Long-term Outcome After Intravenous Thrombolysis of Basilar Artery Occlusion

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Context Basilar artery occlusion (BAO) is an infrequent disease with high morbidity and mortality. Intra-arterial thrombolysis is advocated for treatment but is limited to use at specialized centers.

Objective To evaluate outcomes for patients with BAO treated with intravenous thrombolytic therapy.

Design, Setting, and Participants During 1995 to 2003, 50 consecutive patients with angiographically proven BAO were treated according to an institutional therapy protocol based on intravenous thrombolysis with recombinant tissue plasminogen activator (alteplase). Patients were treated at an urban university teaching hospital receiving all patients with ischemic stroke who were considered for thrombolysis in a catchment area of 1.5 million inhabitants in Helsinki, Finland.

Intervention Intravenous administration of alteplase (0.9 mg/kg) during a 1-hour infusion.

Main Outcome Measures Basilar artery recanalization determined by magnetic resonance angiography and clinical outcomes at 3 months and at 1 year or longer determined by modified Rankin Scale and Barthel Index scores.

Results Recanalization was studied in 43 patients and verified in 26 (52%) of all patients. By 3 months, 20 patients (40%) had died while 11 had good outcomes (modified Rankin Scale score, 0-2); 12 (24%) reached independence in activities of daily living (Barthel Index score, 95-100), and 6 (16%) were severely disabled (Barthel Index score, 0-50). In the long term (median follow-up 2.8 years), 15 patients (30%) reached good outcomes (modified Rankin Scale score, 0-2) while 23 (46%) died.

Conclusions Intravenous administration of alteplase for patients with BAO appears to be associated with rates of survival, recanalization, and independent functional outcome comparable with those reported with endovascular approaches. These data suggest that a randomized trial is needed to compare these approaches for treatment of BAO.

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For editorial comment see p 1883.

METHODS

With a catchment area of 1.5 million, the Helsinki University Central Hospital annually admits 20 to 30 stroke emergencies with BAO. Thrombolysis for BAO represented 20% of all strokes treated with thrombolytic therapy at our center. The primary inclusion criteria for this study were an angiographically verified (magnetic resonance angiography [MRA] or digital subtraction angiography) BAO and a consistent clinical syndrome of severe posterior circulation strokes that account for about 20% of ischemic strokes. Basilar artery occlusion has a dismal natural course and the mortality rate is 85% to 95% even with anticoagulant and fibrinolytic therapy if the artery is not recanalized.1,2 Transient prodromal symptoms are common, but complete BAO precipitates a sudden or gradually progressing clinical syndrome. The most devastating sequela is the locked-in state.3 Randomized trial data on the efficacy of recanalization therapies do not exist,4,5 and many stroke centers have adopted ad hoc BAO thrombolysis protocols, mainly with intra-arterial approaches.

Previous reports3,4,6,7 have advocated thrombolytic therapy delivered with an invasive endovascular approach to the occlusion site of the posterior circulation, but even short delays in therapy onset have been reported to be the single most critical factor affecting outcome.2 We report the results of the first 50 consecutive patients with proven BAO treated according to our institutional protocol.8 Due to unacceptable delays, we changed our approach to treatment of BAO from intra-arterial to noninvasive intravenous delivery of alteplase (recombinant tissue plasminogen activator [rtPA]), a protocol used in anterior circulation strokes.9
circulation ischemia in a previously independently functioning person. The onset could be preceded by nonspecific, transient prodromal symptoms before sudden dense symptoms or gradually progressing acute phase. For patients with sudden disturbance of consciousness and tetraparesis, the protocol allowed treatment delays up to 12 hours, and for patients with gradually increasing symptoms such as ophthalmoplegia, dysarthria, and bilateral weaknesses, treatment delays up to 48 hours were permitted. The treatment time (symptom-to-needle time) was defined as the interval between the onset of brainstem symptoms that did not resolve and the onset of rtPA infusion. Magnetic resonance angiography was performed on a 1.5-T imager (Siemens Vision; Siemens Medical Systems, Erlangen, Germany) with a standard 3-dimensional time-of-flight (TOF) sequence. Raw images were evaluated to determine vessel patency.

Exclusion criteria were widespread ischemic changes and any signs of intracranial bleeding on computed tomography (CT). Limited or unilateral hypodensity of the brainstem was not an exclusion criterion provided the patient still had spontaneous breathing, whereas absence of all brainstem reflexes was an exclusion. Because the BAO therapy protocol was an institutionally accepted management guideline, formal ethics committee approval was not applicable. Nevertheless, we obtained oral informed consent from each patient or next of kin.

After considering our general criteria for stroke thrombolysis and the BAO therapy protocol, patients with suspected BAO based on the initial CT were immediately treated with standard full-dose anticoagulation with unfractionated heparin adjusted to maintain activated partial thromboplastin time between 50 and 100 seconds. Intravenous labetalol was given as necessary to stabilize arterial blood pressure below 185/105 mm Hg. Alteplase (0.9 mg/kg) was infused (10% as a bolus) in 1 hour. Repeat MRA examinations were carried out the next day. If only partial vessel recanalization was found and the patient's condition deteriorated during follow-up with intracranial hemorrhage ruled out, or if reoclusion took place, intravenous abciximab (0.6 mg/h) was administered as rescue therapy (to a total of 4 patients). Four patients with systemic hypotension were treated with norepinephrine or dopamine. Parenteral anticoagulation was continued until oral warfarin therapy could be administered and reached the desired level of anticoagulation. Sedatives (diazepam or propofol) were given as required to permit imaging.

Following thrombolysis in the emergency department, patients were transferred to the stroke unit for individualized early rehabilitation by multidisciplinary personnel and for workup of etiology. A 3-month outcome follow-up was performed for survivors by a stroke neurologist and a study nurse. It included the modified Rankin scale (mRS): no or minimal symptoms (0-1), mild to moderate disability (2-3), severely disabled or bedridden (4-5), dead (6); and the Barthel Index score: functional independence (95-100), moderate dependency (90-55), full dependency (50-0). For patients institutionalized or still in a rehabilitation hospital, scoring was performed by the treating physician and the nurse, determined from patient records, or by contacting the patient or relatives.

In addition, the functional outcome (Barthel Index, mRS) during the late follow-up (12 months to several years later) was obtained by a stroke study nurse assisted by a stroke neurologist via telephone conversation with a family member or the nursing institute. At the same time, we assessed—from a year to several years after thrombolysis—perceived quality of life using a modification of a standardized questionnaire that assessed the patient's satisfaction with 10 different aspects of life (going out, walking, activities, physical health, personal care, happiness, communication, sleep, recreation, and family, along with an overall average score) on a 10-point scale. (The questionnaire is available on request.) Surviving patients or their caretakers either completed and returned a mailed survey or answered the survey questions in a telephone conversation with standard instructions provided by the same study nurse.

Although our patients form a prospective series based on predefined published criteria, and the 3-month data were collected prospectively, all patient records also were reexamined to ascertain all parameters, including the type of clinical presentation, treatment delays, possible protocol violations, hemorrhagic complications, and the most probable etiology. Recanalization, either partial or complete, was estimated based on TOF images performed after the thrombolysis. However, in 5 patients recanalization was presumed to have occurred by distinctive postthrombotic clinical improvement followed by confirmation on MRA obtained several weeks later. If the patient had a known cardiac embolic source such as atrial fibrillation, or patent foramen ovale, with sudden symptom onset and the occlusion located typically distally in the basilar artery, cardioembolic etiology was presumed. The etiology was presumed atherothrombotic if the arterial contour was stenotic and/or severely affected by atherosclerosis after recanalization in the absence of cardioembolic findings.

Distributions of the continuous variables were assessed with the Shapiro-Wilk test. We carried out the univariate analysis using a t test or Mann-Whitney U test, as appropriate. Dichotomous variables were compared with a χ² test or 2-tailed Fisher exact test. Association of quality-of-life scales to the degree of disability and outcome scale was evaluated with Spearman rank correlation coefficient. A 2-tailed P<.05 was considered statistically significant. We used the statistical software Statistica, version 5.5 (StatSoft, Tulsa, Okla).

RESULTS
Of the 50 consecutive patients with BAO treated with intravenous throm-
bolic therapy from 1995 to mid-2003, 13 were women and 37 men, with a mean age of 61.9 (range, 27-84) years. The mean (SD) admission blood pressure was 151 (27) mm Hg systolic and 84 (15) mm Hg diastolic, and labetalol was administered to 15 patients. The mean (SD) admission blood glucose concentration was 137 (39.5) mg/dL (7.6 [2.2] mmol/L) and hemoglobin, 14.1 (1.6) g/dL. The most commonly diagnosed cardiovascular risk factors were hypertension (40%), coronary artery disease (26%), atrial fibrillation (24%), previous transient ischemic attack/stroke (22%), generalized atherosclerosis (8%), hemostatic abnormality (6%), peripheral artery disease (8%), and type 1 or 2 diabetes (4%).

The mean symptom-to-needle time was 9 hours in patients classified as having the sudden-onset type of BAO (n=26) and 17.5 hours in patients with gradually progressing symptoms (n=24). Twenty-three patients (46%) were unconscious, and 38 (76%) were intubated. Thirty patients (60%) needed respiratory support to maintain adequate ventilation or for sedation, and 9 patients (18%) with reduced consciousness received mechanical ventilation without sedation. The major etiologic conditions were vertebrobasilar atherothrombosis (44%), cardiombolism (32%), and dissection of the vertebral artery (14%).

Basilar artery occlusion was diagnosed using MRA in 45 patients, DSA in 3, and by both methods in 2 patients. Recanalization was reinvestigated with MRA (TOF) after thrombolysis (median, 1.0 days; interquartile range, 1-3 days) in 43 patients and confirmed as complete or partial in 26 of these (60%; 52% for the whole cohort). The main reason for not repeating MRA was an unimproved clinical condition with an obviously poor prognosis. The recanalization rate was 60% in both cardioembolic and atherothrombotic BAO and 71% in vertebral artery dissection. Following rtPA treatment, 12 patients had intracranial hemorrhage; 4, multifocal hemorrhages; 1, subarachnoid; 3, intraparenchymal; and 4, asymptomatic hemorrhagic transformations. Seven hemorrhages (14% of all 50 patients) were symptomatic based on acute worsening of the patients’ neurologic condition.

At 3 months, 20 patients had died (40% case-fatality rate). Nine patients (18%) died within 7 days and 6 (12%) died within 30 days. The case-fatality rate was 12% (3/26) in patients with partial or complete recanalization and 71% (17/24) in those with no evidence of recanalization (Fisher exact test, P<.001). The case-fatality rate was also significantly higher in patients who were unconscious on admission (13/23 vs 7/27; χ² test, P=.03). None of the 7 symptomatic hemorrhages occurred in patients with evidence of recanalization (Fisher exact test, P=.003).

At 3 months, 11 patients (22%) scored 0 to 2 on mRS (good outcome), and 12 patients (24%) were independent in activities of daily living (Barthel Index score, 95-100) (FIGURE). Eight patients (16%) were fully dependent, scoring 0 to 50 on the Barthel Index. None of those with failed recanalization were independent at 3 months, whereas 46% of those with verified recanalization were independent at 3 months, whereas 46% of those with verified recanalization were independent at 3 months, whereas 46% of those with verified recanalization were independent at 3 months...
clusion or exclusion criteria of our institutional protocol. In these cases, the treating physicians together with the relatives deliberately agreed on thrombolysis as the last resort for survival. Two such patients did not fulfill the inclusion criterion of prestroke functional independence and scored 3 and 4 on the mRS. Three patients’ symptom-to-needle times were too long (exceeding the 12-hour limit by 13 to 50 minutes). In 5 patients, there were CT exclusion criteria of widespread posterior circulation and brainstem infarcts. Another 2 instances had both of these exclusion criteria. In the per protocol treated patients, the case-fatality rate was 32% and the functional outcome was better (Figure).

During the extended follow-up (median follow-up time, 2.8 years; interquartile range, 1.1-4.2 years), the condition of 8 survivors improved as assessed by the mRS and 5 deteriorated. Individuals with mRS scores of 4 to 2 often improved, while those with the most severe disability at 3 months (5) did not maintain this score (3 died and 2 improved to score 4). In the long term, 30% (15/50) of the patients reached good outcome (mRS score, 0-2) while 46% (23/50) died. Of patients treated per protocol, 34% (13/38) reached good outcome. Two patients with failed recanalization eventually did reach good outcome (2 and 1 on the mRS, 85 and 100 on the Barthel Index). Patients with good long-term recovery were not significantly younger than those with poor outcome (mean, 59.8 vs 63.5 years; P=.20).

The quality-of-life assessment was performed in 23 of the 27 survivors after a mean (and median) follow-up time of 2.9 years (interquartile range, 1.5-4.6 years). The range of the total scores was 20 to 99 (possible range, 0-100; best score, 100 [mean, 71.7; median, 74]). The 2 lowest scores were 20 and 37 and the rest exceeded 50. The mean scores for the specified 10 items were above mid point (range, 5.9-8.4; SD, 1.7-3.6), and the median values were consistently higher (range, 7-9). The total scores were strongly correlated with the Barthel Index (R=0.65, P<.001) and with the mRS (R=−0.79, P<.001).

**COMMENT**

In this case series of 50 patients with BAO treated with intravenous thrombolysis, the overall recanalization rate was 52%, the likelihood of good outcome (mRS score 0-2 or Barthel Index score 95-100) was 24%, and survival at 3 months was 60%. These outcomes are equal or more favorable than outcomes achieved with intra-arterial endovascular thrombolytics in series of similar size and in a meta-analysis. The case-fatality rates in the meta-analysis summarizing data from 164 patients and in a recent series of 83 patients, which also included distal bilateral vertebral artery occlusions, were 67% and 60%, while it was 40% in our series. We included many unconscious patients, those with extensive baseline infarctions, and elderly patients. In anterior circulation stroke, the recommendation is to treat as soon as possible with intravenous rtPA, and the sooner rtPA is administered the greater the benefit. We cannot find an a priori reason that BAO should be treated differently, thereby preventing the unavoidable delays incurred by invasive endovascular procedures. Intravenous rtPA may be a reasonable alternative and an efficient way to provide thrombolysis in this devastating disorder.

We excluded patients with widespread ischemic changes on initial CT, typically involving several posterior circulation territories, even extensively in some cases of protocol violation. Limited/unilateral hypodensity of the brainstem was not an exclusion criterion if the patient still breathed spontaneously. Although many earlier series of BAO thrombolysis excluded patients with brainstem infarctions, our series had at least equally high prevalence of unconsciousness (46%), and the majority of patients (60%) eventually needed mechanical ventilation. Thus, despite differences in the initial diagnosis, our cohort had at least comparably severe posterior circulation symptoms as did earlier series of BAO thrombolysis.

Physicians treating patients with stroke and reduced consciousness, immediate need of assisted ventilation, and established brain damage may find it difficult to justify rescue therapies without scientific proof and question their long-term implications to the patient and his/her family. Although unconsciousness has been noted as a predictor of death, unconsciousness as the presenting symptom in our cohort did not preclude good outcome. Without thrombolysis, unconsciousness in BAO invariably predicted a fatal outcome. Our data suggest that the condition of survivors who initially stabilize at the poorest outcome (mRS score, 5) tend to either decease or improve in the long term. Eventually, half of recanlized patients will reach good outcome (mRS 0-2). Differences in imaging methods may compromise the comparison of our recanalization rates to those of studies using intra-arterial thrombolysis protocols.

Survivors in our study reported fair quality of life, based on a simple scale of perceived well-being. The average scores of the equivalent items compare well with those reported in adults with and without chronic disease. The fair quality of life of survivors also supports the use of intravenous thrombolysis in view of the higher survivorship achieved in our series.

A limitation of this study is that we lacked a comparison group to show the safety and efficacy of our thrombolytic protocol, but nonrecanlized BAO allowed only 4% chance of good outcome in the long term. The safety of intravenous thrombolysis of BAO was supported by the fact that symptomatic hemorrhages occurred only to patients without recanalization. This cohort had relatively long symptom-to-needle times, which have recently improved by the use of CT angiography instead of CT followed by MRA.

Endovascular techniques have been proposed as the optimal treatment for BAO but without referring to data on
the noninvasive approach.5,7 We now report the highest rates of survival and good outcome in BAO published so far, based on use of intravenous rtPA, which is more noninvasive, quicker, and more widely available than endovascular techniques (which require neuroradiological interventionist service). Despite these findings from our case series, the evidence is not sufficient to recommend a change in treatment guidelines. A randomized multicenter trial is needed to directly compare intraarterial and intravenous thrombolysis in BAO. Until results of such a study become available, centers unequipped with 24-hour access to immediate invasive neuroradiology may consider noninvasive thrombolysis once the diagnosis of BAO is confirmed.

**Author Contributions:** Drs Lindsberg and Soinne had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Lindsberg, Soinne, Kaste.

**Acquisition of data:** Lindsberg, Soinne, Tatlisumak, Roine, Kallela, Häppölä.

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**Statistical analysis:** Lindsberg, Soinne.

**Administrative, technical, or material support:** Tatlisumak, Kaste.

**Study supervision:** Lindsberg, Kaste.

**REFERENCES**


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Every great mistake has a halfway moment, a split second when it can be recalled and perhaps remedied.
—Pearl S. Buck (1892-1973)