Does the Application of X-Ray Contrast Agents Impair the Clinical Effect of Intravenous Recombinant Tissue-Type Plasminogen Activator in Acute Ischemic Stroke Patients?

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Background and Purpose—Experimental data suggest a negative interaction between x-ray contrast agents and fibrinolytic efficacy of recombinant tissue-type plasminogen activator (rtPA). We hypothesized that the application of a contrast agent before intravenous thrombolysis with rtPA reduces its clinical efficacy in acute ischemic stroke.

Methods—We retrospectively studied consecutive ischemic stroke patients receiving contrast agents for computed tomography angiography before intravenous treatment with rtPA. We compared functional outcomes with an historical control group from the Canadian Alteplase for Stroke Effectiveness Study who did not receive contrast agents before thrombolysis with rtPA. Primary end point was favorable functional outcome at 90 days defined as modified Rankin Scale scores 0 to 2. We performed logistic regression analysis and a propensity score matching analysis to estimate the effect size of contrast agent use as a negative predictor of outcome.

Results—We identified 111 patients for the computed tomography angiography and 1119 patients for the control group. Proportions of favorable functional outcome were 47.7% (53/111 patients) for the computed tomography angiography group and 49.5% (542/1094 patients) for the control group (P = 0.77). Adjusted probabilities for favorable outcome were 0.48 (95% CI, 0.37–0.58) and 0.51 (95% CI, 0.47–0.54), respectively. Contrast use was associated with reduced odds of favorable outcome (OR, 0.62; 95% CI, 0.38–0.99). Propensity score matching suggested a larger effect size (OR, 10.0%; 95% CI, 0.5%–19.3%).

Conclusions—Our study did not show a significant negative clinical effect of x-ray contrast agents applied before intravenous thrombolysis with rtPA. However, to confirm a possible small negative interaction between contrast agents and rtPA, additional experimental and prospective clinical studies are needed. (Stroke. 2012;43:1567-1571.)

Key Words: acute stroke ■ CT ■ thrombolysis

In acute ischemic stroke, noncontrast computed tomography (NCCT) is the preferred imaging modality in most stroke centers worldwide. NCCT can exclude intracerebral hemorrhage and allows an inclusive diagnosis of ischemic stroke before initiation of intravenous (IV) thrombolysis in many cases. Multimodal computed tomography techniques are increasingly used to determine intra- and extracranial arterial status and to determine cerebral perfusion parameters.1,2 Moreover, intra-arterial (IA) interventions seem promising to improve recanalization rates and clinical outcomes3 and are currently tested in a large phase III clinical trial.4

All of these evolving techniques require the application of x-ray contrast agents. Widely used contrast agents used in CT diagnostics are typically iodinated, nonionic, and iso- or low-osmolar. The traditional safety concern regarding these contrast agents is the development of radio-contrast nephropathy, which has recently been shown to occur at very low rates in the setting of acute ischemic stroke.5,6 Other effects of radiographic contrast agents, such as negative change in the Hgb-O2 dissociation curve,7 changes in arterial caliber, hyperkalemia,8 and blood-brain barrier disruption9 are all suggestive of adverse pharmacological properties that remain largely unexplored in the clinical setting.

A less recognized concern is a possible interaction between x-ray contrast agents and thrombolysis.10 Experimental data from the cardiology literature suggest that contrast agents markedly delay the onset of thrombolysis of recombinant tissue-type plasminogen activator (rtPA), streptokinase, and urokinase.11 In coronary thrombosis in dogs, rtPA-induced reperfusion was significantly delayed in the presence of both ionic and nonionic iodinated contrast agents.12 Whereas in current cardiology clinical practice, the interaction between...
contrast agents and fibrinolysis is negligible because of prevailing mechanical recanalization techniques, it might play an important rule for acute ischemic stroke.

We retrospectively studied whether the application of x-ray contrast agents impairs the effectiveness of IV rtPA on improved functional outcome in acute ischemic stroke patients to decide whether a prospective observation is warranted.

Materials and Methods

Patients

With approval of our institutional ethics review board, we used a retrospective cohort design to study consecutive patients with acute ischemic stroke who received x-ray contrast agent to perform a CT angiography (CTA) before IV thrombolysis with rtPA. We compared their functional outcomes with an historical control group of patients who did not receive x-ray contrast agents for CTA before standard IV thrombolysis, ie, patients from the Canadian Alteplase for Stroke Effectiveness Study (CASES).13

Patients Receiving CTA Before Thrombolysis

We analyzed consecutive patients (April 2002–September 2006) who received CTA for acute ischemic stroke at a single tertiary care stroke center. All patients were prospectively documented in a CTA database that contains clinical baseline data, including the National Institute of Health Stroke Scale (NIHSS) score and the modified Rankin Scale (mRS) score; these were documented prospectively on admission. In cases where these scores were unavailable, they were derived retrospectively. Patients were regularly seen at 90 days poststroke for clinical follow-up and the mRS score was prospectively recorded. Missing functional outcome data were imputed from the discharge mRS using the last-score-carried-forward principle. To qualify for our analysis, patients had to be treated with IV rtPA within 6 hours from symptom onset. Exclusion criteria were a premorbid mRS score >3 and any primary or additional IA intervention.

All patients were examined with standard NCCT followed by CTA of the circle of Willis and optional CTA of the neck. The decision to perform a CTA was made at the discretion of the treating stroke neurologist and did not follow an institutional protocol. Overall, CTA was only sporadically performed at the beginning of the study period and evolved to frequent/routine use in potential rtPA cases.13 We identified 111 patients for the CTA group and 1119 patients to decide whether a prospective observation is warranted.

Control Group: CASES Patients

Detailed methods and results from the CASES study have been published previously.13 In brief, the CASES study was a prospective observational cohort study assessing the safety and effectiveness of IV rtPA for acute ischemic stroke. The study was mandated by the federal government as a condition of licensure of rtPA for the treatment of acute stroke in Canada. Over 2.5 years (1999–2001), a total of 1135 consecutive patients were enrolled at 60 centers across Canada. Each center obtained Institutional Review Board approval as required for the data collection protocol. Functional outcomes were collected at 90 days after stroke using mRS score. Patients in CASES did not receive contrast agents before IV thrombolysis. Those few patients who received x-ray contrast agents for combined IV/IA therapy were excluded from this analysis.

For both groups, we assessed the presence and extent of early ischemic changes by applying the Alberta Stroke Program Early CT Score (ASPECTS) to all baseline NCCT for 3-reader consensus. Readers were blinded to all clinical information except for symptom side. Accordingly, day-1 NCCT scans were assessed for the presence of parenchymal hematoma type 1 (PH-1) and type 2 (PH-2) using the ECASS classification.14

Statistical Analysis

We report data using standard descriptive statistics. Our primary end point was favorable functional outcome at 90 days, defined as mRS scores 0 to 2. Comparisons of proportions were made using Fisher’s exact test. We compared proportions of favorable functional outcomes at 90 days between the CTA and control group and adjusted for common baseline confounders (age, baseline NIHSS score, history of diabetes, onset-to-treatment time, prethrombolysis antiplatelet therapy). We developed multivariate logistic regression models including the variables age, sex, history of diabetes mellitus, baseline NIHSS score, onset-to-treatment time, baseline ASPECTS score, and antiplatelet therapy to predict favorable functional outcome at 90 days. Subsequently, we used propensity score matching to estimate the effect size of performing a CTA on the prediction of functional outcome. Variables used to predict the propensity score were age, sex, history of diabetes mellitus, baseline NIHSS score, onset-to-treatment time, and baseline ASPECTS score. The propensity scores were then used to match cases using stratified matching and nearest-neighbor matching, simulating a randomized controlled trial.

Results

We identified 111 patients for the CTA group and 1119 patients for the control group. Patients receiving CTA before thrombolysis tended to be more severely affected (P=0.065) and showed more extensive signs of ischemia on NCCT (P=0.049) than did patients in the control group (Table 1). Although patients in the CTA group received rtPA up to 6 hours from onset, the average onset-to-treatment time was only 5 minutes longer in the CTA group compared with the control group (P=0.21). Remaining baseline characteristics did not differ among groups, apart from a higher proportion of prethrombolysis antiplatelet therapy in the control group (P<0.001).

Unadjusted proportions of patients who had a favorable functional outcome were 47.7% (53/111 patients) for the CTA group and 49.5% (542/1094 patients) for the control group (P=0.77). After adjustment for baseline confounders, probabilities for favorable functional outcome were 0.477 (95% CI, 0.37–0.58) for the CTA group and 0.513 (95% CI, 0.47–0.54) for the control group. In the subgroup of patients who received rtPA within 3 hours from onset, probabilities were unchanged (0.485 versus 0.515, respectively).

In multivariate logistic regression analysis, performance of CTA was associated with reduced odds of favorable functional outcome (OR, 0.62; 95% CI, 0.38–0.99; Table 2). Additional independent predictors of functional outcome were age, baseline NIHSS score, history of diabetes, baseline
Discussion
In our study, we did not find evidence confirming our hypothesis that the beneficial effect of IV rtPA is reduced in acute stroke patients who received CTA before thrombolysis. Patients who received CTA were 3% less likely to be functionally independent at 3 months compared with an historical control group; however, this effect was not statistically significant. Propensity score analysis, simulating a randomized controlled trial, suggested a negative effect of performing a CTA with an absolute effect size of 10%, though precision of this estimate was low. In multivariate analysis, performing a CTA before IV thrombolysis was a weak independent negative predictor of favorable functional outcome. So overall, our data does not rule out a small magnitude negative biological effect of radio-contrast media.

We regard this observation as hypothesis generating and requiring confirmation. Only a few experimental and clinical studies have assessed the effects of contrast agents on thrombolysis. Over 2 decades ago, cardiologists began a debate about the interaction of x-ray contrast agents and blood function. Robertson and colleagues observed blood clot formation in angiographic syringes containing nonionic contrast media. When coronary thrombolysis was introduced into clinical practice, experimental studies examined the interaction with contrast agents. Dehmer and colleagues demonstrated that fibrinolysis with streptokinase, urokinase, or rtPA was markedly delayed in the presence of ionic or nonionic contrast agents. This effect was dose-dependent, but already occurred at clinically relevant drug concentrations. In experimental coronary thrombosis in dogs, Pislaru et al showed that reperfusion after standard thrombolysis with rtPA was significantly delayed after injection of different ionic or nonionic contrast agents. In addition, coronary reocclusion was observed more frequently in dogs receiving contrast agents compared with saline controls. A possible explanation for the failure of clot lysis is that contrast agents alter the assembly and structure of fibrin, thereby making clots more resistant to thrombolytic drugs. Another mechanism for disturbed clot lysis seems to be the inhibition of plasminogen activation.

Nonionic contrast agents usually can be visualized by CTA or CT perfusion imaging during their first pass through the brain vasculature, and parenchyma with minimal delay after contrast injection. Under normal conditions and as evidenced by CT perfusion studies, there is a rapid and almost complete washout of contrast after the first bolus pass. This first phase of contrast flooding and washout is followed by a second phase of recirculation. For the nonionic contrast agent ioversol, which was used in our study, elimination half-life is about 1 to 2 hours. Thus, depending on the interval from contrast application to rtPA treatment, effective IA cerebral contrast concentration might be very low. In the setting of a complete intracranial arterial occlusion, however, it seems likely that some contrast material gets trapped intra-arterially proximal to and within the occlusive clot. This hypothetical mechanism would allow for a later interaction with fibrinolysis at the occlusive site.

Our study relates the existing knowledge on interactions between thrombolysis and contrast agents application to the setting of acute ischemic stroke therapy. The potentially decreased chance for independent functional outcome in patients having received contrast agents before thrombolysis.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Control (n=1119)</th>
<th>CTA (n=111)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD (y)</td>
<td>70±13</td>
<td>69±16</td>
<td>0.20*</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>603/1104 (54)</td>
<td>57/111 (51)</td>
<td>0.55†</td>
</tr>
<tr>
<td>Hx antiplatelet therapy, n (%)</td>
<td>227/1053 (22)</td>
<td>6/111 (5)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>235/1053 (22)</td>
<td>26/111 (23)</td>
<td>0.81†</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>534/1053 (51)</td>
<td>65/111 (59)</td>
<td>0.13†</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>202/1053 (19)</td>
<td>18/111 (16)</td>
<td>0.52†</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>263/1053 (25)</td>
<td>25/111 (23)</td>
<td>0.64†</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>169/1053 (16)</td>
<td>15/111 (14)</td>
<td>0.58†</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>161/1053 (15)</td>
<td>25/111 (23)</td>
<td>0.056†</td>
</tr>
<tr>
<td>Dominant hemispheric stroke</td>
<td>481/1094 (44)</td>
<td>56/111 (50)</td>
<td>0.014†</td>
</tr>
<tr>
<td>NIHSS score, median, (IQR)</td>
<td>12 (7–17)</td>
<td>14 (9–19)</td>
<td>0.065†</td>
</tr>
<tr>
<td>OTT (mean±SD; min)</td>
<td>150±37</td>
<td>155±63</td>
<td>0.21*</td>
</tr>
<tr>
<td>OTT or/3 h, n (%)</td>
<td>970/1105 (88)</td>
<td>85/111 (77)</td>
<td>0.002†</td>
</tr>
<tr>
<td>ASPECTS &gt;7, n (%)</td>
<td>552/922 (70)</td>
<td>76/109 (60)</td>
<td>0.049†</td>
</tr>
</tbody>
</table>

CIA indicates computed tomography angiography; Hx, history of; CAD, coronary artery disease; NIHSS, National Institute of Health Stroke Scale Score; IQR, interquartile range; OTT, onset-to-treatment time; ASPECTS, Alberta Stroke Program Early CT Score.

Statistical test for group comparisons: *two-sample t test, †Fisher exact test, ‡Mann-Whitney U test.

ASPECTS, and onset-to-treatment time. Antiplatelet therapy did not affect the proposed relationship.

Using propensity score matching, we found that the CTA group was less likely to achieve a favorable functional outcome, with an average treatment effect size of 10.0% (95% CI, 0.5%–19.3%) using nearest-neighbor matching and 9.3% (95% CI, 4.8%–23.4%) using stratified matching and 9.3% using the nearest-neighbor matching.

In the CTA group, we found 8 parenchymal hematomas (7.2%), of which 3 hematomas (2.7%) were judged as PH-2. In the control group, of 884 follow-up NCCT scans available for interpretation, 100 parenchymal hematomas (11.3%) were diagnosed, and 47 hematomas (5.3%) were classified as PH-2. No statistically significant difference in parenchymal hematomas (OR=0.401) or PH-2 (OR=0.473) was observed.

Table 2. Predictors of Favorable Outcome (mRS 0–2) at 90 Days in Multivariate Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA performed</td>
<td>0.62</td>
<td>0.049</td>
<td>0.38–0.99</td>
</tr>
<tr>
<td>NIHSS baseline (per point increase)</td>
<td>0.89</td>
<td>&lt;0.001</td>
<td>0.87–0.91</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>0.95</td>
<td>&lt;0.001</td>
<td>0.94–0.97</td>
</tr>
<tr>
<td>Hx diabetes</td>
<td>0.59</td>
<td>0.014</td>
<td>0.38–0.89</td>
</tr>
<tr>
<td>ASPECTS (per point increase)</td>
<td>1.19</td>
<td>&lt;0.001</td>
<td>1.10–1.29</td>
</tr>
<tr>
<td>OTT (per minute increase)</td>
<td>0.99</td>
<td>0.091</td>
<td>0.99–1.0</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; CTA, computed tomography angiography; NIHSS, National Institute of Health Stroke Scale Score; Hx, history of; ASPECTS, Alberta Stroke Program Early CT Score; OTT, onset-to-treatment time.
in our study may be caused by the proposed interaction between contrast agents and rtPA; this results in reduced degree and rate of arterial recanalization. However, we cannot exclude the possibility that other effects of contrast agents may be relevant for these outcome differences. For example, contrast agents, especially the ionic type, are known to cross the blood-brain barrier in acute ischemia and might have a toxic effect on ischemic brain tissue.23–26 In addition, IA contrast injections in acute ischemic stroke patients may increase the risk of intracerebral hemorrhage.27 Similar rates of parenchymal hematomas between the CTA and control groups in our study, however, do not suggest a substantial effect on postthrombolysis hemorrhagic transformation. In this regard, our study confirms a recent observation that IV contrast application does not seem to increase the risk for intracerebral hemorrhage after thrombolysis.28

A possible interaction between contrast agents and rtPA is relevant given that, in acute ischemic stroke, CT imaging studies requiring contrast agent application (ie, CTA and CT perfusion imaging) often precede IV thrombolysis with rtPA. In addition, many stroke centers perform endovascular acute stroke thrombolysis with rtPA, a procedure that repeatedly uses contrast agents. The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial randomized acute stroke patients to IA application of prourokinase plus heparin or to heparin alone after angiographic confirmation of a middle cerebral artery occlusion; it showed improved functional outcomes at 3 months compared with controls. Hence, this trial demonstrated benefit of IA thrombolysis despite repeated contrast agent application. However, the recanalization rate remained suboptimal (66% Thrombolysis in Myocardial Infarction grade 2 and 3) and this trial used prourokinase rather than rtPA.3 Such an interaction would also be relevant for current stroke thrombolysis trials that require the application of contrast agents for identification of an arterial occlusion on CTA (Desmoteplase in Acute Ischemic Stroke III and IV studies) or digital subtraction angiography (Interventional Management of Stroke III [IMS] Study).4 The IMS III study is a prospective, multicenter, randomized open label trial that compares the efficacy of combined IV and endovascular recanalization versus IV rtPA alone. Because this trial allows performing a CTA before thrombolysis, this subset of data might be used to study prospectively the effect of contrast agents on efficacy of thrombolysis. A recent systematic review compared recanalization rates in anterior circulation stroke patients that were exposed versus not exposed to different iodinated contrast agents before standard thrombolysis.29 The authors did not find a significant difference in pooled proportions for recanalization (53% [95% CI, 36%–70%] versus 61% [95% CI, 52%–71%]) and concluded that a randomized trial would require at least 240 subjects, but likely a much higher number.

Our study has several limitations. First, we retrospectively compared 2 nonrandomized stroke cohorts. Although our study design was pragmatic, it would be ideal to have concurrent controls. Patients in the CTA group tended to be more severely affected and showed larger infarctions at baseline. Although we adjusted for baseline imbalances, differences in functional outcome might simply reflect baseline differences between the 2 groups. Our results might therefore be subject of a type II error. For this reason, we performed a propensity score analysis that aimed to simulate a randomized trial. Second, only a limited number of prognostically relevant factors were available and were included in our model that might have influenced 3-month outcomes: baseline characteristics such as premorbid mRS score and blood glucose level; data on clinical course and interventions between hospital admission and day 90, such as carotid artery stenting or endarterectomy; and infections. Given that we have compared 2 average stroke populations, these latter factors should be balanced. The comparison of a multicenter with a monocentric patient cohort, however, might have introduced systematic differences, such as different secondary prevention and rehabilitation strategies.

Third, patients in our historical control group were studied several years earlier than were patients in the CTA group (1999–2001 versus 2002–2006), thus potentially resulting in differences of functional outcomes caused by secular trends in general stroke care. Fourth, the control group may have contained patients with nonischemic symptom etiology and, thus, favorable clinical course, as no vascular imaging was performed. In addition, we were not able to compare recanalization rates, as no follow-up vascular imaging was performed in most of the CTA and control patients. Fifth, the individual decision to order a CTA might have introduced a selection bias to our CTA cohort. Furthermore, the CTA results might have changed patient management, eg, triggered IA intervention or early carotid revascularization. Finally, our results may not be generalizable to contrast agents other than Optiray (ioversol), which was applied in our stroke center. Other x-ray contrast agents have other chemical and pharmacological properties and may have differing interactions with thrombolysis. Similarly, we do not know whether other plasminogen activators (eg, prourokinase, desmoteplase, tenecteplase) might show different properties in combination with x-ray contrast agents. For example, Parsons et al demonstrated a significantly better major vessel recanalization with tenecteplase compared with alteplase (10/15 versus 7/29; P=0.01) in acute stroke patients selected with multimodal CT imaging.30

Conclusions

Our study did not show a significant negative clinical effect of x-ray contrast agents applied before IV thrombolysis with rtPA. However, to confirm a possible small negative interaction between contrast agents and rtPA, additional experimental and prospective clinical studies are needed. Until additional data are available, the potential diagnostic advantage of performing a CTA in acute stroke patients may outweigh the risks of iodinated contrast agent application.

Disclosures

None.

References

1. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke
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