Intra-Arterial Thrombolysis for Basilar Artery Thrombosis

Trial It

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Abstract—The poor prognosis for recovery of basilar artery thrombosis has led to the adoption at many institutions of intra-arterial thrombolysis as part of clinical care. However, because neither randomized clinical trials nor observational data provide evidence for treatment efficacy and there are substantial risks and costs associated with this procedure, this treatment should only be performed in the context of a randomized, controlled clinical trial subject to appropriate Institutional Review Board review and independent safety monitoring. (Stroke. 2007;38[part 2]:704-706.)

Key Words: acute stroke ■ brain stem stroke ■ thrombolysis ■ thrombolytic Rx

In 1946, Kubik and Adams described the clinical syndrome of progressive brain stem dysfunction in association with thrombosis of the basilar artery at autopsy.1 While this seminal article greatly increased our knowledge of the pathophysiology of posterior circulation stroke, it provided a picture of the clinical presentation and outcome of basilar artery thrombo-occlusive disease that was skewed toward more severe cases. Initial case series described mortality of 75% to 86% based on patients who underwent arteriography because of their severe clinical presentation.2-3 These reports of almost universally disastrous outcome, even in patients treated with anticoagulation, led to the search for new treatments for this condition. In the early 1980s, intra-arterial infusion of thrombolytic agents began to be used to treat acute basilar artery occlusion.4 Since then, this approach has become more widespread and is currently practiced in a variety of institutions with a variety of different eligibility criteria and time windows.5 In this article, we shall examine the quality of the evidence for intra-arterial thrombolytic therapy for basilar artery occlusion to determine whether it is sufficient to establish clinical efficacy.

When physicians consider available evidence regarding treatment decisions, they are generalizing from results obtained in people other than the individual patient under consideration. The strength of these generalizations depends on the quality of the data. Systematic reviews of methodologically strong randomized clinical trials with consistent results provide the strongest evidence for generalization. Strong evidence can also be gleaned from single well-conducted clinical trials as long as it has enrolled a wide spectrum of patients. Data from nonrandomized observational studies provide considerably weaker evidence. Data based on physiological end points or uncontrolled case series provide the weakest evidence of all.6

Randomized clinical trial data for intra-arterial thrombolytic therapy for basilar artery occlusion is restricted to a single small study that was prematurely terminated.7 This study enrolled patients between ages 18 and 85 who were judged to be suitable for long-term anticoagulant therapy, had acute ischemic posterior circulation stroke considered to be attributable to occlusion of a major vessel and in whom a first dose of medication could be administered within 24 hours after onset. Those with lighter ischemic symptoms (Glasgow Coma scale <9 for at least 6 hours before entry) were excluded. Patients were randomized to receive treatment with intra-arterial urokinase or control. All received heparin to an activated partial thromboplastin time of 60 to 80 seconds for a minimum of 2 days and then oral warfarin. Clinical efficacy was determined in 6 months by the Barthel and Rankin scales. When 16 patients had been randomized, the study was terminated because of slow recruitment and withdrawal of the sale of urokinase in Australia. In the 8 patients who receive thrombolysis, 4 died and the median Rankin scale was 1 in the survivors. In 8 patients in the control group, 4 died and the median Rankin score was 3 in the survivors. Analysis of these data for favorable outcome by Fisher exact test shows an insignificant difference (P=0.28). This randomized clinical trial showed no significant difference in outcome between the 2 groups although it did suggest a benefit for thrombolytic therapy. However, it is certainly too small and the results are not sufficient to provide randomized clinical trial evidence for the general application of intra-arterial thrombolytic therapy to patients who meet the study eligibility criteria.

Observational studies are generally considered to be inferior to randomized controlled clinical trials for evaluating treatment efficacy because of bias that may be introduced by nonrandom-assignment patients to treatment and control arms.
and unmasked (nonblinded) assessment of treatment efficacy. However, not every treatment requires a randomized clinical trial to establish efficacy. Observational studies may provide compelling evidence of treatment efficacy if treatment effects are sufficiently large and consistent. Thus, the following 2 conditions must be met: (1) outcomes in untreated patients are consistent; and (2) outcomes in treated patients are consistently superior by a large margin.

Examples of observational studies that provide compelling evidence for treatment decisions by fulfilling the above criteria include the use of insulin for the treatment of diabetic ketoacidosis and the use of antibiotics for the treatment of meningococcal infections. Do the observational data available for intra-arterial thrombolytic therapy provide similar compelling evidence and preclude the need for a randomized trial to establish efficacy?

A review of the observational data available from small selected case series regarding the outcome of patients with basilar artery thrombosis not treated with intra-arterial thrombolysis reveals data that are far from consistent. Some report poor outcome in 60% to 90% of patients. Other reports have selected patients specifically to demonstrate that favorable outcome may occur. Four recent hospital-based observational studies of basilar artery occlusion treated without intra-arterial thrombolytic therapy have shown much better outcomes that many of the previous reports. In a series of 40 patients from Samsung Medical Center, 12 (30%) had a favorable outcome defined as a modified Rankin score of 0 to 2. In a study of 26 patients (Group A with angiographically or autopsy-proven disease) from 3 hospitals in Europe, 9 (36%) had a favorable outcome. Six of 9 patients (67%) in the Lausanne Stroke Registry had favorable outcomes. Data from the New England Medical Center posterior circulation registry reported favorable outcome in 59% of patients with basilar artery occlusion. This latter study probably gives the best idea of the spectrum of outcome in this condition since was based on a prospectively collected data in consecutive patients with symptomatic vertebral basilar territory ischemia.

In the observational trial of patients with basilar artery occlusion treated with intra-arterial thrombolysis, the reported treatment effect is insufficient to provide strong evidence for efficacy when compared with the data cited above. Lindsberg and Mattle have recently reviewed data on 344 patients from 11 different publications who were treated with intra-arterial thrombolytic therapy for acute basilar artery occlusion. Good outcome was achieved in 17% to 40% cases with a mean value of 24%. Those treated within <6 hours did not have a better outcome than those treated after 6 hours. These values are not superior to the 30% to 67% good outcomes in patients who did not receive intra-arterial therapy reported in 4 recent hospital-based series cited above. However, such comparisons across observational studies are problematic because of differences in eligibility criteria and in definitions of favorable outcome among the different studies. In 1988, Hacke et al published an observational study in which they compared 43 patients who receive intra-arterial thrombolytic therapy for vertebral basilar thrombosis to 22 historical controls from their center using the same outcome definition. In this study, they reported a highly significant benefit of intra-arterial thrombolysis in producing favorable outcome ($P = 0.017$) and survival ($P = 0.0005$). However, this conclusion was based on a flawed comparison of 22 controls to only those 19 patients in whom successful recanalization was achieved, not to the total group of 43 who underwent thrombolytic therapy. This analytic approach is not valid. Spontaneous recanalization of basilar artery occlusion occurs in a substantial number of patients. Patients with high levels of plasminogen activator inhibitors have both reduced recanalization to exogenous thrombolytic agents and reduced endogenous thrombolysis. Thus, selecting only those patients with successful recanalization to exogenous thrombolytic agents will also select those with the best chance for spontaneous endogenous thrombolysis. Comparing this selective subgroup to the full spectrum of control patients will yield an invalid, overestimation of the treatment effect. The more appropriate analysis based on the intention-to-treat principle reveals that favorable outcome was achieved in 10 of 43 treated patients and 3 of 22 untreated patients ($P = 0.22$). This study actually failed to demonstrate, even with the use of historical controls, any significant benefit for intra-arterial thrombolytic therapy in this condition. Thus, the observational data for the use of intra-arterial thrombolytic therapy for basilar artery occlusion do not meet the criteria necessary to provide compelling evidence of treatment efficacy.

Nevertheless, given that the outcome in patients who present with severe neurological deficits is generally poor, what is the harm in attempting intra-arterial thrombolysis? If the treatment carried no risk or expense, then there could be no adverse clinical or monetary consequences and this would be a reasonable approach to take, even in the absence of any evidence for efficacy. Unfortunately, this therapy is not without either risk or expense. The risk of symptomatic hemorrhage is 8% and these may be fatal. Costs for thrombolytic drugs ($1000 to $3000), cerebral arteriography ($4000 to $8000) and an intensive care unit bed ($2300 to $3000 per day) add substantial burdens to a healthcare system that is already strained with no room to grow. These procedural risks and expenses can be justified only if the treatment is sufficiently effective to provide an improvement in clinical outcome to outweigh the procedural risks and a reduction in long-term costs to outweigh the procedural expenses. In the absence of evidence for efficacy, the procedural risks and expenses remain with nothing to outweigh them.

In conclusion, neither randomized clinical trials nor observational data provide evidence for efficacy of intra-arterial thrombolysis for basilar artery occlusion. There are substantial risks and expenses associated with this procedure. Unless efficacy has been proven, it is erroneous to assume that there are improvements in clinical outcome or long-term cost savings that outweigh the procedural risks and expenses. Intra-arterial thrombolytic therapy for basilar artery occlusion simply puts patients at risk and increases the cost of medical care without any good evidence that it helps. Therefore, this treatment is not justifiable as clinical care, even in selected patients. Further research is necessary to determine whether there is any benefit in either functional outcome or cost savings. This determination can never be made if the therapy
continues to be used without concurrent randomized control patients. Therefore, intra-arterial thrombolysis for basilar artery thrombosis should only be performed in the context of a randomized, controlled clinical trial subject to appropriate Institutional Review Board review and independent safety monitoring.

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**Disclosures**

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**References**

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