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The Safety and Efficacy of Thrombolysis for Strokes After Cardiac Catheterization

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Objectives The purpose of this study was to systematically compare clinical outcomes of patients treated with thrombolysis with those without treatment in a multi-year, multicenter cohort of strokes after cardiac catheterization.

Background Ischemic strokes after cardiac catheterization procedures, although uncommon, lead to the morbidity and mortality of thousands of patients each year. Despite the availability of Food and Drug Administration–approved thrombolytic therapy for acute ischemic stroke since 1996, thrombolysis remains unestablished in the setting of cardiac catheterization, owing to unique concerns regarding safety and efficacy.

Methods Consecutive cases of ischemic stroke after cardiac catheterization were abstracted retrospectively and reviewed by clinicians at 7 major North American academic centers with acute stroke teams. Safety and efficacy outcome measures were pre-defined.

Results A total of 66 cases of ischemic strokes after cardiac catheterization were identified over 3 to 4 years; 12 (18%) were treated with thrombolysis, consisting of 7 intravenous and 5 intra-arterial recombinant tissue plasminogen activator cases. Improvement in stroke symptoms, as measured by the primary efficacy measure of median change in National Institutes of Health Stroke Scale score from baseline to 24 h, was greater in treated versus nontreated cases ($p < 0.001$). Additional secondary measures of efficacy also showed better outcomes in the treated group. There were no significant differences in bleeding events, defined as symptomatic intracerebral hemorrhage, hemopericardium, or other systemic bleeding resulting in hemodynamic instability or blood tranfusions. Mortality rates were also similar.

Conclusions Thrombolysis might improve early outcomes after post-catheterization strokes and seems safe in this context. Emergent cerebral revascularization should be a routine consideration. (J Am Coll Cardiol 2008;51:906–11)

More than 2 million cardiac catheterization procedures are performed in the U.S. annually. Although strokes after cardiac catheterization (SCCs) are relatively rare, this high volume of cardiac catheterizations in the U.S. leads to thousands of SCCs each year. Rates of SCCs, including both ischemic and hemorrhagic subtypes, range widely from 0.07% to 7.0%. Large contemporary registries of exclusively diagnostic and invasive coronary procedures report rates from 0.07% to 0.38%, and smaller studies of other invasive studies report higher rates (1).

See page 912

The majority of SCCs are likely ischemic infarcts, for which there is Food and Drug Administration–approved therapy. Intravenous thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) within 3 h of ischemic stroke symptom onset has been shown to be efficacious and cost-effective in the general stroke population (2,3). Unfortunately, this proven therapy is provided to

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only a small fraction of all ischemic strokes, primarily owing to delayed presentation to emergency departments (4). In addition, intra-arterial thrombolytic drugs and devices might be effective at later time windows (5,6). The SCCs typically occur in hospitalized patients under close observation and therefore offer the potential for early and rapid detection and treatment. However, there is debate about the safety and efficacy of thrombolysis in the peri- and post-cardiac catheterization setting (7,8).

No study has yet attempted to systematically collect data on all SCCs and characterize their treatment in either a single or multicenter cohort. Therefore, we designed a retrospective cohort study of consecutive SCCs managed at major academic stroke centers with organized stroke teams, and we compared outcomes of patients treated with thrombolysis to those without treatment. We hypothesized that (1) intravenous and intra-arterial thrombolytic therapy for strokes in the cardiac catheterization setting would be relatively safe, with complication rates comparable to SCCs not receiving thrombolytic therapy, and (2) patients treated with thrombolytic therapy would have better outcomes than those not treated with thrombolysis.

Methods

We invited 15 academic centers with stroke teams to contribute, and 7 centers (National Institutes of Health Stroke Center, New York Presbyterian Hospital-Weill, University of Calgary, University of California Los Angeles, University of Cincinnati, University of Iowa, University of Pennsylvania) elected to participate. A designated principal investigator at each participating center identified potential patients by reviewing all medical records or their existing stroke databases with both a stroke diagnosis (International Classification of Diseases of the World Health Organization-9th edition [ICD-9] codes: 997.02, 436, 433.0–433.3, 433.8–434.1, and 434.9) and a cardiac procedure (ICD-9 codes: 36.01–337.21–37.23, 37.26, 37.27, 37.34, 88.52–88.57) during the same admission. Cardiac procedures included left heart catheterization, coronary angiography, coronary angioplasty or stenting, left ventriculography, valvuloplasty, patent foramen ovale/atrial septal defect (PFO/ASD) closure, and electrophysiologic diagnostic and ablative studies. Seven centers collected cases from September 2000 to September 2003, and 1 center collected data from September 2000 to September 2004. At each center, all consecutive ischemic strokes within 36 h of cardiac catheterization were included, regardless of the indication for cardiac catheterization, post-stroke treatment decision, or outcome. A clinician collected the following de-identified information on standardized case report forms: demographic information, medical history, cardiac catheterization technical details, post-stroke course, stroke localization and etiology, complications, and clinical outcome. National Institutes of Health Stroke Scale (NIHSS) scores were determined with data in the medical records, which is considered a highly reliable approach (9). This protocol received institutional review board approval at each institution under expedited or exempted mechanisms. Data were entered into spreadsheets with double-entry.

Abbreviations and Acronyms

CT = computed tomography
ICH = intracerebral hemorrhage
NIHSS = National Institutes of Health Stroke Scale
rt-PA = recombinant tissue plasminogen activator
SCC = stroke after cardiac catheterization

The pre-defined primary efficacy outcome measure was the change in NIHSS score from baseline to 24 h in the rt-PA group, compared with non–rt-PA group. Categorical analyses were also performed, comparing the proportions of patients with complete resolution (NIHSS = 0) or ≥5-point improvement from baseline to 24 h in both groups. We also planned secondary analyses excluding the mildest stroke cases (NIHSS <5), in anticipation of these patients being excluded from thrombolytics (10). Additional pre-specified secondary outcome measures were 7- and 30-day NIHSS scores, discharge modified Rankin Scores (mRS), and death during hospital stay.

The pre-defined primary safety measures were the rate of significant bleeding events and the rate of mortality during the hospital stay, comparing the rt-PA to the non–rt-PA group. Data on all bleeding events were collected, including puncture site hemorrhage, retroperitoneal hemorrhage, hemopericardium, and symptomatic and asymptomatic intracerebral hemorrhage (ICH) within 48 h of stroke. Significant bleeding events were defined as those requiring blood transfusion or causing hemodynamic instability and those specifically consisting of hemopericardium or symptomatic ICH. The ICHs were defined as "symptomatic" if the patient had any symptoms attributed to a new ICH by the local principal investigator. All transfusions given during the hospital stay were recorded on case report forms to ensure that bleeding events were not missed due to lack of documentation.

Statistical analysis. Patient characteristics were compared with unpaired *t* tests (age) and Wilcoxon rank sum test for variables that were not normally distributed (NIHSS and time factors). Chi-square or Fisher exact tests were used for categorical variables, depending on individual cell sizes.

Power calculations were difficult a priori. Assuming alpha = 0.05, power = 80%, and planned convenience sample of approximately 100 patients, we estimated an ability to detect a 5-point difference in NIHSS (primary efficacy outcome) between rt-PA cases and control subjects if only 9 cases were treated with rt-PA. A smaller total would be needed if more patients received thrombolytics.

Results

A total of 66 SCCs were identified; 12 (18%) were treated with thrombolysis: 7 with intravenous rt-PA, and 5 with intra-arterial rt-PA. Age, medical comorbidities, and car-