Intra-Arterial Thrombolytic Therapy for Acute Basilar Occlusion

Pro

Wade S. Smith, MD, PhD

Abstract—Acute thromboembolic occlusion of the basilar artery accounts for 6% to 10% of large-vessel stroke in humans. Because of the brain region supplied by this artery, the case fatality rate is the highest for all ischemic stroke subtypes, ranging from 40% to 86%. Patients who undergo successful recanalization of the basilar artery by intra-arterial thrombolysis have lower mortality of ≈39%. Considering all published series, a consistent survival benefit is predicted by revascularization (mortality 87% nonrecanalized compared with 39% recanalized; P<0.001). Although no large randomized studies of revascularization for acute basilar artery occlusion have been performed, it is unlikely that endovascular efforts are inferior to the natural history of the disease, and it is likely that patients benefit from this aggressive approach. (Stroke. 2007;38[part 2]:701-703.)

Key Words: endovascular ■ locked-in state ■ posterior circulation ■ prognosis ■ t-PA ■ treatment ■ urokinase

Acute basilar occlusion accounts for 6% to 10% of stroke in trials of large-vessel intracranial occlusion1,2 and remains the most mortal ischemic stroke subtype. Perhaps because of this high morbidity and mortality, it was one of the first types of stroke in which physicians attempted endovascular intervention. Multiple case series support the contention that intra-arterial (IA) thrombolysis works to open blood vessels, and such therapy has become standard in various comprehensive stroke centers. Yet, randomized data of the clinical efficacy of this treatment is lacking, in part because those who believe it works are uncomfortable randomizing such patients, and those who believe it is risky or provides no benefit are unlikely to take part in a randomized clinical trial; the extremely poor natural history of the disease limits the pool of physicians in equipoise. Only 1 randomized trial has been attempted but unfortunately was stopped prematurely because the thrombolytic drug (urokinase) was discontinued by the manufacturer; however, among the 16 patients enrolled, there was a trend toward better outcome in patients treated with thrombolysis.3 Because of this lack of prospective randomized data, there remains controversy as to whether IA thrombolysis should be offered to patients with stroke attributable to basilar occlusion. This review will take the affirmative position on offering IA thrombolysis and will support that position with 3 lines of evidence. First, the natural history of basilar occlusion is poor. Second, IA thrombolysis can open the basilar artery at a rate exceeding that of spontaneous thrombolysis. Thirdly, opening the basilar artery is associated with a substantial reduction in mortality and the neurological outcome among survivors is acceptable.

Natural History of Basilar Occlusion
After the initial systematic report of autopsy-proven basilar artery occlusion by Kubik and Adams,4 occlusion of the basilar artery has been associated with high mortality and extreme morbidity. The natural history of angiographically confirmed basilar occlusion has been reported in small series. Hacke et al reported as part of a consecutive clinical series of IA thrombolysis a group of 22 patients with angiographically confirmed basilar occlusion who were treated medically. Of the 22 patients reported, 19 (86%) died and 3 (14%) made a favorable recovery. In another study in 25 patients treated medically, 10 (40%) patients died and 9 (36%) had a good outcome.5

The spontaneous recanalization rate in basilar occlusions is not known. The closest benchmark for spontaneous recanalization of an intracranial vessel is the control group of the Prolyse in Acute Cerebral Thromboembolism (PROACT-II) trial.6 After angiographic documentation of complete middle cerebral artery occlusion within 6 hours of symptom onset, 18% of vessels recanalized 2 hours after the first angiogram while patients received intravenous heparin and no other intervention. This may overestimate the rate of spontaneous basilar occlusion because the etiology of basilar occlusion is more commonly in situ thrombosis of an atheromatous vessel, and middle cerebral artery occlusion is more likely embolic. Another estimate of spontaneous recanalization can be derived from reports of nonocclusion rates (documenting open cerebral vessels when the clinical suspicion is a large vessel occlusion).7 This rate is between 25% to 30% within 6 hours of stroke and around 50% in the first 3 to 4 days.7 This rate likely overestimates the true spontaneous recanalization rate

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of the basilar artery but helps establish an upper limit. Given both lines of evidence, it is likely that the rate of spontaneous recanalization of the basilar artery during a clinically meaningful time window (12 to 24 hours) is no higher than 20% and is likely much lower.

IA Thrombolysis Mitigates Basilar Occlusion

Three relatively large series of patients have been reported. In the first series, Hacke et al reported their consecutive experience with 43 patients. Only patients with CT evidence of significant infarcts were excluded; patients with coma and quadriplegia were included. Recanalization was achieved in 44%. Overall, 70% of patients died, but mortality was strongly dependent on whether the vessel recanalized: if the vessel was opened, 32% of patients died, compared with 100% (24/24) of patients who were not recanalized. Noncontemporary controls (reported above) had a mortality of 86%, suggesting that IA thrombolysis lowered mortality. Overall, 3 patients (6.9%) treated with IA thrombolysis had a symptomatic intracranial hemorrhage, compared with none in the control population.

In 1996, Brandt et al published a consecutive series of 51 patients treated with IA thrombolysis and found a higher rate of recanalization. These investigators excluded patients with CT documented infarct, or patients with deep coma and absence of brain stem reflexes for >4 hours. They achieved a recanalization rate of 51%, reported a mortality of 69%, and observed no symptomatic intracranial hemorrhages. They too found a significant dependence of survival on recanalization. Multivariate analysis of mortality showed that younger age, short-segment occlusion of the basilar, and recanalization independently favored survival, whereas nonrecanalization, absence of collaterals and longer length of basilar occlusion were independently associated with mortality.

The most recent large series by Eckert et al reported outcomes in 83 consecutive patients studied retrospectively. The recanalization rate was 66%, the highest of the 3 major series, with a lower mortality (66%) and a similar dichotomy in survival based on recanalization. Using univariate analysis, favorable outcome (Barthel Index >90 points) was associated with recanalization, embolic occlusion, and treatment before 6 hours of symptom onset.

Each of these series reports a recanalization rate that is higher than the approximate upper limit of 20% for spontaneous recanalization, suggesting that IA thrombolysis works to physically open the basilar artery.

Reduction in Mortality With Basilar Recanalization and Outcomes in Survivors

Because each case series of basilar thrombolysis differs in the clinical assessment at follow-up, the latency to follow-up, and the method of documenting good versus poor outcome, it is problematic to attempt a meta-analysis of clinical outcomes. Mortality is likely a more reliable outcome on which to combine the results of multiple case series. If it can be shown that mortality is significantly lower in patients who have successful recanalization compared with those whose arteries remain closed, it follows that IA thrombolysis likely reduces mortality. The reduction in mortality associated with successful recanalization of the basilar artery appears consistent across published case series. In the Table, all studies in the English literature are shown that reported mortality data dichotomized by recanalization. These 10 studies in aggregate involved 316 patients and reported an overall recanalization rate of 64% and 56% mortality. Overall, 37% of patients who recanalized died, whereas 87% died if recanalization was unsuccessful. This 48% absolute risk reduction of death is highly significant (P<0.001; Fisher exact test). It is unlikely that this remarkable mortality difference is confounded by iatrogenic deaths because the symptomatic intracranial hemorrhage rate was only 7% overall; therefore, the mortality seen in the nonrecanalized group is unlikely inflated by complications of the invasive procedure.

Outcomes among survivors of basilar occlusion who undergo IA thrombolysis have been reported in several follow-up studies. In a systematic review of all published series, using an intention-to-treat analysis, 23% of patients make a good outcome.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Recanalization</th>
<th>Mortality Overall</th>
<th>Mortality Recanalization</th>
<th>Mortality Non Recanalization</th>
<th>P Value</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hacke</td>
<td>43</td>
<td>44 (19)</td>
<td>70 (30)</td>
<td>32 (6/19)</td>
<td>100 (24/24)</td>
<td>&lt;0.001</td>
<td>6.9 (3)</td>
</tr>
<tr>
<td>Brandt</td>
<td>51</td>
<td>51 (26)</td>
<td>69 (35)</td>
<td>46 (12/26)</td>
<td>92 (23/25)</td>
<td>0.001</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Becker</td>
<td>12</td>
<td>75 (9)</td>
<td>75 (9)</td>
<td>67 (6/9)</td>
<td>100 (3/3)</td>
<td>n.s.</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Cross</td>
<td>20</td>
<td>65 (13)</td>
<td>65 (13)</td>
<td>46 (6/13)</td>
<td>100 (7/7)</td>
<td>0.044</td>
<td>6.7 (1)</td>
</tr>
<tr>
<td>Egger</td>
<td>15</td>
<td>80 (12)</td>
<td>33 (5)</td>
<td>17 (2/12)</td>
<td>100 (3/3)</td>
<td>0.022</td>
<td>6.7 (1)</td>
</tr>
<tr>
<td>Berg-Dammer</td>
<td>20</td>
<td>80 (16)</td>
<td>35 (7)</td>
<td>19 (3/16)</td>
<td>100 (4/4)</td>
<td>0.007</td>
<td>6.7 (1)</td>
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<tr>
<td>Silwack</td>
<td>36</td>
<td>56 (20)</td>
<td>53 (19)</td>
<td>35 (7/20)</td>
<td>75 (12/16)</td>
<td>0.023</td>
<td>6.7 (1)</td>
</tr>
<tr>
<td>Eckert</td>
<td>83</td>
<td>66 (54)</td>
<td>60 (50)</td>
<td>54 (29/54)</td>
<td>72 (21/29)</td>
<td>n.s.</td>
<td>8.4 (7)</td>
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<tr>
<td>Ezaki</td>
<td>26</td>
<td>92 (24)</td>
<td>27 (7)</td>
<td>21 (5/24)</td>
<td>100 (2/2)</td>
<td>n.s.</td>
<td>20 (2)</td>
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<td>Ostrem</td>
<td>10</td>
<td>80 (8)</td>
<td>30 (3)</td>
<td>25 (2/8)</td>
<td>50 (1/2)</td>
<td>n.s.</td>
<td>20 (2)</td>
</tr>
</tbody>
</table>

| Totals     | 316      | 64 (201)       | 56 (178)         | 39 (78/201)             | 87 (100/115)               | <0.001  | 7.0 (15/214) |

*Fisher exact test, differences between mortality of recanalization and nonrecanalization groups; **intracranial hemorrhage associated with clinical deterioration.

n.s., indicates not significant (P > 0.05),
However, if one considers the outcomes of those who survive, which is what is most relevant to patients and their families, clinical outcome is remarkably more optimistic. Considering the 3 largest case series, 71% (10/14) of surviving patients in one series had a good neurological outcome. Among the 16 survivors reported by Brandt et al., 63% (10/16) had no or slight deficits, 31% (5/16) had modified Rankin score of 3, and 6% (1/16) had a modified Rankin score of 5. In another series, outcomes were favorable in 57% (19/33). Recurrent rates of stroke after the initial basilar occlusion appears to be infrequent, likely because of use of successful secondary prevention strategies.

**Discussion**

The natural history of basilar occlusion is poor with mortality ranging from 40% to 86%. Clinical factors that increase the risk of death include older age, coma, quadriaparesis, time from stroke onset, presence of basilar atherosclerosis and absence of basilar artery collaterals. The basilar artery likely does not reopen spontaneously any more often than 20% within a clinically meaningful time window. IA thrombolysis likely significantly increases recanalization to 67% considering multiple case series. Recanalization is significantly associated with increased survival (absolute decrease in mortality of nearly 50%), and the clinical outcomes in survivors is favorable in 57% to 71%

Perhaps the most feared outcome in any stroke therapy is saving the life of a patient only to commit the patient to a life of severe disability. This is no more significant a concern than it is for basilar occlusion because of the fear that a patient could survive but be “locked in”. This disability is perhaps best described by a patient who experienced this fate and wrote of his experience using eye movements alone. It is essential that the physician enter a dialog with the patient and the patient’s family as to the uncertainty of the data that exist currently and tailor clinical decisions to the individual. It is important to clarify the concept of outcome in survivors, rather than potentially confuse patients about intention-to-treat analysis because most patients want to know 2 things: “Will I die?” and “If I live, what will I be like?” The case series reviewed here can provide some answers if the patient is taken for endovascular therapy, and as clinicians, it is our responsibility to translate what is known and arrive at a clinical decision. I have also been influenced by remarkable patient successes in our own hands. My answers to the questions are “If we do nothing, it is likely that you will die” and “If we go to the angiography suite, and you survive, your chance of doing well is better than 50:50”. What I can’t answer is what is the best treatment method (IA versus IV), IA plus IV, device versus thrombolytic, or device plus thrombolytic. A randomized trial could help to clarify some of this, and if a control arm is included, we would be closer to the claim that a particular treatment is superior. However, given the proven difficulty in performing a randomized trial, it is unlikely that this quality of data will be available soon. So, the next time you meet someone in your emergency department with an acute basilar occlusion, what will you say and do? I will continue to recommend endovascular methods for this disease.

**Disclosure**

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**References**

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