of early seizures on outcome after IAT seems to be a robust result. This worsening effect is supported by animal studies. Seizures significantly increased infarct size, histological damage, and mortality in the setting of cerebral ischemia or hypoxia.26–28 In our study, collaterals ($P=0.804$) and recanalization rates ($P=0.519$) in patients with early and seizure-free patients did not differ. Therefore, we assume that early seizures have a negative effect on outcome in patients with stroke treated with IAT.

**Figure.** Percentage of survival and favorable outcomes at 3 months.

![Graph showing percentage of survival and favorable outcomes at 3 months](http://stroke.ahajournals.org/)
seizures exert their negative effect mainly in the penumbral tissue because the penumbra is likely the origin of early seizure activity and thus also most affected by it.\textsuperscript{21} Seizures increase energy demand and metabolic stress and accelerate cell death in the already hypoperfused and vulnerable penumbral tissue. This is the most likely explanation for the negative effect of seizures on outcome.

Because of the small number of patients with early seizures, we cannot state whether early seizures before or during or after angiography have a more deleterious effect on outcome. We can only state that patients with a favorable outcome after early seizures had a lower baseline NIHSS, better collaterals, and less frequent ICH compared with those with an unfavorable outcome or those who died.

Early seizures after stroke are thought to result from a lower seizure threshold that is caused by local ionic shifts and possibly also extracellular release of excitotoxic neurotransmitters in the affected areas.\textsuperscript{25,29} As independent risk factors for early seizures, we identified asymptomatic hemorrhage ($P=0.019$; OR, 2.763; 95% CI, 1.185–6.442), higher baseline NIHSS ($P=0.041$; OR, 1.050; 95% CI, 1.001–1.101), and younger age ($P=0.021$; OR, 0.969; 95% CI, 0.945–0.994).

These results are in agreement with findings of patients with stroke without thrombolysis.\textsuperscript{5,6}\textsuperscript{29} Infection, diabetes mellitus, and history of transient ischemic attacks were identified as additional risk factors in the study of Krakow et al.,\textsuperscript{30} which included 58 874 patients. Radiological studies found cortical involvement and watershed infarcts as risk factors for seizures.\textsuperscript{31,32} The cause for co-occurrence of asymptomatic ICH or ICH in general (like found in other studies) and the prediction of early seizures is not clear. The plausible explanation that blood triggers epileptic activity cannot be corroborated by our findings because seizures occurred mainly before or during angiography, which represents probably a too early stage for ICH occurrence. An alternative explanation for the co-occurrence might be the size of the infarct because it is an independent predictor of both hemorrhagic transformation and first seizures and epilepsy.\textsuperscript{22,25,33–35}

Previous studies of prophylactic antiseizure therapy in stroke have given conflicting results.\textsuperscript{36} A recent postischemic seizure model in mice showed improved posts ischemic survival of animals with prophylactic phenytoin and diazepam treatment.\textsuperscript{28}

These animal data and our findings of a deleterious effect of early seizures raise the question whether immediate anticonvulsant therapy after early seizures or even prophylactic antiseizure therapy could improve outcome and reduce mortality. It indicates the need for further research to identify patients with stroke at risk for early seizures and to search for effective prophylaxis and treatment.

Our study has the inherent limitations of selection bias of the study of Krakow et al.,\textsuperscript{30} which included 58 874 patients. Radiological studies found cortical involvement and watershed infarcts as risk factors for seizures.\textsuperscript{31,32} The cause for co-occurrence of asymptomatic ICH or ICH in general (like found in other studies) and the prediction of early seizures is not clear. The plausible explanation that blood triggers epileptic activity cannot be corroborated by our findings because seizures occurred mainly before or during angiography, which represents probably a too early stage for ICH occurrence. An alternative explanation for the co-occurrence might be the size of the infarct because it is an independent predictor of both hemorrhagic transformation and first seizures and epilepsy.\textsuperscript{22,25,33–35}

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Our study has the inherent limitations of selection bias of a nonrandomized single-center study. Although our data were collected continuously and recorded in our database, they were analyzed retrospectively. Patients treated with endovascular therapy are highly selected and their strokes are much more severe compared with the average patient with stroke. Although the seizure rate in our study is similar to previous studies, the true poststroke seizure rate is probably underestimated; at least seizures occurring during relaxation and unobserved seizures will be missed and might influence our results. Furthermore, given the lack of an untreated control group, a causal association between early seizures and unfavorable outcome remains a hypothesis. Therefore, our results cannot be generalized to all ischemic strokes and need to be confirmed by further studies.

In conclusion, in our large cohort of patients with stroke treated with endovascular therapy, younger age, more severe strokes, and asymptomatic ICH represent risk factors for early seizures, and early seizures constitute an independent risk factor for death and unfavorable outcome. Our findings indicate that prophylactic anticonvulsant therapy in some patients with stroke might improve their outcome. However, before we can advocate this further, studies will have to confirm our results and the effect of prophylactic antiseizure treatment in severely affected stroke victims will have to be tested in randomized trials.

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Disclosures

None.

References


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