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The Effect of Diagnostic Catheter Angiography on Outcomes of Acute Ischemic Stroke Patients Being Considered for Endovascular Treatment

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Abstract

Background—The risk of catheter-based angiograms alone (non-therapeutic angiogram that does not lead to therapeutic intervention) in acute ischemic stroke patients who are considered for endovascular treatment is not well studied.

Methods—We compared the rates of neurological deterioration within 24 h; symptomatic intracranial hemorrhage (ICH) within 30 h; acute kidney injury (AKI) and major non-ICH within five days; and functional independence (defined by modified Rankin scale of 0–2) at three months among subjects who underwent a non-therapeutic catheter-based angiogram with subjects who did not undergo catheter-based angiogram in a multicenter clinical trial. Logistic regression analyses was performed to adjust for age, baseline Alberta stroke program early CT score (ASPECTS) strata (0–7 and 8–10), and baseline National Institutes of Health Stroke Scale (NIHSS) score strata (≤9, 10–19, and ≥20).

Results—Compared with subjects who did not undergo any catheter-based angiogram (n = 222), 89 subjects who underwent a non-therapeutic catheter-based angiogram had similar adjusted rates of neurological deterioration [odds ratio (OR) = 1; 95% confidence interval (CI) 0.4–2.3; p = 1] and symptomatic ICH (OR = 0.4; 95% CI 0.1–1.8; p = 0.2). There was no difference in the adjusted rates of AKI, or non-ICH between the two groups. The rate of functional independence at three months was significantly higher among the patients who received a catheter-based angiogram (OR = 2; 95% CI 1.1–3.5; p = 0.016) after adjusting for potential confounders.

Conclusion—Non-therapeutic catheter-based angiograms in acute ischemic stroke patients who are being considered for endovascular treatment do not adversely affect patient outcomes.

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Keywords

Catheter-based angiogram; acute ischemic stroke; clinical trial; acute kidney injury (AKI); functional independence

Introduction

The American Heart Association Stroke Council guidelines for the early management of patients with acute ischemic stroke [1] recommend non-invasive imaging with computed tomography (CT) or magnetic resonance (MR) angiography of the intracranial vasculature to exclude the presence of proximal intracranial stenosis and/or occlusion (Class I; Level of Evidence A). The guidelines acknowledge that catheter-based angiography may be necessary for reliable diagnosis of the abnormalities detected with noninvasive testing. However, catheter based need not be the initial imaging modality in part due to the risk associated with catheter-based angiography, citing two large studies that ascertained the risk within 24 h of procedure [2,3]. Neurological complica-

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tions were observed in 2.6% of 19,826 patients [2] and 1.3% of 2899 patients [3], undergoing cerebral angiography for various indications. Both studies reported higher rates of neurological complications when the indication of the procedure was evaluation of ischemic atherosclerotic disease. Non-therapeutic angiograms (that do not lead to therapeutic intervention) in acute ischemic stroke patients who are considered for endovascular treatment [4] are unavoidable and expected to increase as endovascular treatment for acute ischemic stroke continues to increase [5]. A focused study ascertaining the risk of ultra-early catheter-based angiography in acute ischemic stroke patients with short-term and intermediate-term independent assessment has not been performed.

We performed this study to provide data regarding risks of non-therapeutic catheter-based angiograms in acute ischemic stroke patients who are considered for endovascular treatment to facilitate evidence-based decision making and risk-benefit assessment.

Methods

Study population

We analyzed data from Interventional Management of Stroke (IMS) III that randomized eligible subjects who had received intravenous recombinant tissue plasminogen activator (rt-PA) within 3 h after symptom onset to receive additional endovascular therapy or additional intravenous rt-PA, in a 2:1 ratio [6]. The trial enrolled subjects aged 18–82 years with acute ischemic stroke with a moderate-to-severe neurologic deficit [defined as a National Institutes of Health Stroke Scale (NIHSS) score ≥10 or, and in later part of the trial those with a score of 8–9 with CT angiographic evidence of an occlusion of the proximal middle cerebral artery, internal carotid artery, or basilar artery]. The subjects were randomized within 40 min after the initiation of the infusion (when 0.6 mg/kg of rt-PA had been administered). The subjects randomized to the intravenous rt-PA alone group received the remainder of the standard dose (total dose of 0.9 mg/kg). Patients who were randomized to endovascular treatment underwent catheter-based angiography as soon as possible either at the hospital that initiated treatment with intravenous rt-PA or at another participating hospital. Intravenous rt-PA was discontinued at 40 min in those randomized to endovascular treatment and femoral puncture and access was performed during or after completion of the intravenous rt-PA. The angiographic procedure had to begin within 5 h and be completed within 7 h of symptom onset. Subjects who had no angiographic evidence of a treatable occlusion received no additional treatment (non-therapeutic catheter-based angiograms), and those with a treatable vascular occlusion received endovascular treatment according to specified protocol.

Outcomes analyzed

The following outcomes were analyzed:

Symptomatic intracranial hemorrhage (ICH): as defined previously [6] using CT scans was performed at baseline, at 24 (±6) h, if there was a neurologic decline.

Early neurological deterioration: as defined previously [6] based on a four or more point increase in the NIHSS score from baseline to subsequent evaluation at 24 (±6) h. In subjects in whom 24-h NIHSS score was not available, designation of symptomatic ICH by site investigator was considered as neurological deterioration.

Acute kidney injury (AKI): defined by an increase in serum creatinine value at 5 (±1) day or discharge from hospital compared with baseline creatinine value with severity graded according to AKI Network classification. The grades were: stage 1, ≥0.3 mg/dl (≥ 26.4 umol/l) or ≥ 150%–200%; stage 2: >200%–300% (>2–3 fold); and stage 3, >300% (>3 folds).

Major non-ICH: defined as non-intracranial bleeding related to drug, device, or procedure within 5 (±1) day or discharge from hospital.

Independent functional status: defined by a modified Rankin scale score of 2 or less at 90 days. All modified Rankin scale assessments at 90 (±14) days were performed by study investigators who were not involved in the treatment of the patient and who were blinded to the treatment assignment.

Recurrent stroke: defined as an adverse event with Medical Dictionary for Regulatory Activities preferred term of ischemic stroke or cerebrovascular accident within 90 days post-randomization.

Any death: defined by death regardless of cause within 90 days post-randomization.

Statistical analysis

We compared the baseline demographic and the clinical characteristics of subjects who underwent non-therapeutic catheter-based angiograms with those who had received intravenous rt-PA alone. We used chi-square and analysis of variance tests for categorical and continuous variable comparisons, respectively. We performed seven different logistic regression analyses to determine

Table 1. Baseline Demographic and Clinical Characteristics of Subjects Included in the Analysis

	Subjects who underwent non-therapeutic catheter-based angiogram (n = 89)	Subjects randomized to intravenous rt-PA alone (n = 222)	p-value
Age (years) [median (range)]	69 (35–83)	68 (23–84)	0.34
Gender	48 (53.9)	122 (55)	0.88
Men	41 (46.1)	100 (45)	
Women			
Race or ethnic group	12(13.4)	19 (8.6)	0.2
African–American	73 (82)	190 (85.6)	
White	4 (4.6)	23 (5.8)	
Other ethnicities			
NIHSS score [median (range)]	15 (7–39)	16 (8–30)	0.04**
Baseline NIHSS score strata	2 (2.2)	4 (1.8)	0.05**
≤9	70 (78.7)	146 (65.8)	
10–19	17 (19.1)	72 (32.4)	
≥20			
Baseline ASPECTS 8, 9, or 10	73 (82)	131 (59)	<0.001**
Time interval between symptom onset to ED arrival (minutes ±SD)	57.7 ±29.4	57 ±27.3	0.87
Time interval between symptom onset to randomization (minutes ±SD)	145.5 ±34.8	143.1 ±35.3	0.6
Time interval between ED arrival to IV rt-PA initiation (minutes ±SD)	65.5 ±22.9	64.7 ±28	0.82
Vascular risk factors	64 (71.9)	171 (77)	0.64
Hypertension	25 (28.1)	54 (24.3)	0.8
Diabetes mellitus	13 (14.6)	31 (14)	0.12
Congestive heart failure	23 (25.8)	72 (32.4)	0.35
Coronary artery disease	22 (24.7)	63 (28.4)	0.51
Cigarette smoking	25 (28.1)	70 (31.5)	0.55
Atrial fibrillation	15 (16.9)	36 (16.2)	0.68
History of myocardial infarction	50 (56.2)	112 (50.5)	0.6
Hyperlipidemia			
Modified Rankin scale (status prior to stroke)	80 (89.9)	197 (88.7)	0.08
0	4 (4.5)	21 (9.5)	
1	5 (5.6)	4 (1.8)	
2			
Presumptive stroke location	55 (61.8)	106 (47.7)	0.07
Left hemisphere	30 (33.7)	109 (49.1)	
Right hemisphere	3 (3.4)	4 (1.8)	
Brain Stem or cerebellum	1 (1.1)	3 (1.4)	
Unknown or multiple locations			
Baseline systolic blood pressure (mmHg ±SD)	150 ±22.8	147.4 ±23.9	0.38
International normalized ratio [median (range)]	1 (0.9–1.7)	1 (0.9–1.7)	0.85
Baseline serum glucose (mmol/liter) (mean ±SD)	7.4 ±2.6	7.6 ±3.1	0.52
Antiplatelet use at baseline*	40 (44.9)	108 (48.6)	0.68
Statin use at baseline*	32 (36)	83 (37.4)	0.6

Abbreviations: NIHSS: National Institutes of Health Stroke Scale; ASPECTS: Alberta stroke program early CT score; SD: standard deviation; ED: emergency department; rt-PA: recombinant tissue plasminogen activator.

*Antiplatelet and statin use at baseline: is defined as ongoing use at the day of randomization or with discontinuation date within two weeks of randomization.

**Significant p-values at <0.05 level of significance.

the effect of non-therapeutic catheter-based angiogram on occurrence of outcomes of interest; symptomatic ICH, early neurological deterioration, AKI, major non-ICH, independent functional status, any death, and recurrent stroke. Each of the analyses was adjusted for age (continuous variable), baseline Alberta stroke program early CT score (ASPECTS) strata (0–7 and 8–10), and baseline NIHSS score strata (≤9, 10–19, and ≥20). All analyses were performed using IBM SPSS STATISTICS Version 20 (IBM Corp, Armonk, NY, USA).

Results

A total of 89 subjects [mean age ±standard deviation (SD); 67 ±11.2; 48 were men] underwent a non-therapeutic catheter-based angiogram among the 434 subjects randomized to endovascular treatment. The mean time interval (±SD) between symptom onsets to initiation of catheter-based angiogram in 89 subjects was 231.7 (±51.4) min. The mean time interval (±SD) between CT scan to initiation of catheter-based angiogram was 155.8 (±45.5) min. A total of 222 subjects were randomized to intravenous rt-PA treatment alone without catheter-based angiography. The comparison of demographic and clinical characteristics of subjects who underwent non-therapeutic catheter-based angiogram and those who received intravenous rt-PA alone are presented in Table 1. There were no differences in regards to age, gender, and race/ethnicity distribution between the two groups. There were higher proportion of subjects with previous history

Table 2. Unadjusted and Adjusted Rates of Short-Term or Intermediate-Term Events in Subjects Included in the Analysis

Outcomes	Subjects who underwent non-therapeutic angiograms (n = 89)	Subjects who received IV rt-PA alone (n = 222)	Unadjusted OR (95% CI);p-value	Adjusted OR (95% CI);p-value
Neurological deterioration within 24 (±6) h*	9/83 (10.8)	29/209 (13.9)	0.7 (0.3–1.7); p = 0.49	1 (0.4–2.3); p = 1
Symptomatic ICH within 30 h	2 (2.2)	13 (5.9)	0.4 (0.1–1.7); p = 0.2	0.4 (0.1–1.8); p = 0.2
AKI within 5 (±1) days or hospital discharge	1 (1.1)	3 (1.3)	0.8 (0.1–8.1); p = 0.87	0.8 (0.1–8.3); p = 0.89
Major non-ICH within 5 (±1) days or hospital discharge	1 (1.1)	5 (2.3)	0.5 (0.1–4.3); p = 0.52	0.5 (0.1–4.8); p = 0.55
Any deaths within 90 days	6 (6.7)	48 (21.6)	0.3 (0.1–0.6); p = 0.003**	0.3 (0.1–0.8); p = 0.015**
Recurrent stroke within 90 days	2 (2.2)	14 (6.3)	0.3 (0.1–1.5); p = 0.16	0.5 (0.1–2.4); p = 0.38
Functional independence at 90 (±14) days	56 (62.9)	90 (40.5)	2.5 (1.5–4.1); p < 0.001**	2 (1.1–3.5); p = 0.016**

Abbreviations: OR: odds ratio; CI: confidence interval; IV: intravenous; rt-PA: recombinant tissue plasminogen activator; AKI: acute kidney injury

*NIHSS score at 24 (±6) h was available for 83/89 patients who underwent catheter-based non-therapeutic angiograms and for 209/222 patients who did not undergo catheter-based angiogram.

**Significant p-values at <0.05 level of significance.

of stroke among those who underwent non-therapeutic catheter-based angiogram. There was a trend toward higher proportion of subjects in NIHSS score strata ≥20 among those who received intravenous rt-PA alone (p = 0.05). The proportion of subjects with ASPECTS of 8–10 on baseline CT scan was higher among those who underwent non-therapeutic catheter-based angiogram (p < 0.001).

Compared with subjects who did not undergo any catheter-based angiogram, subjects who underwent a non-therapeutic catheter-based angiogram had similar rates of neurological deterioration within 24 h [odds ratio (OR) = 1; 95% confidence interval (CI) 0.4–2.3; p = 1] and symptomatic ICH (OR = 0.4; 95% CI 0.1–1.8; p = 0.2). The rates of AKI (1.1% and 1.3%), major non-ICHs (1.1% and 2.3%), and recurrent strokes (2.2% and 6.3%) were low in subjects who underwent a non-therapeutic catheter-based angiogram. There was no difference in the rates of AKI, major non-ICHs, and recurrent strokes in the adjusted analyses (see Table 2). The rate of functional independence at three months was significantly higher among subjects who received a non-therapeutic catheter-based angiogram (OR = 2; 95% CI 1.1–3.5; p = 0.016) after adjusting for age, baseline ASPECTS strata, and NIHSS score strata. The adjusted rate of any death within 90 days was significantly lower among subjects who received a non-therapeutic catheter-based angiogram (OR = 0.3; 95% CI 0.1–0.8; p = 0.015).

Discussion

We determined the effect of non-therapeutic catheter-based angiograms in acute ischemic stroke patients who are being considered for endovascular treatment on rates of adverse events and three-month functional interdependence and mortality. We did not find any evidence that non-therapeutic catheter-based angiograms, adversely affect patient outcomes either on analysis of short-term or intermediate-term prospectively ascertained events with standard definitions. The use of emergent catheter-based angiography is very common in patients with acute myocardial infarction who receive intravenous fibrinolysis. The current guidelines of the American College of Cardiology Foundation/American Heart Association strongly recommend immediate coronary angiography in patients presenting with ST segment elevation myocardial infarction who demonstrate evidence of failed reperfusion or reocclusion after intravenous fibrinolytic treatment even if the patient has to be transferred for the procedure [7]. In Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis trial [8] patients with ST-segment elevation myocardial infarction who demonstrate evidence of failed reperfusion were randomized to immediate angiography and percutaneous coronary intervention (PCI), repeat thrombolysis, or conservative management. Of the 128 patients who underwent coronary angiography, 13 did not require angioplasty because of patent vessels. Non-fatal bleeding, mostly at the sheath-insertion site, was more common with rescue PCI. However, event-free survival after failed thrombolytic therapy was significantly higher with coronary angiography and rescue PCI. In a meta-analysis of 15 randomized trials [9], immediate coronary angiography and rescue PCI for failed fibrinolysis reduced mortality and the rate of death or reinfarction compared with a conservative approach in ST-segment elevation myocardial infarction

patients. There was no difference in rate of major bleeding between the two approaches.

Several adverse events have been reported with catheter-based cerebral angiography including hemorrhage from the pseudo-aneurysm at femoral access site, arterial dissections at sites of catheter or wire manipulations, and ischemic stroke [2,3]. We found a very low rate of clinically significant events in patients who underwent a non-therapeutic catheter-based angiogram as evident from low rates of neurological deterioration, recurrent stoke, and major non-ICH using protocol defined prospective assessments. There are several possibilities that may explain the relative safety of catheter-based angiogram in such settings. The procedure was performed in a carefully selected group of ischemic stroke patients with limited co-morbidities [6]. Patients aged 83 and older and those with history of stroke within last three months, large regions of ischemic changes on CT scans, or suspicion of aortic dissection were not included in the trial. Patients with known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR greater than 1.7 were excluded. Patients with acute hypertensive response at the time of treatment, systolic blood pressure >185 or diastolic blood pressure >110 mm Hg—those who required hemodialysis or peritoneal dialysis–or who had a contraindication to a catheter-based angiogram for another reason were also excluded. The high level of qualification and experience of neurointerventionalists performing the catheter-based angiogram was another important factor. This experience requirement included performance and interpretation of 100 (with advanced neurointerventional training) or 200 catheter-based angiograms, with documentation of indication, success, and complications, according to published quality improvement guidelines. The low rates of new ischemic cerebral events may be due to the fact that all patients had already received 0.6 mg/kg of intravenous rt-PA with residual thrombolytic activity at the time of catheter-based angiography. Due to pre-existing neurological deficits, newer minor neurological deficits occurring during the angiographic procedure may have been difficult to detect.

The question that which imaging modality provides the necessary information in the most time-efficient manner for adequate decision making needs to be considered. Ultra-early catheter-based angiography in patients with acute ischemic stroke can provide information regarding site of occlusion and characterize the collateral flow to the affected region [10]. CT or MR angiography can provide similar information but incurs delay in treatment, may be limited in visualization of distal arterial occlusion, and requires multiphasic acquisition and post-processing for adequate visualization of collateral circulation [11–13]. There have been concerns regarding frequent use of catheter-based angiography in acute ischemic stroke patients due to risk involved with the procedure, particularly if no further endovascular treatment may be required. Our data do not provide a direct comparative analysis between catheter-based and non-invasive angiography in regards to time delay incurred, information acquired, or risk involved. Our data support the use of catheter-based angiography in acute ischemic stroke patients, particularly when pre-selection with CT or MR angiography is not possible in a time-effective manner. Certain scenarios such as patients with severe neurological deficits and/or those with hyperdense middle cerebral artery on CT scan where the chance of proximal arterial occlusion is high [14–16] may be triaged directly to angiographic suite to avoid any delay incurred during acquisition of non-invasive angiography. A previous study had demonstrated that there was a significantly higher rate of achieving time of less than 90 min between CT scan acquisition and microcatheter placement in patients who were transferred from CT scan facility directly to angiographic suite (no turn back approach) compared with return to emergency department and subsequent transfer to angiographic suite (57.6% versus 31.6%; $p = 0.0007$) [17]. In an exploratory analysis in the same study, there was a trend toward higher rate of favorable outcomes at discharge (OR = 1.6; 95% CI 0.9–2.8; $p = 0.07$) among those treated with no turn back approach after adjusting for potential confounders. One of the issues that are part of medical decision making in selecting the angiographic imaging modality is cost effectiveness [18,19]. In a previous analysis [20], the incremental cost of multimodal CT scan including CT angiography was $769 and catheter-based angiography was $3,571 per patient. In a patient who failed to improve after 1 h of receiving intravenous rt-PA, multimodal CT scan was considered more cost effective by obviating the need for catheter-based angiography.

In general, a more permissive attitude toward catheter-based angiography in acute ischemic stroke patients treated with intravenous rt-PA may be considered. Catheter-based angiography may be considered as first-line angiographic study in certain situations that may still need to be defined in further studies, among acute ischemic stroke patients who are being considered for endovascular treatment after receiving intravenous rt-PA. Such a paradigm is commonly used in patients with ST-segment elevation myocardial infarction with acceptable risk and reduction in adverse outcomes [9]. Even if per-

formance of catheter-based angiogram does not lead to any endovascular treatment, such procedures do not appear to adversely affect patient outcomes when performed by adequately qualified neurointerventionalists.

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