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Iodinated Contrast Media and Cerebral Hemorrhage After Intravenous Thrombolysis

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Background and Purpose—Iodinated contrast is increasingly used in CT perfusion or angiographic examinations in acute stroke. Increased risk of intracranial hemorrhage (ICH) complicating microcatheter contrast injections has recently been reported in the second Interventional Management of Stroke (IMS 2) trial with contrast toxicity potentially contributory.

Methods—We reviewed clinical and radiological data on all patients treated with intravenous alteplase at a single center between May 2003 and November 2008.

Results—Of 312 patients treated with intravenous alteplase, 69 (22.1%) received intravenous iodinated contrast in volumes between 50 and 150 mL. Incidence of symptomatic ICH defined as per European Cooperative Acute Stroke Study 2 was 16 of 312 (5.1%; 95% CI, 2.7% to 7.6%); among patients not given contrast, it was 12 of 243 (4.9%; 2.2% to 7.7%) compared with 4 of 69 (5.8%; 0.3% to 11.3%) in those given contrast. Incidence of symptomatic ICH defined as per Safe Implementation of Thrombolysis in Stroke-MONitoring Study (SITS-MOST) criteria was 12 of 312 (3.9%; 1.7% to 6%), 9 of 243 (3.7%; 1.3% to 6%) among those not given contrast, and 3 of 69 (4.4%; 95% CI, -0.5% to 9.2%) among those given contrast. Patients with symptomatic ICH were older, had higher pretreatment National Institutes of Health Stroke Scale, and blood glucose than those without symptomatic ICH. In logistic regression analysis, pretreatment blood glucose was the only significant predictor of symptomatic ICH by either definition (OR, 1.23; 95% CI, 1.03 to 1.48 per mmol/L increment; $P=0.024$). Contrast administration or dose was not associated with symptomatic ICH.

Conclusions—Intravenous iodinated contrast in doses typically required for CT angiography and perfusion imaging was not associated with symptomatic intracranial hemorrhage in patients treated with alteplase. (*Stroke*. 2011;42:2170-2174.)

Key Words: cerebrovascular disease ■ contrast ■ CT ■ imaging ■ intracerebral hemorrhage ■ stroke ■ thrombolysis

Brain imaging has the potential to improve patient selection for intravenous (IV) thrombolysis by excluding from treatment those with predominantly irreversible ischemia and confining treatment to those with potentially viable penumbra. Selection using MRI-based penumbral assessment was associated with lower risk of symptomatic intracranial hemorrhage (SICH) in prospective cohort studies.^{1,2} Multimodal CT imaging, comprising CT perfusion and CT angiography in addition to noncontrast CT, offers an alternative method of penumbral imaging that is potentially widely applicable. However, analysis of the second Interventional Management of Stroke II (IMS-2) study has suggested that microcatheter injection of iodinated radiographic contrast may increase the risk of intracranial hemorrhage (ICH) after intra-arterial recombinant tissue-type plasminogen activator (rtPA)^{3,4} independent of conventional predictors such as the extent of hypoattenuation on CT scan, prior antiplatelet use, and hyperglycemia.⁵⁻⁸ Similar findings were also reported in

a retrospective registry study by the same group.⁹ The IMS investigators hypothesized that this effect may be due to either contrast extravasation with toxicity to the blood-brain barrier or physical trauma to the microvasculature consequent to pressure of injections. Contrast doses in multimodal CT are typically 100 to 150 mL, similar to those typically administered during interventional revascularization procedures. The issue of contrast-related risk is therefore pertinent to both multimodal CT selection for IV therapy and for interventional procedures.

We sought to determine whether IV contrast administered for multimodal CT was related to SICH risk in a cohort of patients treated with IV rtPA.

Methods

We reviewed data on all patients treated with IV rtPA at a single comprehensive stroke center between May 2003 and the end of November 2008. All patient data were entered into the Safe Imple-

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mentation of Thrombolysis in Stroke (SITS) register^{10–12} and had follow-up brain imaging with CT approximately 24 hours after treatment or sooner if their condition deteriorated. CT perfusion and CT angiography were available at the discretion of the treating clinician to support decision-making or were undertaken as part of clinical research studies. All patients received IV rtPA in a National Institute of Neurological Disorders and Stroke dose schedule (0.9 mg/kg total dose to a maximum of 90 mg).

Iodinated contrast of 2 types was used during the study period: Xenetix 350 (iobitridol) since 2005 and Niopam (iopamidol) before this. Contrast examinations were not performed in patients with a glomerular filtration rate of <30 mL/min.

Data on patient age, pretreatment National Institutes of Health Stroke Scale (NIHSS) score and blood glucose concentration, onset to treatment time, and ICH type were extracted from the local SITS database. Information on contrast exposure was obtained by review of neuroradiology departmental records crossreferenced with imaging reports and patient case notes. To include only contrast exposure preceding, or concurrent with, IV thrombolysis, we included only contrast CT examinations on the same date as the first CT. Standard practice in the unit was for additional contrast CT examinations to be performed either immediately before administration of the bolus of alteplase or (where scans were undertaken for research purposes and a treatment decision was made on noncontrast CT) immediately after the bolus was administered but before the alteplase infusion was started. Onset to treatment time therefore closely reflects the onset to imaging time. Intra-arterial treatment was not routinely undertaken at our center.

Definition of ICH

We categorized ICH according to the European and Australian Cooperative Stroke Study (ECASS) classification¹³ incorporating size and morphology to define hemorrhagic infarction Types 1 and 2 and parenchymal hematoma Types 1 and 2. We analyzed the incidence of any ICH on follow-up imaging (hemorrhagic infarction 1 or 2 or parenchymal hematoma 1 or 2) and also SICH, which we defined according to both the SITS-Monitoring Study (SITS-MOST; deterioration of NIHSS score by ≥ 4 points within 24 hours of treatment associated with parenchymal hematoma 2 on follow-up imaging)¹² and ECASS-2 (blood at any site on the CT scan in combination with clinical deterioration or adverse events indicating clinical worsening or causing a deterioration in the NIHSS score by ≥ 4 points.¹⁴) criteria.

Statistical Analysis

Statistical analysis was performed using SPSS 15 (SPSS Inc, Chicago, IL) and STATSDIRECT (StatsDirect Ltd, Cheshire, UK) software. For baseline data, Fisher exact test was used to compare proportions in 2×2 tabulated data, normally distributed variables were compared by unpaired *t* tests, and nonnormal data by Mann-Whitney *U* tests. Binary logistic regression analysis was carried out using SPSS to seek predictors of any ICH or SICH by both SITS and ECASS-2 definitions. Univariate analysis included onset to treatment time, treatment within 3 hours of onset, age, hypertension, diabetes, atrial fibrillation, blood glucose, NIHSS score, systolic and diastolic blood pressure, contrast dose, and contrast administration as a binary variable. All variables with $P < 0.1$ in univariate analysis were entered into a forward stepwise conditional model. Findings were confirmed in a backward stepping model beginning with all potentially predictive variables.

Results

Data from 319 consecutive patients were available, for whom complete data on contrast use and follow-up imaging were available on 312. One patient who had a rescue intra-arterial procedure after initial IV thrombolysis was excluded from analysis. No other patients had intra-arterial procedures. One patient had received a 200-mL dose of contrast during percutaneous coronary intervention that was performed im-

mediately before stroke onset. This patient subsequently had an additional 150 mL of contrast during multimodal imaging. Baseline clinical data for patients exposed to contrast and those not exposed are summarized in Table 1. The patients exposed to contrast were significantly younger and had a lower rate of documented atrial fibrillation, but otherwise there were no significant differences between the contrast-exposed and nonexposed groups. Patients who had multimodal imaging were not treated significantly later than those treated with noncontrast CT alone (174 minutes versus 169 minutes, $P = 0.346$).

Overall median NIHSS score pretreatment was 15 (interquartile range, 9 to 19). The mean onset-to-treatment time was 170 minutes.

The incidence of ICH of all radiological categories, or of SICH by either ECASS-2 or SITS-MOST definitions, did not differ between those who received IV contrast and those who did not. Detailed comparison of relevant factors between hemorrhage categories is described in Table 2.

In binary logistic regression analysis, univariate analysis identified age, treatment within 3 hours, NIHSS score, systolic blood pressure, and pretreatment blood glucose as possible predictors. These were entered into multivariate models together with contrast dose and contrast use as a dichotomous variable. In multivariate regression, SICH by ECASS-2 definition was associated with only pretreatment blood glucose (OR, 1.20; 95% CI, 1.003 to 1.42 per mmol/L increment; $P = 0.046$); presence of any ICH was associated only with pretreatment NIHSS score (OR, 1.07; 95% CI, 1.03 to 1.12; $P = 0.002$). Use of contrast was not associated with ICH risk by any definition.

Conclusions

The potential for multimodal imaging to improve clinical outcomes by targeting thrombolytic treatment to those with a perfusion scan signature of the ischemic penumbra, or to extend the time window by identifying individuals with viable tissue beyond conventional times, has been recognized and partly supported by observational data that used MRI definitions of penumbra.² Multimodal CT imaging is increasingly available as multidetector scanners with large detectors proliferate and arguably has advantages over MRI in accessibility and possibly patient safety (fewer contraindications, shorter acquisition times, and an easier physiological monitoring environment). However, evidence in support of multimodal CT's use is much less than for MRI, and it has other safety issues, notably additional radiation exposure and significant volumes of iodinated contrast administration. In addition to rare allergic reactions, iodinated contrast administration may impair renal function and may be associated with lactic acidosis in patients taking metformin. A hypothetical concern that iodinated contrast may interfere with the fibrinolytic properties of rtPA based on animal data was not supported by a recent systematic review of clinical studies in stroke,¹⁵ but this review was able to use only indirect comparisons of recanalization rates and the possibility cannot be excluded.

Recently, a possible increase in risk of ICH was reported to be associated with the number of intra-arterial microcatheter

Table 1. Baseline Variables and Outcomes Stratified by Contrast Exposure

Clinical Features	Contrast (n=69)	No Contrast (n=243)	P
Age, y (mean±SD)	62.9±13.4	70±12	<0.0001
Male, no. (%)	35 (51)	155 (64)	0.052
Baseline NIHSS, median (IQR)	13 (8–15)	15 (10–20)	0.114
Serum glucose, mmol/L (mean±SD)	6.7±2.7	6.8±1.8	0.899
Atrial fibrillation, no. (%)	13 (18.8)	81 (33.3)	0.030
Diabetes mellitus, no. (%)	4 (5.8)	26 (10.7)	0.257
Hypertension, no. (%)	33 (47.8)	138 (56.8)	0.217
Current smoker, no. (%)	23 (33.3)	58 (23.9)	0.122
Previous stroke, no. (%)	6 (8.7)	38 (15.6)	0.172
Initial systolic BP, mm Hg (mean±SD)	143.6±30.8	147.8±26.8	0.3708
Initial diastolic BP, mm Hg (mean±SD)	76.8±16.5	75.5±16.1	0.367
Treatment <3 h, no. (%)	40 (58)	181 (66.5)	0.201
Onset-to-treatment time, min (mean±SD, median)	174.3±45 median 172.5	169.3±37 median 175	0.346
IA treatment, no. (%)	1 (1.4)	0	0.221
CTA only, no. (%)	15 (21.7)	0	
CTP only, no. (%)	20 (29)	0	
CTA and CTP, no. (%)	34 (49)	0	
Contrast dose CTA, mL (mean±SD)	58.5±3.7		
Contrast dose CTP, mL (mean±SD)	58.7±3.5		
Total contrast dose, mL (mean±SD)	110.9±8.6		
Asymptomatic ICH, no. (%)	8 (11.6)	45 (18.5)	
PH1, no. (%)	2 (2.8)	17 (6.8)	
PH2, no. (%)	5 (7.2)	10 (4.1)	
Symptomatic ICH (ECASS), no. (%), 95% CI	4 (5.8) (CI, 0.3 to 11.3)	12 (4.9) (CI, 2.2 to 7.7)	0.753
Symptomatic ICH (SITS-MOST), no. (%), 95% CI	3 (4.4) (CI, -0.5 to 9.2)	9 (3.7) (CI, 1.3 to 6)	0.722

NIHSS indicates National Institute of Health Stroke Scale; IQR, interquartile range; BP, blood pressure; IA, intra-arterial; CTA, computed tomography angiography; CTP, computed tomography perfusion; ICH, intracerebral hemorrhage; PH, parenchymal hemorrhage; ECASS, European and Australian Cooperative Stroke Study; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; CI, confidence interval; SD, standard deviation.

injections of iodinated contrast in patients given combined IV and intra-arterial thrombolytic treatment in the second IMS trial.⁴ The IMS investigators considered that increased ICH risk reflected loss of blood–brain barrier integrity and could have resulted either from contrast toxicity or from pressure-

related damage consequent to microcatheter injections.⁴ The first possibility raises concern about the increasing use of iodinated contrast in multimodal CT in addition to interventional revascularization procedures. The IMS-2 report used the widest possible definition of ICH, including hemorrhagic

Table 2. Comparison of Features by Hemorrhage Incidence*

	Non-SICH Group	ICH		
		Asymptomatic ICH	ECASS-2 Definition	SITS-MOST Definition
Total no. (%)	243 (77.9)	53 (17)	16 (5.1)	12 (3.8)
Age mean (95% CI), y	67.8 (66–69)	70 (66–74)	71.7 (65–78)	75.2 (70–80)
Admission blood glucose mean (95% CI), mmol/L	6.7 (6.4–6.9)	6.9 (6.3–7.4)	7.9 (5.7–810.1)	8.2 (5.4–11)
Baseline NIHSS median (IQR)	14 (7–19)	17 (13–21)	18 (11–26)	18 (10–25)
No. treated within 3 h, (%)	156 (64.5)	37 (69.8)	7 (43.8)	4 (33.3)
Time to treatment mean (95% CI), min	171 (166–176)	166 (158–175)	165 (149–182)	177 (164–190)
No. receiving iodinated contrast, (%)	56 (23)	8 (15.1)	5 (31)	4 (33.3)
Contrast volume median, mL	100	60	110	110

ICH indicates intracerebral hemorrhage; SICH, symptomatic intracerebral hemorrhage; ECASS, European and Australian Cooperative Stroke Study; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; NIHSS, National Institute of Health Stroke Scale; IQR, interquartile range; CI, confidence interval.

*Patient characteristics in groups defined by presence of blood on follow-up imaging.

infarction as well as the clinically important parenchymal hematomas to increase the numbers for analysis. The IMS group reported ICH of any type in 58% of their patients, a considerably higher rate than the 22% that we found with a similarly all-inclusive definition of ICH. Although greater stroke severity and longer time to treatment of patients treated in the IMS-2 study are expected to be associated with higher ICH risk than in our population receiving IV treatment, and other factors such as heparin use in IMS-2 study may also contribute, the very large difference in reported rates raises the possibility that the IMS-2 methodology resulted in over-reporting of ICH, particularly hemorrhagic infarction, as a consequence of minor local contrast extravasation being indistinguishable from blood, something that was acknowledged as a potential confounder by the investigators.

Animal studies have produced conflicting evidence on the potential blood–brain barrier toxicity of contrast media.^{16,17} A recent study in transient middle cerebral artery occlusion in rats reported that intra-arterial contrast administration, heparin administration, and coadministration of heparin and contrast significantly increased the incidence of cortical hemorrhage compared with control.¹⁸

It should be noted that our retrospective cohort of patients is very different from those enrolled in the IMS trials. In the IMS studies, the median NIHSS score at admission was higher.^{3,19} The patients exposed to contrast in our study were of a similar age to those in the IMS studies but the noncontrast-exposed patients were significantly older. We cannot therefore rule out a possible influence of contrast administration in a more severe clinical population. Our study also cannot address issues surrounding the intra-arterial administration of contrast or the greater volumes of contrast that may be administered if an intra-arterial procedure is preceded by multimodal CT imaging.

After adjustment for baseline imbalance in relevant prognostic factors between the contrast-exposed and nonexposed groups, we found no association of either IV contrast administration or contrast dose with SICH in our series of patients treated with IV rtPA. The only significant predictor of SICH was pretreatment blood glucose, consistent with other observations^{5,8,20,21}; both the PROACT II study and an analysis of the SITS database have reported an association of pretreatment hyperglycemia (thresholds of 200 mg/dL in Pro-Urokinase for Acute Cerebral Thromboembolism [PROACT] II and 180 mg/dL in SITS) with SICH,^{22,23} although an analysis of the ECASS-2 trial suggested that sustained rather than pretreatment hyperglycemia was the significant predictor.⁶ Our SICH rates are within the 95% CI for incidence by the ECASS-2 definition (4.6%; 4.1 to 5.1) but slightly higher by the SITS-MOST definition compared with the SITS-MOST series overall, possibly explained by an older population and more severe pretreatment NIHSS scores. Although the lack of association of IV contrast administration with SICH is reassuring, the similar rates of SICH in contrast and noncontrast groups (and possibly slightly higher rate of parenchymal hematoma 2 categorized ICH in the contrast group) despite these patients being younger and having less severe strokes, together with the small absolute numbers of SICH, indicates that replication of our findings in larger

series would be advisable. Our findings also cannot exclude potential problems related to intra-arterial contrast use, in which local concentrations will exceed those resulting from IV bolus administration.

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None.

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