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ORIGINAL RESEARCH

Endovascular Interventions following Intravenous Thrombolysis May Improve Survival and Recovery in Patients with Acute Ischemic Stroke: A Case-Control Study

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BACKGROUND AND PURPOSE: Since the introduction of recombinant tissue plasminogen activator (rtPA) into clinical practice in the mid 1990s, no adjunctive treatment has further improved clinical outcomes in patients with ischemic stroke. The safety, feasibility, and efficacy of combining intravenous (IV) rtPA with endovascular interventions has been described; however, no direct comparative study has yet established whether endovascular interventions after IV rtPA are superior to IV rtPA alone. A retrospective case-control study was designed to address this issue.

MATERIALS AND METHODS: Between 2003 and 2006, 33 consecutive patients with acute ischemic stroke and National Institutes of Health Stroke Scale (NIHSS) scores ≥10 were treated with IV rtPA in combination with endovascular interventions (IV plus intervention) at a tertiary care facility. Outcomes were compared with a control cohort of 30 consecutive patients treated with IV rtPA (IV only) at a comparable facility where endovascular interventions were not available.

RESULTS: Baseline parameters were similar between the 2 groups. We found that the IV-plus-intervention group experienced significantly lower mortality at 90 days (12.1% versus 40.0%, $P = .019$) with a significantly greater improvement in NIHSS scores by the time of discharge or follow-up ($P = .025$). In the IV-plus-intervention group, patients with admission NIHSS scores between 10 and 15 and patients ≤80 years of age showed the greatest improvement, with a significant change of the NIHSS scores from admission ($P = .00015$ and $P = .013$, respectively).

CONCLUSIONS: In this small case-control study of patients with acute ischemic stroke and admission NIHSS scores ≥10, there was a suggestion of incremental clinical benefit among patients receiving endovascular interventions following standard administration of IV rtPA.

In 1996, intravenous (IV) recombinant tissue plasminogen activator (rtPA) was the first treatment to show improvement in the clinical outcome of patients with acute ischemic stroke.[1] However, 58% of the patients still ended up with death or disability as a consequence of the stroke, despite treatment with IV rtPA. In particular, IV rtPA has been shown to have limited benefit in patients with proximal occlusions[2] and in those with National Institutes of Health Stroke Scale (NIHSS) scores ≥10, in whom arterial occlusions persists in >80% after IV rtPA treatment.[2-4] This reality mandates further investigation into the treatment of acute ischemic stroke, especially with regard to improvements in endovascular recanalization strategies for patients with ischemic stroke demonstrating severe neurologic deficits. Several endovascular interventions have been developed to treat acute ischemic stroke more effectively. First, intra-arterial (IA) thrombolytics[5-7] may be delivered locally at or near the site of occlusion. Second, mechanical techniques have been developed to retrieve or disrupt the clot.[8-12] Third, acute angioplasty and/or stent placement of occluded or stenotic vessels may be emergently performed if needed to secure reliable perfusion.[4,13] However, currently these treatments are usually offered to those with contraindications to IV rtPA or to those who arrive outside of the approved 3-hour window for IV rtPA administration. Furthermore, intervention is not recommended as a first-line treatment in patients who are eligible for IV rtPA,[8,10,11] due to delays associated with endovascular interventions, which may limit the clinical benefit. Therefore, a combined approach has been proposed that involves initiation of IV rtPA in eligible candidates, with additional endovascular interventions available for patients who do not rapidly improve with IV rtPA alone.

To compare outcomes of patients treated with IV rtPA only versus IV rtPA followed by endovascular interventions, we performed a retrospective case-control analysis comparing the outcomes of patients receiving endovascular intervention in combination with IV rtPA with those patients receiving IV rtPA alone at 2 comparable tertiary care facilities.

Materials and Methods

Patients and Treatments

Consecutive patients with acute ischemic stroke, admitted to 2 different tertiary care centers between 2003 and 2006 and eligible for IV rtPA, were included. In center A (IV-only group), eligible patients received 0.9-mg/kg IV rtPA (Activase; Genetech, South San Francisco, Calif). IV rtPA was given only if it could be initiated within 3 hours of symptom onset. Ten percent of the dose was infused as a

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bolus, with the remainder infused during 1 hour.[13] At center B (IV-plus-intervention group), consecutive patients with acute ischemic stroke and eligible for IV rtPA were included, using the same criteria as previously mentioned and treated identically to those at center A. Additionally, patients with an admission NIHSS score ≥10 at center B were taken to the angiographic suite for further diagnostic and treatment procedures, except if rapid improvement was observed after initiation of IV rtPA or the family did not agree to the procedure. Appropriate adjunctive treatments were selected by the neurointerventionalist on the basis of the angiographic findings. Endovascular interventions included IA delivery of reteplase,[14] mechanical clot retrieval via a Merci retriever device (Concentric Medical, Mountain View, Calif), or clot disruption by using snare devices or angioplasty. Rarely, stent placement was used to secure perfusion to the ischemic region.[15]

Data Collection and Statistical Analysis

Records were obtained for patients at the 2 academic tertiary care referral centers for acute stroke on approval by the respective institutional review boards. Data were collected regarding age, sex, race, pre-existing medical conditions, admission NIHSS score, time from symptom onset to administration of IV rtPA, time to catheterization, and follow-up NIHSS score. Follow-up status was ascertained at day 7 or discharge, and mortality was determined at 90 days. However, for some patients from center A (IV-only group), NIHSS information was not available before discharge, and we obtained a conservative estimate of discharge NIHSS scores from the first available follow-up visit after discharge. Hereafter, these scores will be collectively referred to as "follow-up NIHSS scores." In the absence of follow-up documentation beyond 90 days, a patient's vital status was determined through the Social Security index. Data regarding all patients receiving IV rtPA at both institutions were collected, though only those with admission NIHSS scores ≥10 were included in the comparative analysis. Two patients at center A (IV-only group) were excluded, due to receiving endovascular intervention by visiting physicians.

Immediate pre- and posttreatment angiograms were obtained and graded by a previously described grading scheme. The Qureshi grading scheme[16] accounts not only for the location of the vascular occlusion but also adjusts for the presence or absence of collateral flow, an important factor in determining the eventual outcome following cerebral ischemia. The grading scheme was shown to correlate with the initial severity of the stroke and is highly predictive of infarction volume and clinical outcome.[17] The Qureshi grading scheme has been used in previous studies[15,17-21] and is made up of 6 grades, with grade 0 denoting no occlusion and grade 5 denoting complete occlusion of either the internal carotid artery or the basilar artery. It was used in this study to assess the initial and postintervention severity of arterial occlusion among patients in the IV-plus-intervention group. Recanalization was defined as improvement of 1 grade or more in the posttreatment angiographic images compared with pretreatment images. Complete recanalization was defined as achieving a grade 0 on the posttreatment angiographic images.

Primary outcome measures were follow-up NIHSS scores and changes in NIHSS scores from baseline (each assessed as continuous variables), as well as 90-day survival. Other categoric and subgroup analyses were performed on a post hoc basis. Comparison of continuous variables between groups was performed by using 1-way analysis of variance (ANOVA). The Student *t* test was used for comparisons between time points within groups. Categoric comparisons were performed by using contingency table χ^2 analysis with differences determined by using the Fisher exact test. Effect size was estimated by using Cohen D for continuous datasets and an odds ratio with a 95% confidence interval (CI) for categoric comparisons. Significance was defined as $P < .05$ by using 2-tailed tests.

Table 1: Baseline characteristics of patients

Characteristic	IV + Intervention ($n = 33$)	IV Only ($n = 30$)
Mean age (mean ± SD)	66.6 ± 12.0	66.4 ± 17.4
Women (%)	22 (66.7%)	21 (70.0)
Mean admission NIHSS score	15.8 ± 3.5	16.0 ± 3.5
Median admission NIHSS score (median, 25%, 75%)	15 (13, 19)	16.5 (14, 18.75)
Time to IV rtPA (mean ± SD)	118 ± 27.4	103.1 ± 37.1
Time to cath (mean ± SD)	239.9 ± 61.6	n/a
Vascular risk factors		
Hypertension	25 (76%)	16 (53%)
Atrial fibrillation	8 (24%)	6 (20%)
Previous MI/CAD	9 (27%)	4 (23%)
Congestive heart failure	5 (15%)	8 (27%)
Previous stroke/TIA	6 (18%)	8 (27%)
Diabetes mellitus	11 (33%)	6 (20%)
Cigarette smoking history	8 (24%)	5 (17%)
Race/ethnicity*		
White	7 (21%)	17 (57%)
African American	20 (61%)	8 (27%)
Hispanic	5 (15%)	4 (13%)
Other/unknown	1 (3%)	1 (3%)

Note:—n/a indicates not applicable; MI, myocardial infarction; CAD, coronary artery disease; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; IV rtPA, intravenous recombinant tissue plasminogen activator.
* $P = .0048$.

Results

Baseline Demographic and Clinical Characteristics of Patients

At center A, 30 patients with acute ischemic stroke and admission NIHSS scores ≥10 received IV rtPA alone (IV only) between 2003 and 2006. At center B, 54 patients with acute ischemic stroke and admission NIHSS scores ≥10 received IV rtPA between 2003 and 2006. Of these, 33 additionally received 1 or multiple endovascular interventions and compose the "IV-plus-intervention" group. Baseline characteristics were comparable between groups with the exception of ethnicity. The IV-plus-intervention group contained a significantly higher proportion of African American patients ($P = .0048$, Table 1). Distributions of baseline NIHSS scores in the IV-only versus IV-plus-intervention groups are graphically represented in Fig 1.

Additional Recanalization in the IV-Plus-Intervention Group

Preprocedure occlusion severity ranged from Qureshi grade 0 to 4A, with a median Qureshi grade of 2. Treatment led to complete recanalization in 40% of cases, partial recanalization in 33%, and no recanalization in 27%, with a median Qureshi grade after intervention of 1. Of those with complete recanalization ($n = 12$), all showed significant recovery (NIHSS improvement, ≥4 points; mean NIHSS improvement, 10 ± 3.4). By comparison, only 3 (25%) of those with persisting postpro-

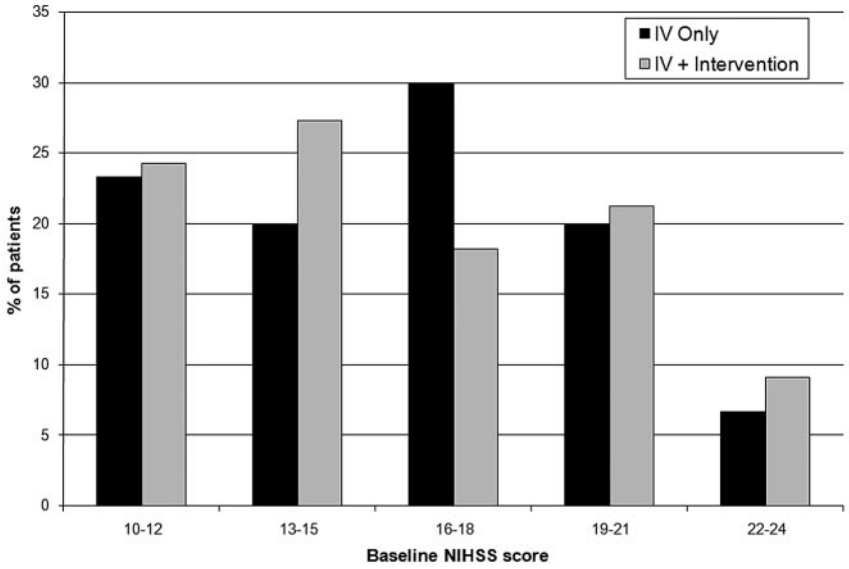

Fig 1. Graph shows the distribution of admission NIHSS scores for patients in each group displayed in a relative-frequency histogram. Black bars indicate patients who received IV rtPA but no endovascular intervention. Gray bars indicate patients who received IV rtPA followed by endovascular intervention. Mean NIHSS scores at admission were not different between the 2 groups ($P = .822$).

Table 2: Interventional treatments received

Treatments Received	No.	1st NIHSS Score	FU NIHSS Score	Pre-Qureshi Grade	Post-Qureshi Grade	Mortality (No.)
IA reteplase	14	18.5 (13.25, 19.75)	7 (2, 13.5)	2 (1, 3A)	1 (0, 1.75)	2
IA reteplase only	8	17 (12.75, 22)	6.5 (2, 9.75)	1 (1, 1.25)	0 (0, 1)	0
IA reteplase + other*	6	18.5 (15, 19)	7.5 (3, 33.75)	3A (3A, 3A)	1 (0.75, 1.25)	2
MERCI Retriever	8	15 (12, 16.25)	11 (2.75, 14.25)	2 (1, 3A)	2 (1, 2.5)	1
MERCI only	3	15 (13.5, 16)	2 (1, 2.5)	1 (1, 1)	0.5 (1, 0)	0
MERCI + other	5	15 (12, 16)	13 (12, 18)	3A (2, 3B)	2 (2, 3A)	1
Snare devices	15	14 (12, 18)	10 (5, 13.5)	3A (2, 3B)	2 (1, 3A)	1
Snare only	5	17 (14, 19)	14 (4, 38)	3A (2, 3B)	2 (0, 2)	1
Snare + other	10	13 (12, 15.75)	9.5 (6.75, 11.5)	3A (2, 3A/B)	2.5 (1, 3A)	0
Acute angioplasty†	10	16 (13.5, 17.75)	10 (3.75, 20.25)	3A (2.25, 3B)	2 (0, 3A)	2
Angioplasty only	5	16 (15, 17)	2 (0, 12)	2 (1.5, 2.25)	0 (0, 0.25)	0
Angioplasty + other*	5	16 (12, 18)	10 (10, 42)	3B (3A, 3B)	3A (3A, 3A)	2

Note:—FU indicates follow-up; NIHSS, National Institutes of Health Stroke Scale.
* Includes 1 patient who received suction thrombectomy.
† Includes 1 patient who received acute stent placement.

cedure occlusion of Qureshi grade 2 or higher ($n = 12$) experienced significant recovery (mean NIHSS deterioration, 6 ± 13.9). The difference between NIHSS improvements from admission to follow-up in patients with a post-treatment Qureshi grade 0 versus those with a Qureshi grade ≥2 was highly significant ($P = .0008$, ANOVA). The number of patients receiving each intervention is summarized in Table 2, along with baseline and follow-up NIHSS and Qureshi grades.

Intracerebral Hemorrhage and Mortality in IV-Only and IV-Plus-Intervention Groups

Intracerebral hemorrhage (ICH) was observed in 6 patients (18.2%) undergoing endovascular interventions. Of these, 4 (12.1%) were symptomatic, with clinical deterioration of ≥4 points in the NIHSS. Three of these patients died, 2 due to ICH or edema within 1 week; the third died after 3 weeks due to cardiopulmonary failure. The 1 surviving patient with symptomatic ICH remained severely disabled at follow-up, with a NIHSS score of 38. The overall 90-day mortality rate in the IV-plus-intervention group was 12.1%, of which 75% was due to ICH, which was observed in 2 patients (6.7%) in the IV-only group, of whom 1 (3.3%) was symptomatic and died. Additionally, 11 other patients in the IV-only group died; therefore, the overall mortality rate in the IV-only group was 40.0%. This difference in mortality was statistically significant ($P = .019$), with an odds ratio of death in the IV-plus-intervention group of 0.21 (95% CI, 0.06–0.74).

Neurologic Improvement in the IV-Only and IV-Plus Intervention Groups

The median time of follow-up evaluation in the IV-plus-intervention group was 8 days. At this time, in contrast to a median admission NIHSS score of 15, the median NIHSS score was 8 (a trend toward improvement, $P = .071$). Follow-up NIHSS scores in the IV-only group were significantly worse than those in the IV-plus-intervention group ($P = .037$). The incidence of marked recovery (≥10 points in the NIHSS) trended toward higher fre-

Table 3: Comparison of clinical outcomes in IV-only versus IV-plus-intervention groups*

Variable	IV + Intervention	IV Only	*P*	Effect Size†
No. patients	33	30		
Admission NIHSS score‡ (mean ± SD)	15.8 ± 3.5	16.0 ± 3.5		
Admission NIHSS score (median, 25%, 75%)	15 (13, 19)	16.5 (14, 18.75)	.822	0.033
Follow-up NIHSS score	8 (2, 14)	14 (11.5, 7)	.037	0.535
NIHSS score improvement	9 (2, 12)	12 (3.5, −22)	.025	0.575
Significance of change from admission	$P = .071$	$P = .173$		
≥4 NIHSS points	22 (66.7)	15 (50%)	.208	2.00 (0.72–5.53)
≥10 NIHSS points	16 (48.5%)	7 (23.3%)	.066	3.09 (1.04–9.17)
Favorable outcome (NIHSS scores, 0–2)	11 (33.3%)	4 (13.3%)	.080	3.25 (0.91–11.66)
90-Day mortality	4 (12.1%)	12 (40.0%)	.019	0.21 (0.06–0.74)

Note:—NIHSS indicates National Institutes Health Stroke Scale.
* Follow-up assessment performed at day 7 or discharge for the intervention group and discharge or follow-up visit for the control group (see text).
† Effect size measured as Cohen D for continuous variables or odds ratio (95% CI) for categoric variables.
‡ Admission NIHSS scores for all patients ≥10.

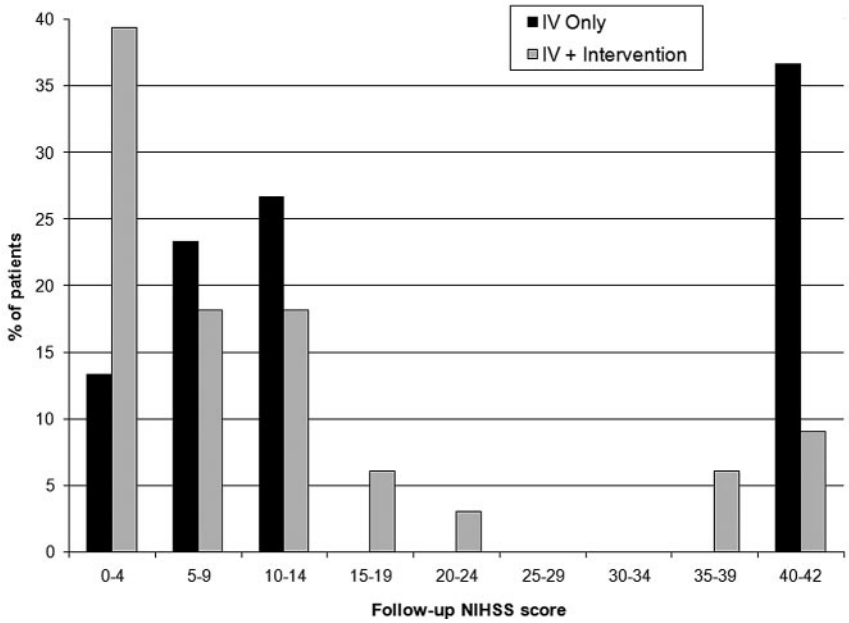

Fig 2. Graph shows the distribution of NIHSS scores at follow-up for patients in each group, displayed in a relative-frequency histogram. Black bars indicate patients who received IV rtPA but no endovascular intervention. Gray bars indicate patients who received IV rtPA followed by endovascular intervention. NIHSS scores at follow-up were significantly better in patients who received IV rtPA plus endovascular intervention ($P = .037$).

quency in the IV-plus-intervention group (48.5%) than in the IV-only group (23%, $P = .066$), resulting in a trend toward a higher proportion of patients with a favorable outcome of NIHSS scores of 0–2 ($P = .080$; odds ratio, 3.25; 95% CI, 0.91–11.66; Table 3). The distribution of follow-up NIHSS scores is shown graphically in Fig 2, whereas the changes in NIHSS scores from admission to follow-up in each group are depicted in Fig 3.

Predictors of Favorable Response

To determine whether favorable response was related to either baseline NIHSS score severity or age, we divided patients into subgroups on the basis of admission NIHSS scores: 10–15 and >15 as well as age >80 and ≤80 years. The NIHSS improvement in patients in the IV-plus-intervention group with admission NIHSS scores of 10–15 was highly significant ($P = .00015$), with a median improvement of 10 points. By contrast, the IV-only group showed no significant change at follow-up compared with baseline ($P = .909$). Patients aged ≤80 years in the IV-plus-intervention group showed a significant improvement in the NIHSS scores ($P = .013$), which was not observed in the IV-only group (mean nonsignificant worsening of NIHSS scores, $P = .650$). It has not been the practice at our institution for patients to be excluded on the basis of age alone. As such, of the 33 patients in our IV-plus-intervention group, 5 were >80 years old. Of these, 3 showed improvement in their NIHSS scores and 2 (40%) died. This mortality rate was not significantly different from that in the IV-only group, in which 6 of 9 patients (66.7%) >80 years old died (on-line Table).

Discussion

The rates of recovery and survival were higher among patients treated with additional endovascular interventions among patients receiving IV rtPA with an admitting NIHSS score ≥10. This finding was demonstrated by comparison of outcomes between the 2 tertiary care centers with differential use of IV-plus-intervention. The difference in the rates of these end points maybe related directly to additional recanalization achieved by using endovascular interventions. However, we

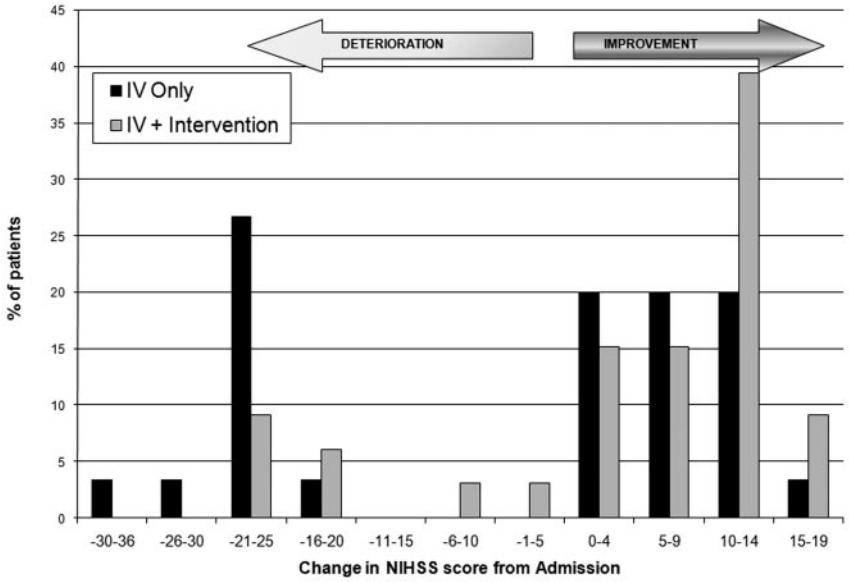

Fig 3. Changes in NIHSS scores from admission to follow-up for patients, displayed in a relative-frequency histogram. Black bars indicate patients who received IV rtPA but no endovascular intervention. Gray bars indicate patients who received IV rtPA followed by endovascular intervention. Patients who worsened after admission have negative scores (toward the left), whereas patients who improved have positive scores (toward the right). Improvement in NIHSS scores is significantly higher in patients who received IV rtPA plus an endovascular intervention ($P = .025$).

cannot exclude the possibility that these differences may be related in part to differences in patient characteristics or overall care between the 2 institutions. Therefore, we consider our results to be hypothesis-generating and not practice-changing in nature. The study provides data from a nonrandomized concurrent cohort study, categorized as level of evidence III by the Stroke Council of the American Stroke Association.[13]

Previous Studies Reporting on a Combination of IV and IA Thrombolysis

Recently, in recognition of the limits of both IV rtPA and IA strategies in isolation, IV rtPA has been used as bridging therapy to endovascular interventions in eligible patients with large neurologic deficits, even at standard IV rtPA doses of 0.9 mg/kg with no additional complication risk.[22] The Emergency Management of Stroke (EMS) Bridging Trial compared IV plus IA rtPA with IA rtPA alone and failed to find a significant difference in outcomes between groups, though combined therapy was associated with improved recanalization.[5] The feasibility, safety, and efficacy of combined IA thrombolytic therapy and endovascular interventions have been described in several other publications.[3,5,23-26]

Flaherty et al[24] reported a series of patients treated with both therapies. This group achieved favorable outcomes in patients <80 years of age, with outcomes perhaps better than those previously published for IV rtPA alone; however, a direct comparison with control patients was not performed and a statistical comparison with historic controls was not attempted. Sekoranja et al[25] provided IA rtPA to patients who did not achieve recanalization after 30 minutes of IV rtPA and found that 56% of such patients obtained additional clinical benefit. Normally, failure to respond to IV rtPA would be expected to carry a poorer prognosis; however, after receipt of IA rtPA, outcomes appeared similar to those of patients who had initially responded to IV rtPA. The Interventional Management of Stroke (IMS) trials have each compared a series of patients receiving combined IV and IA rtPA with historic results from the National Institute of Neurologic Disorders and Stroke (NINDS) IV rtPA study and found a nonsignificant survival advantage in addition to significant functional benefits at 3 months.[3,23] In the IMS-II trial, investigators performed regression analysis to compare their results with those obtained in the NINDS rtPA trial.[23] A lower mortality (16%) than that in the NINDS trial (21%) was observed; however, this difference was not significant. In light of these promising results, a prospective multicenter randomized open-label trial (IMS-III) is in progress to directly compare outcomes in patients randomized to IV rtPA alone versus IV rtPA plus endovascular interventions. This large well-powered study is scheduled for completion in June 2010.

Comparison of 90-day Mortality with That in Prior Studies

The 90-day mortality rate in the IV-only group for our study was quite high (40%) by comparison with that of patients with NIHSS scores ≥10 but ≤80 years of age in the NINDS rtPA trial (24% mortality in the control arm and 21% in the treatment arm). The fact that almost one third of the patients in the IV-only group ($n = 9$) were >80 years of age, with a high mortality rate (67%), might have accounted for an overall increased mortality. Another possibility is the difference in the availability of specialized neurocritical care with dedicated service established at center B. Both institutions were otherwise comparable in the treatment of acute stroke in regard to emergency department response, expedient neuroimaging, dedicated stroke teams, and established stroke protocols. The high mortality rate in the IV-only group makes the difference, with the mortality in the IV-plus-intervention group more noticeable; however, the 90-day mortality in the IV-plus-intervention group was per se quite low ($n = 4$, 12%) compared with other endovascular intervention treatment studies. The mortality rate was 16% in the treatment group of the IMS I and II

trials[3,23]; 25% and 27% in the treatment and control groups, respectively, in the Prolyse in Acute Cerebral Thromboembolism (PROACT II) trial[7]; 29% in the treatment group of the EMS trial[5] (patients with NIHSS >5); and 43.5% in the Mechanical Embolectomy in Acute Ischemic Stroke (MERCI) trial (patients with NIHSS ≥8).[9] Considering that patients >80 years of age (not included in the IMS trials) and those with strokes affecting the posterior circulation (not included in the PROACT trials) were not excluded from our study, we believe that our results show more differences because both groups are believed to carry high mortality rates.[27,28]

Comparison of Techniques in Our Study with Previous Combination Studies

The patients in the IV-plus-intervention group were treated with 0.9 mg/kg of IV rtPA before the endovascular intervention. Previous studies have predominantly used 0.6 mg/kg of IV rtPA before the endovascular intervention. However, some studies have used the 0.9-mg/kg dose before endovascular intervention without an incremental rate of intracranial and systemic bleeding complications.[22] Another feature of our study is that multiple combinations of endovascular interventions were used by the interventionalists (Table 2), whereas interventions in the IMS II trial were limited to IA thrombolytic delivery, with or without delivery by using sonography microcatheter technology.[23] The use of mechanical devices in combination with IA thrombolytics has been described[16,29]; however, the clinical benefit of this combination remains unclear.[30] The IA thrombolytic used in our study was the third-generation drug reteplase,[14] which has a longer half-life than the rtPA used in most IV rtPA-plus-endovascular-intervention studies to date, including the EMS bridging trial and IMS studies. Our study also used acute angioplasty as needed to ensure reliable perfusion. Collectively, it is conceivable that these differences in procedural aspects may have contributed to lower mortality compared with previous endovascular intervention treatment studies. At the opposite end of the outcome spectrum, the benefit observed in our IV-plus-intervention group also appeared robust. A favorable clinical outcome (NIHSS scores 0–2) was achieved by 33% of our patients at a median follow-up time of 8 days. The 3-month favorable outcome rates for patients with admission NIHSS scores ≥10 in the NINDS rtPA trial and the IMS-II trial were similar at 34% and 33%, respectively.[1,23] These rates are somewhat difficult to compare with our study, however, because our baseline NIHSS score in the IV-plus-intervention group was less severe (median value of 15 compared with 17 in the NINDS trial and 19 in the IMS II trial). However, our follow-up ascertainment was performed earlier (median, 8 days), compared with 3 months in other studies.

Patient Selection for a Combination of IV and IA Thrombolysis

Similar to previously published protocols, endovascular interventions were only used in combination with IV rtPA in patients with admission NIHSS scores ≥10. Endovascular interventions, however, may be appropriate for patients with NIHSS scores <10 who are not candidates for IV rtPA. However, they are not considered routinely due to the existing results observed with IV rtPA alone. Of the various subgroups represented in Table 2, the combination of IA reteplase with an adjunctive intervention appeared to provide a most robust angiographic recanalization among patients treated with endovascular interventions. This appeared also to correlate with robust functional recovery, with a reduction in the NIHSS score observed from 18.5 at admission to 7.5 at follow-up. A frequently discussed potential caveat to IA thrombolytic delivery is the reportedly increased risk of ICH. Indeed, our series had a high rate of symptomatic ICH of 12%, which is comparable with 13% and 10% in the IMS I and II trials, respectively.[3,23] By contrast, our rate of symptomatic ICH was 3% in the IV rtPA group. Patients with symptomatic ICH tended to fare poorly, usually resulting in death. To date, ICH has been associated with more severe NIHSS scores, increased time to recanalization, and increased blood glucose levels.[31] The substantial decrease in overall mortality with IV-plus-intervention in this series would seem to justify the increased risk of ICH.

Considerations before Interpretation of Data

The present study has several limitations. Follow-up data are only provided at a single time point, and this time point is imprecisely defined as being either day 7 or discharge in the IV-plus-intervention group versus discharge or follow-up in the IV-only group. The substantial range of this follow-up time point reflects the retrospective nature of this study and our preference to obtain NIHSS scores directly from clinical examination rather than to estimate NIHSS scores from often incomplete reports. This arrangement of follow-up time points, being on average slightly later in the control group, ensured that no patients were excluded on the basis of missing data. Moreover, given that many who survive to discharge may continue to improve with time, the differences detected between our groups may, if anything, be slightly underestimated. The choice of a relatively early follow-up time point in this study, in contrast to the more commonly used 90-day time point at our tertiary referral centers, was because records of follow-up visits conducted at another facility were often not available for retrospective review. Necessarily, the lack of standard 90-day outcome data limits our ability to appreciate the longer term differential effects of treatment and further limits direct comparison of these data with those of other studies using a 90-day end point. Finally, small case-control studies such as this may be subject to inherent selection bias and should be interpreted in the context of other available literature.

A major consideration is that the 2 groups were treated at different institutions. One baseline parameter significantly different between sites was race. Only 27% of patients in the IV-only group were African Americans, in contrast to 61% in the IV-plus-intervention group ($P < .05$). Functional recovery following stroke has previously been shown to be significantly reduced in African Americans, compared with whites,[32] which should have biased our results toward worse outcomes in the IV-plus-intervention group, the opposite of what we observed. Finally, subgroup analysis revealed comparable odds ratios for the benefit of IV plus intervention in subgroups defined by sex and NIHSS score, supporting the generalizability of the benefit, though small sample sizes limited statistical comparisons.

The analysis described previously considers only those patients from center B (NIHSS scores ≥10) who received IV rtPA in addition to interventional treatment between 2003 and 2006 ($n = 33$). During this time, 24 other patients at center B with NIHSS scores ≥10 received IV rtPA only, similar to the protocol at center A. Patients at center B were generally excluded from endovascular interventions if they demonstrated rapid improvement after IV rtPA or if informed consent was not available. Therefore, patients with worse clinical characteristics at center B would be the most likely to receive an endovascular intervention. Nevertheless, we wished to acknowledge the potential selection bias, wherein it may be argued that patients selected for endovascular interventions were more likely to respond well on the basis of the initial evaluation.

Conclusions

In this small case-control study, patients undergoing additional endovascular interventions experienced greater survival and recovery compared with those treated with IV rtPA only. Therefore, endovascular intervention after a full dose of IV rtPA in eligible patients with admission NIHSS scores ≥10 was feasible and safe and may be an effective therapy for acute ischemic stroke. Results of large randomized clinical trials investigating this approach are eagerly awaited.

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