Endovascular Recanalization Therapy in Acute Ischemic Stroke

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Background and Purpose—To assess the outcome in acute ischemic stroke patients not eligible for systemic thrombolysis (outside the 3-hour time window, after surgery, or on anticoagulant) undergoing endovascular recanalization therapy (ERT) at the Columbia University Medical Center (CUMC) and to determine US nationwide usage and outcome of ERT in acute ischemic stroke.

Methods—Patients treated at CUMC from 2001 to 2004 and the Nationwide Inpatient Sample (NIS) comprising 20% of all admissions in the United States from 1999 to 2002 were analyzed retrospectively.

Results—Thirty-one patients underwent ERT. Mean age was 68±14 years, 68% were female, and 45% nonwhite (occlusion sites: internal carotid artery 29%; middle cerebral artery 39%; posterior circulation 32%). Pharmacological or mechanical ERT was initiated beyond 3 hours after symptom onset (median time 4.4 hours) in 61%, 29% had surgery, and 39% were on anticoagulant medication. At discharge, 32% had modified Rankin Scale scores of 0 to 2 (52% discharged home or to rehabilitation facilities); overall mortality was 29%, of which 19% were fatal intracerebral hemorrhages. From the NIS cohort, 477 patients (0.17% of all strokes and 14% of all thrombolysis cases) underwent ERT. Fifteen percent died, and ~50% were discharged home or to rehabilitation facilities. Intracerebral hemorrhage occurred in 6%. Fewer good outcomes of the CUMC cohort may be explained by more unfavorable premorbid patient characteristics compared with the NIS cohort.

Conclusion—Despite significant variability in patient characteristics and treatment methods among 2 sources of data analyzed, ERT in stroke patients not eligible for intravenous thrombolysis appears to be a relatively safe and effective treatment alternative that is being used increasingly nationwide. (Stroke. 2006;37:419-424.)

Key Words: endovascular therapy ■ stroke, acute ■ treatment outcome ■ thrombolysis

To date, only intravenous administration of recombinant tissue plasminogen activator (rtPA) within 3 hours after symptom onset has been approved by the US Food and Drug Administration and declared “standard of care” for acute stroke treatment.1,2 However, far from being optimal, only a small proportion of stroke patients are eligible for “standard” intravenous thrombolytic therapy. Ongoing investigations involving different thrombolytic drugs or refinement of criteria for patient selection3,4 with possible extension of the traditional 3-hour time window for intravenous therapy,5,6 intra-arterial access for thrombolysis,7 and combined intravenous and intra-arterial treatment8,9 are efforts to further improve the outcome.

Although endovascular procedures like intra-arterial thrombolysis,7 mechanical embolectomy, and acute angioplasty are considered by many to be experimental10,11; these methods extending the present definition of thrombolysis to “recanalization” or “revascularization” therapy are increasingly being offered to acute stroke patients who present outside the 3-hour time window or have other contraindications to systemic thrombolysis. Because treatment is done locally closer to the site of the occlusion and (additional) mechanical devices may be used, major advantages of endovascular recanalization therapy (ERT) are a lower dose of thrombolytics is needed to recanalize the occluded vessel, higher recanalization rates, and possibly a lower rate of subsequent hemorrhages. However, the safety and efficacy of ERT remain less well studied.

This article reviews ERT results in patients with acute ischemic stroke treated at the Columbia University Medical Center and attempts to determine nationwide usage and outcome of ERT.
Methods

Columbia Experience

Patient Selection
In this retrospective analysis, consecutive patients treated by 2 stroke interventionalists (J.P.S., S.M.) at the Stroke Center in collaboration with the Academic Interventional Neuroradiology from June 2001 to November 2004 were included. Treatment decisions were made by consensus among the stroke/endovascular team within the clinical guidelines of the institution. Stroke patients were selected for ERT who met the following inclusion criteria: persistent or worsening stroke syndrome beyond 3 hours after symptom onset or within 3 hours when contraindications to intravenous tPA were present (see Data Acquisition); up to 6 hours after symptom onset for nonvertebrobasilar occlusion types, > 6 hours for vertebrobasilar occlusion. Mechanical devices were used to reduce the dose of thrombolitics. Concentric clot retriever devices were used as primary treatment means up to 8 hours after symptom onset. Patients with hemorrhage, tumor, or hypodensity more than one third of middle cerebral artery (MCA) territory on cranial computed tomography (CT) were excluded, as were those without angiographically confirmed occlusion of brain-supplying vessel(s). Institutional review board approval was obtained to review patient data for the study period. (For ERT, see the online Appendix available at http://stroke.ahajournals.org.)

Data Acquisition
Baseline National Institutes of Health Stroke Scale (NIHSS) scores, follow-up, and outcome evaluations at discharge (NIHSS and modified Rankin Scale [mRS] scores) were obtained by neurologists of the stroke team. Outcome at discharge was stratified into 2 groups: mRS ≤ 2 (good) and mRS > 2 (poor).

Contraindications for intravenous therapy were exceeding of time window, hypodensity more than one third of vessel territory visible on CT, preceding surgery (within 3 months), and anticoagulation therapy at the time of admission.

Occlusion and recanalization were graded by using thrombolysis in myocardial infarction (TIMI) grades 0 to 3.12 Intraprocedural and postprocedural complications were obtained from patients’ records. All patients underwent cranial CT within 24 hours after the procedure or when neurological deterioration was notified. Parenchymal hyperdensity on 2 follow-up CTs in context with neurological worsening was defined as symptomatic hemorrhage.

Nationwide Inpatient Sample
The Nationwide Inpatient Sample (NIS) is the largest all-payer inpatient care database in the United States representing ~ 20% stratified random sample of all patients admitted to nonfederal hospitals. From 1999 to 2002, between 984 and 995 hospitals from 24 and 35 states contributed 100% of their discharges. Hospital characteristics include location (urban/rural) and teaching status (academic medical center). Adult patients (≥ 18 years of age) with the primary diagnosis “acute ischemic stroke” were identified by selecting specific International Classification of Diseases-9 CM codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, and 436. Of those, patients receiving systemic thrombolysis (code 99.10) were selected. Because there is no procedural code, the rate of intra-arterial thrombolysis was estimated indirectly by identification of patients undergoing arteriography (code 88.41).

Statistical Methods
Univariate statistical methods were used to test the effect of demographic, morphological, and clinical variables on outcome of the Columbia cohort (outcome dichotomized into good versus poor: Wilcoxon signed rank test, χ² test/Fisher exact test). Multivariate logistic regression was used for predictors of poor outcome (mRS > 2).

Outcome of the study groups (Columbia, NIS) were compared using the χ² test and the Wilcoxon 2-sample test. Tests were considered significant when P = 0.05. Multivariate logistic regression was applied for predictors of poor outcome defined as “no home disposition” (NIS cohort).

Results

Columbia Experience

Baseline Characteristics
From a total of 1568 registered stroke patients, 52 (3.3%) underwent intravenous thrombolysis, and 31 (2%) underwent ERT.

The baseline characteristics are summarized in Table 1. The most frequent contraindication to intravenous thrombolysis was that treatment exceeded the 3-hour time window (61%). The median stroke severity at baseline was 17 (mean 16; SD 6) measured by the NIHSS. Total occlusion (TIMI 0) was found in 28 patients (90%). Radiological findings are presented in Table 2.

Treatment and Outcome
The mean time to start of treatment was 6.4 hours (SD 7.1: median 4.4). Of the study cohort, 26 patients (84%) received

| TABLE 1. Baseline Characteristics of the Columbia Cohort |
| Age, years, mean±SD, median | 68±14 | 74 |
| Female, n (%) | 21 (68%) |
| Race/ethnicity, n (%) | Nonwhite 14 (45%) |
| | Premorbidity, n (%) | 29 (94%) |
| | Hypertension | 22 (71%) |
| | Atrial fibrillation | 16 (52%) |
| | Diabetes mellitus | 4 (13%) |
| | Hyperlipidemia | 8 (26%) |
| | Peripheral arterial disease | 8 (26%) |
| | (History of) smoking | 11 (36%) |
| | History of myocardial infarction | 3 (10%) |
| | History of cerebral stroke | 10 (32%) |
| | Old stroke on brain imaging | 14 (45%) |
| | Surgery within last 3 months | 9 (29%) |
| Premedication, n (%) | Antiaggregation therapy 7 (23%) |
| | Statin therapy | 8 (26%) |
| Time to treat, hours, mean±SD, median | 6.4±7.1 | 4.4 |
| End of treatment time, hours | 1.9±0.8 | 1.7 |
| mean±SD, median | Contraindication for intravenous therapy* |
| Time window | 19 (61%) |
| Anticoagulation | 12 (39%) |
| Preceding surgery | 9 (29%) |
| Initial NIHSS†‡, mean±SD, median | 16±6 |

*Total No. may exceed 31 because of multiple counts of contraindications; †comparison of outcome group mRS < 3 vs ≥ 3: Wilcoxon signed-rank test (P < 0.001); ‡multiple logistic regression: odds ratio for outcome mRS > 2 (95% CI) is 1.32 (1.06–1.65).
intra-arterial thrombolytic drugs, and 5 (16%) were treated with mechanical devices only (Table 3). Of the former 26 patients, 12 underwent combined pharmacological and mechanical recanalization therapy.

After ERT (mean treatment time 1.9 hours; SD 0.8) and a mean hospital stay of 13 days (SD 20; median 7), 10 patients (32%) had mRS scores of 0 to 2, and the median NIHSS score was 9 (mean 10; SD 7; \( P < 0.001 \); Table 2). Total (42%) or partial recanalization was achieved in 77%. Postprocedural hemorrhage occurred in 7 patients (23%), of which 6 were symptomatic and led to death. The total in-hospital mortality was 29%. Arterial dissections were identified during endovascular intervention in 2 patients, but after immediate intervention (stent placement), there were no clinical stroke effects associated with the finding. Of the survivors, 16 (73%) were transferred to rehabilitation hospitals or were discharged home (4 patients).

**Predictors of Outcome**

In the univariate analyses, initial NIHSS score \( (P < 0.001) \) and postprocedural hemorrhage \( (P = 0.044) \) were significant factors for poor outcome. Multiple logistic regression for independence \( (mRS \geq 2) \) showed significance only for initial NIHSS score (odds ratio, 1.32; 95% CI, 1.06 to 1.65) with a linear dependence.

**Nationwide Inpatient Sample**

Obtained between 1999 and 2002, a total of 282,276 patients in the NIS had the diagnosis “ischemic stroke.” Of those, 3358 patients (1.19%) underwent intravenous thrombolysis and 477 patients (0.17% of the total cohort or 14% of all thrombolysis cases) received an angiogram at 172 hospitals from 32 states (numbers of hospitals not available from 8 states). Of those 477 patients, 319 (67%) were treated at urban academic medical centers and 324 (68%) were treated at day 1 of admission.

Baseline characteristics are listed in Table 4. The outcomes after endovascular intervention and at discharge were as follows: 15% died, intracranial hemorrhage occurred in 6%, 39% were discharged home either with or without home health care, and 43% were sent to other (rehabilitation or nursing) facilities.

Age, length of hospital stay, and urban/teaching hospital were negative predictors of outcome (no home disposition; Table 4).
TABLE 4. NIS*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NIS* Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Ischemic Stroke, n total</td>
<td>282,276</td>
<td></td>
</tr>
<tr>
<td>Patients receiving thrombolysis, n (%)</td>
<td>33,581</td>
<td>0.199</td>
</tr>
<tr>
<td>Patient receiving intra-arterial thrombolysis, n (%)</td>
<td>477 (0.17%)</td>
<td></td>
</tr>
<tr>
<td>Patients receiving intra-arterial thrombolysis</td>
<td>91 (0.33%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.** NIS* table with various outcomes and corresponding numbers.

Discussion

The multivariate analysis of the Columbia cohort revealed that only the initial NIHSS score and IS/IS independently and linearly predicted outcome. Why recanalization rate had no effect on outcome in the Columbia-cohort is unclear, but this may be attributable to the small number of patients or the cohort specific characteristics. Six of 7 patients with postprocedural bleedings died. In other ERT studies, age, higher initial NIHSS scores, infarct progression, low recanalization grade, and higher rates of posterior or anterior circulation occlusions were factors associated with postthrombolysis complications such as intracranial hemorrhage and unfavorable outcome.4,13–20

The studies dealing mainly with ERTs8,10,11,13,17,21–24 showed variable, but overall good results after ERT (supplemental Table, available online at http://stroke.ahajournals.org), especially when compared with the results of the previous randomized trials (NINDS, PROACT II). Mechanical devices were used only rarely. Despite some similarities among the study characteristics, variability in factors like premorbid patient characteristics, type of thrombolytic drug, treatment time, treatment techniques, and distribution of occlusion sites may be sources for bias, making direct comparisons difficult. Differently from identifying death or assessing outcome with widely used tools like the mRS or the Barthel Index, postprocedural hemorrhage may largely depend on the protocol definition and the radiologist who reviews the images.

The results of the NIS suggest that ERT is safe and effective. Comparably good outcome has also been reported as single-center experiences in >200 patients with mainly MCA occlusions undergoing ERT.13,21 Despite the same primary diagnostic code, “ischemic stroke” no systematic coding for the exact time to treatment from symptom onset exists for the NIS. However, more than two thirds were treated at day 1 of admission, which may represent the acute strokes presented in the emergency rooms. In 16%, treatment was delayed between the second and fifth days; this may indicate stroke occurrence during hospital stay or in part vary late recanalization attempts. Further, there is no information about the occlusion sites, endovascular recanalization technique, or the initial stroke severity of the patients. Standard outcome measurements of stroke are missing as well. Absence of those information is a limiting factor when comparing outcome.

Worse outcomes in the Columbia cohort may be attributable to a “sicker” cohort, in whom endovascular therapy is more often a last-resort consideration.25 Two thirds of the patients presented >3 hours after symptom onset, about one third had preceding surgery, and 39% were on anticoagulation therapy. Two thirds experienced occlusions of the posterior circulation and of the internal carotid artery (ICA), both possibly associated with higher mortality and morbidity compared with occlusions of the MCA.15,17,22,24,26 ERT in surgical patients has been rarely studied; in a study of 36 postsurgery patients undergoing pharmacological ERT (rtPA/urokinase), 25% died in the hospital and 38% had mRS scores of 0 to 2 at discharge.27 Intracranial hemorrhage occurred in 25% and led to neurological deterioration in 8%. Patients on anticoagulation medication experiencing major

Comparison

**Columbia Cohort Versus NIS**

The Columbia cohort was significantly older, had more women and nonwhite patients, and more patients had hypertension, atrial fibrillation, and peripheral arterial diseases (Table 4). Mortality was significantly higher in the Columbia cohort than in the NIS cohort (P=0.044). More patients from the NIS were discharged home (P=0.004). Hemorrhage rate of the NIS cohort were not explicit, so no statistical comparison with the Columbia cohort could be undertaken.
ischemic stroke are presently withheld from systemic thrombolysis. From 12 patients on anticoagulants, 8 had elevated international normalized ratio >1.8, but this was not associated with more hemorrhage or worse outcome. However, further systematic investigation into those “sicker” patient groups is needed.

The analyses of the NIS cohort showed that 1.2% (n=3358) of all hospitalized ischemic stroke patients underwent thrombolytic therapy. This low rate is comparable to numbers found in the literature.25 What is surprising, though, is that 14% of those 3358 patients may have been treated with endovascular intervention. Assuming any invasive intervention would add to the risk of adverse events, it is likely that conventional angiography in conjunction with acute ischemic stroke was undertaken primarily with the aim at detecting and endovascularly treating the occlusion. The incidence of hospitalization because of ischemic stroke in the NIS cohort was 119 per 100 000 persons and year, which is about half of that reported in the literature (≈240 per 100 000 and year).26 First, the NIS comprises patients ≥18 years of age, whereas the literature studied older patients between 45 and 85 years of age. Second, diagnostic misclassification bias may have occurred because of erroneous diagnostic coding. Finally, the fact that ∼20% of US hospitals contributed to the NIS, an extrapolation of this data may inherit and exaggerate errors.

Thirty-two states and >172 identified hospitals contributed to the NIS (Table 4). Hospitals from 8 states could not be identified. However, patient and hospital characteristics were completely coded, and we found that two thirds of the NIS cohort were treated at urban academic medical centers. Differently from the negative predictors age and length of stay, it is surprising that patients treated at “big” centers had lower odds for home disposition. It is possible that with better expertise at academic institutes, more difficult and experimental procedures are done. Further, severe cases may have been referred from the periphery. However, one third of the NIS cohort was treated in rural hospitals, and this may be a very encouraging fact.

Conclusions
From the results of the present review, intra-arterial recanalization seems to be a reasonably safe and effective alternative to treat patients who cannot undergo “standard” intravenous therapy. The results of the NIS cohort support the safety and efficacy of ERT. Further adjustments in choice and dose of drug, improvement of criteria for patient selection with possible extension of the time window for intravenous treatment, and the addition of mechanical devices may improve outcome.

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References


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