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Advanced modality imaging evaluation in acute ischemic stroke may lead to delayed endovascular reperfusion therapy without improvement in clinical outcomes

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Abstract

Purpose—Advanced neuroimaging techniques may improve patient selection for endovascular stroke treatment but may also delay time to reperfusion. We studied the effect of advanced modality imaging with CT perfusion (CTP) or MRI compared with non-contrast CT (NCT) in a multicenter cohort.

Materials and methods—This is a retrospective study of 10 stroke centers who select patients for endovascular treatment using institutional protocols. Approval was obtained from each institution's review board as only de-identified information was used. We collected demographic and radiographic data, selected time intervals, and outcome data. ANOVA was used to compare the groups (NCT vs CTP vs MRI). Binary logistic regression analysis was performed to determine factors associated with a good clinical outcome.

Results—556 patients were analyzed. Mean age was 66 ± 15 years and median National Institutes of Health Stroke Scale score was 18 (IQR 14–22). NCT was used in 286 (51%) patients, CTP in 190 (34%) patients, and MRI in 80 (14%) patients. NCT patients had significantly lower median times to groin puncture (61 min, IQR (40–117)) compared with CTP (114 min, IQR (81–152)) or MRI (124 min, IQR (87–165)). There were no differences in clinical outcomes, hemorrhage rates, or final infarct volumes among the groups.

Conclusions—The current retrospective study shows that multimodal imaging may be associated with delays in treatment without reducing hemorrhage rates or improving clinical outcomes. This exploratory analysis suggests that prospective randomised studies are warranted to support the hypothesis that advanced modality imaging is superior to NCT in improving clinical outcomes.

INTRODUCTION

The establishment of primary stroke centers in the USA has focused attention on efficient treatment of acute stroke patients.^{1–3} The time between symptom onset and intravenous tissue type plasminogen activator administration is inversely related to good outcomes.⁴ Thus the time between arrival at the emergency department and initiation of intravenous tissue type plasminogen activator has been chosen as a measure of system performance.² Similarly, time to angiographic reperfusion has been shown to be a major determinant of good outcome following endovascular therapy.⁵ It is important to identify factors that may create unnecessary delays when implementing a system surrounding endovascular reperfusion therapies.

Although duration of ischemia is an important factor in outcome, reduction of cerebral blood flow may be more correlative to irreversibly injured tissue.^{6,7} Imaging techniques can semiquantitatively demonstrate regional variations in cerebral blood flow within a given area of ischemia.^{8,9} Tissue with profound ischemia is unlikely to be salvageable and may increase the risk of reperfusion hemorrhage.¹⁰ Other areas with mild hypoperfusion may be salvageable even after prolonged ischemic episodes. Assessment of tissue perfusion may aid in selecting patients more likely to benefit from reperfusion with less risk of complications.¹¹ Computed tomography perfusion (CTP) studies are used in several centers to ascertain this information. It can be acquired rapidly, but may have time delays in

processing speed, interpretation of the data, and ultimately decision making to activate endovascular stroke systems. Moreover, CTP does not have standardized or consistent thresholds between software packages for distinguishing benign reductions in blood flow, penumbral tissue, and infarct core. MRI is used in some centers, has a higher sensitivity for detecting core infarct but is not immediately available in many centers and cannot be used in patients with metallic implants. Proponents of MRI argue its utilisation will reduce futile reperfusion by identifying patients with large core infarcts but to date it is not clear if this strategy improves clinical outcomes when directly compared with NCT.

We hypothesized that acquiring advanced modality imaging results in significant delays to groin puncture and may not improve clinical outcomes for patients presenting with acute stroke undergoing endovascular reperfusion therapies. This would provide a premise for a prospective trial comparing imaging modalities in selecting patients for acute stroke interventions.

MATERIALS AND METHODS

This study was a retrospective analysis of patients treated with endovascular therapy at 10 tertiary stroke centers, from September 2009 to July 2011. Approval was obtained from each institution's review board as only de-identified information was used for the purposes of this analysis. Patients who presented within 8 h of symptom onset with an anterior circulation large vessel occlusion involving the internal carotid artery or middle cerebral artery (MCA) were considered in the study. Patients who underwent NCT only were chosen for endovascular treatment based on standard criteria used for assessing NCT for intravenous thrombolysis (eg, no evidence of hemorrhage, absence of hypodensity that occupies greater than one-third of the area of the middle cerebral artery territory). Patients who underwent multimodality imaging were selected based on each institution's protocol for evaluating core and penumbral tissue regions. Patients received endovascular therapy which may have consisted of intra-arterial administration of thrombolytics, mechanical thrombectomy, or a combination based on the discretion of the treating center.

Data were collected regarding demographics (age and sex), previous medical history (hypertension, atrial fibrillation, diabetes mellitus, and dyslipidemia), radiographic interpretation of hemorrhages and final infarct volume, location of thrombus on angiography, reperfusion status, and clinical outcomes. Additionally, the time interval from image acquisition to reperfusion was acquired. The time from CT completion to groin puncture and total procedural time was recorded. If there was failed reperfusion, the time of cessation of the procedure was demarcated as procedural time. Successful reperfusion was defined as achieving a Thrombolysis in Cerebral Infarction score of 2B or better on the final angiographic image. A Thrombolysis in Cerebral Infarction score of 2B signifies reperfusion of more than half of the vascular distribution of the occluded artery. This has been shown to better predict clinical outcomes compared with other recanalization scales.¹² Infarct volume was obtained on MRI or delayed CT through manually measuring each region of interest on each slice of the infarct. The measurements were then summated to obtain the final infarct volume accounting for slice thickness. Symptomatic intracerebral hemorrhage was defined as a parenchymal hematoma type 2 using the European–

Australasian Acute Stroke Study definition, while asymptomatic hemorrhage was defined as hemorrhagic infarction types 1 or 2 or parenchymal hematoma type 1.¹³ Given the challenges of discerning National Institutes of Health Stroke Scale score (NIHSS) deterioration retrospectively, particularly in intubated patients, this designation was felt to best approximate rates of symptomatic intra-cerebral hemorrhage. Patients with a modified Rankin score ≤ 2 at more than 90 days were considered to have a good clinical outcome.

Patients were stratified based on imaging modality employed prior to intervention: NCT, CTP, or MRI of the brain. These three groups were considered separately for analysis to determine if advanced modality imaging led to better clinical outcomes and lower hemorrhage rates.

Statistical analysis

Statistical analysis was performed comparing patients selected by NCT, CTP, and MRI using an ANOVA followed by Tukey's post hoc test for multiple comparisons. A secondary analysis was performed to determine if multimodal imaging improved the probability of a good clinical outcome and reduced symptomatic hemorrhage rates compared with NCT. A binary logistic regression model was constructed with the dependent variable of symptomatic hemorrhage or good clinical outcome controlling for age, NIHSS score, clot location, reperfusion status, and presence of diabetes mellitus. Utilization of CTP or MRI compared with NCT was forced into the model to determine if it was associated with better outcomes.

RESULTS

A total of 556 patients with a mean age of 66 ± 15 years and a median NIHSS score of 18 (IQR 14–22) were analyzed. NCT was used in isolation in 286 (51%) patients while CTP was performed in 190 (34%) patients and MRI of the brain in 80 (14%) patients. Table 1 shows the groups were comparable in terms of age, gender, presence of atrial fibrillation, and diabetes. Patients selected by NCT only had a higher baseline NIHSS score due to a higher proportion of patients with carotid terminus occlusions and were more likely to have been transferred from an outside facility. NCT patients had significantly lower median times from initial imaging to groin puncture (61 min, IQR (40–117)) compared with CTP (114 min, IQR (81–152)) or MRI (124 min, IQR (87–165)). Additionally, patients selected with NCT did not have higher hemorrhage rates, higher final infarct volumes, or differences in rates of good clinical outcomes.

We performed a binary logistic regression model to determine predictors of good clinical outcome and symptomatic hemorrhage, controlling for age, presence of diabetes mellitus, pre-treatment NIHSS score, location of thrombus, and reperfusion status. Table 2 shows the utilization of multimodal imaging did not appear to enhance clinical outcome. Additionally, multimodal imaging did not reduce the rates of symptomatic hemorrhages when controlling for age, NIHSS, clot location, use of intravenous tissue plasminogen activator prior to endovascular therapy, diabetes mellitus, reperfusion, and time from imaging to puncture (data not shown).

DISCUSSION

We evaluated the time to various treatment milestones in 556 acute ischemic stroke patients undergoing endovascular therapy at 10 tertiary medical centers. The use of advanced imaging modalities such as CTP and MRI is associated with increased time to groin puncture without reduction in hemorrhage rates, final infarct size, or improved clinical outcome. Even though the NCT only group had significantly higher initial NIHSS scores and more patients presenting with proximal intracranial carotid occlusions (ie, neurologically more severe), no difference in outcome among the groups was detected. Similar findings have been reported comparing CTP to a time based approach in a single center smaller sample size cohort.¹⁴

The current American Heart Association/American Stroke Association ‘Guidelines for the early management of adults with ischemic stroke’ state that multimodal imaging with CT or MRI “may provide additional information that will improve the diagnosis of ischemic stroke”.² While multimodality imaging is not mandated, the median time to commencement of the procedure is proposed as a core quality improvement metric.¹⁵¹⁶ Few centers employ MRI rapidly enough to triage patients for intravenous thrombolysis or endovascular thrombolysis.¹⁷ One center with an MRI in the emergency room reported a time from MRI acquisition to recanalization of approximately 210 min in a small cohort of 26 patients.¹⁸ This study and others¹⁹ do not report time from imaging to groin puncture, which may help develop uniform reporting standards. Despite ongoing controversies regarding patient selection and efficacy of endovascular therapy, it is widely accepted that successful reperfusion, and clinical outcome, are all time dependent.⁵²⁰

Our results demonstrate, across a range of comprehensive stroke centers with active endovascular programs, that acquisition of advanced neuroimaging is associated with increased time to groin puncture. This delay for advanced neuroimaging was present even when considering transfer status, which one would expect may confer prolonged time to intervention. The delay to groin puncture did not translate to longer procedure times, but provides a target for improvement. Additionally, we did not assess time from arrival to image acquisition, which may identify additional delays for advanced modality imaging, particularly placement of an intravenous line or waiting for a baseline creatinine.

There are several potential limitations and cautions to this analysis. First, the imaging paradigm used in acute stroke evaluation may not have been uniform within and across centers. Patients taken to CTP and MRI may have been those more likely to have increased delays because of patient specific characteristics not captured in our baseline data.

Our analysis also does not address the potential delay caused by vascular imaging, which may also play a role in determining endovascular team activation at some centers. Second, the number of patients required to detect a difference may be larger than the sample size we present. If this is the case, it would suggest that perhaps the number needed to treat to improve one clinical outcome may be larger than anticipated. Finally, we have limited information regarding the denominator, or patients who received advanced neuroimaging who did not proceed to endovascular therapy. Advanced neuroimaging can be used to rule in

patients for endovascular therapy; however, recent evidence suggests that diffusion weighted or perfusion imaging may be used to identify patients in whom revascularization therapies are futile.^{18,21} In the cohort of patients where Alberta Stroke Program Early CT Score (ASPECTS) was recorded, there does not seem to be large discrepancies in the size of the pretreatment infarct prior to treatment. It is important to note that we focused the analysis on patients under 8 h from symptom onset. Patients who present at later time points and with wake-up strokes may be treated based on physiologic data gathered from advanced modality imaging.²² Moreover, the results do not define which modality is the best tool to select patients, but rather show that the supposition that one modality can better select patients will require prospective studies. We acknowledge that some centers are more efficient at obtaining imaging, but current standards are not based on published data in this regard. More work is required to understand how rapidly centers are able to obtain imaging to make timely and efficient decision making.

In summary, significant practice variability exists in the use of advanced neuroimaging in acute stroke evaluation. Our results suggest that the use of advanced neuroimaging is associated with significant delays in initiating endovascular therapy. Moreover, in this cohort, no apparent improvement in outcome or decrease in hemorrhagic complications was demonstrated in those undergoing multimodality imaging prior to revascularization. These results should be confirmed prospectively in centers with routine protocols. Uniform reporting standards for each time point in the care of an endovascular patient are urgently required to help plan clinical studies employing advanced modality imaging.

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Table 1

Univariate ANOVA analysis comparing NCT with CTP and MRI in selecting patients for endovascular reperfusion therapy in acute ischemic stroke

Variable n(%)	NCT (n=286)	CTP (n=190)	MRI (n=80)	p Value
Demographics				
Age, mean (years±SD)	65±15	66±15	67±15	0.20
Female	141 (49)	105 (55)	42 (53)	0.44
Hypertension	206 (72)	143 (75)	48 (60)	0.04
Atrial fibrillation	98 (34)	65 (34)	24 (30)	0.76
Diabetes mellitus	70 (24)	44 (23)	18 (23)	0.91
Outside hospital	193 (67)	85 (45)	32 (40)	0.001
NIHSS score	19 (15–22)	17 (13–21)	18 (15–20)	0.01*
IV tPA	139 (49)	80 (42)	33 (41)	0.26
Clot location				
M1 MCA	159 (56)	119 (64)	58 (73)	0.01
M2 MCA	34 (12)	19 (10)	9 (11)	0.89
Carotid terminus	62 (22)	26 (14)	7 (9)	0.006
Extracranial ICA	2 (0.6)	3 (1.5)	2 (3)	0.53
Tandem occlusion	29 (10)	23 (12)	4 (5)	0.20
Outcomes				
ASPECTS >7	87/133 (65)	100/140 (71)	19/27 (70)	0.55
Time from symptom onset to image acquisition [IQR]	202 (165–231)	207 (173–254)	239 (181–276)	0.31
Time from image to puncture, median in minutes [IQR]	61 (40–117)	114 (81–152)	124 (87–165)	0.001*
Procedure time, median in minutes [IQR]	91 (65–132)	92 (64–129)	97 (78–130)	0.73*
Successful reperfusion	175 (61)	112 (59)	43 (54)	0.48
Symptomatic hemorrhage	20 (7)	12 (6)	4 (5)	0.81
Infarct volume, median in cubic cm [IQR]	48 (24–135)	48 (20–110)	42 (32–130)	0.25*
Good outcome	99/266 (37)	65/173 (38)	25/77 (32)	0.71
Death	68/266 (25)	37/173 (21)	22/77 (29)	0.43

ASPECTS, Alberta Stroke Program Early CT Score; CTP CT perfusion; ICA, internal carotid artery; IV tPA, intravenous tissue plasminogen activator; MCA, middle cerebral artery; NCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale.

* Kruskal–Wallis non-parametric test.

Table 2

Binary logistic regression model to determine factors associated with good clinical outcomes

Variable	OR	95% CI	p Value
Age	0.989	0.975 to 1.002	0.10
Diabetes mellitus	0.65	0.38 to 1.07	0.09
CTP or MRI	0.86	0.64 to 1.16	0.42
NIHSS score	0.88	0.84 to 0.92	0.001
IV tPA	1.12	0.73 to 1.70	0.61
Distal intracranial carotid	0.83	0.44 to 1.55	0.56
Successful reperfusion	7.09	4.38 to 11.49	0.001
Symptomatic ICH	0.22	0.07 to 0.65	0.006

CTP, CT perfusion; ICH, intracerebral hemorrhage; IV tPA, intravenous tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale.