Contrast Enhancement and Contrast Extravasation on Computed Tomography After Intra-Arterial Thrombolysis in Patients With Acute Ischemic Stroke

Woong Yoon, MD; Jeong Jin Seo, MD; Jae Kyu Kim, MD; Ki Hyeon Cho, MD; Jin Gyoong Park, MD; Heoung Keun Kang, MD

Background and Purpose—The goal of this study was to determine the CT findings and clinical consequences of contrast enhancement and contrast extravasation on CT scans obtained after intra-arterial thrombolytic therapy for treatment of acute ischemic stroke.

Methods—Sixty-two patients were treated with intra-arterial thrombolysis. All patients underwent nonenhanced CT scans immediately and 24 hours after thrombolytic therapy. Contrast enhancement was defined as a hyperdense lesion that disappeared on a 24-hour follow-up CT scan. Contrast extravasation was defined as a hyperdense lesion with maximum Hounsfield unit >90 that persisted on a follow-up CT scan. We evaluated the differences in the clinical and radiological data between 3 groups: contrast enhancement, contrast extravasation, and control groups.

Results—Contrast enhancement was found in 14 of 62 patients (22.6%); contrast extravasation was seen in 7 (11.3%). Compared with the control group, the contrast enhancement group had a lower recanalization grade (64.3% versus 34.1%, \( P = 0.048 \)) and a lower incidence of hemorrhagic transformation (14.3% versus 43.9%, \( P = 0.047 \)). The contrast extravasation group had a higher incidence of both hemorrhage (100% versus 43.9%, \( P = 0.006 \)) and symptomatic hemorrhage (100% versus 14.6%, \( P < 0.001 \)) than the control group. Poor outcomes were more frequent in the contrast extravasation group (100% versus 38.9%, \( P = 0.003 \)) than the control group.

Conclusions—Contrast enhancement on CT scans obtained after intra-arterial thrombolysis is usually not associated with hemorrhagic complications. However, contrast extravasation is highly associated with parenchymatous hematoma and should be considered a negative prognostic sign. (Stroke. 2004;35:876-881.)

Key Words: blood-brain barrier ■ contrast media ■ stroke, ischemic ■ thrombolytic therapy ■ tomography, x-ray computed
ing mass effect or cavity. On the contrary, extravasated contrast medium is commonly present as a mixture of blood and contrast material and is noted by its extremely high density on CT scans. Contrast extravasation usually persists within the hematoma cavity on subsequent CT scans. Moreover, the clinical consequences of these 2 phenomena are quite different. The purpose of this study is to determine the CT findings and clinical consequences of contrast enhancement and contrast extravasation on nonenhanced CT scans obtained immediately after intra-arterial thrombolytic therapy for treatment of acute ischemic stroke.

Materials and Methods

Between October 1995 and December 2002, 62 consecutive patients who presented with acute carotid territory stroke were treated with intra-arterial thrombolysis. Intra-arterial thrombolysis for carotid circulation was undertaken if the therapy could be started within 5 hours of symptom onset. During the same period, patients who presented within the 3-hour time window were treated with intravenous administration of tissue plasminogen activator. Those patients were excluded from this study.

In all study patients, an initial CT scan was obtained just after arrival at the hospital. Exclusion criteria for patient selection included the presence of intracranial hemorrhage or mass effect and evidence of hypodensity in more than one third of the middle cerebral artery territory on head CT scanning. Mass effect was defined when the CT depicted cortical sulci obliteration, lateral ventricle displacement, or midline shift of >2 mm. We defined hypodensity as a visible decrease in x-ray attenuation of brain tissue compared with the attenuation in other portions of the brain. All patients or relatives gave informed consent before cerebral angiography and intra-arterial thrombolysis. Approval was granted by our institutional review board.

Cerebral angiography was performed via a femoral approach. After demonstration of an arterial occlusion on diagnostic angiography, a microcatheter was introduced coaxially with the 6F guide catheter into the occlusion site, and urokinase was administered as a thrombolytic drug. We would not perform thrombolytic therapy when angiograms revealed carotid artery occlusion below the carotid bifurcation. Along with the thrombolytic agent, each patient received a bolus of 3000 U heparin intravenously, followed by 1000 U every hour thereafter. Thrombolytic therapy was discontinued when full recanalization was achieved, when 6 hours had elapsed since the onset of symptoms, or when there was a suspicion that hemorrhage may have occurred. The arterial occlusion site on a diagnostic angiogram was recorded for each patient. Recanalization was assessed on the control angiogram after intra-arterial thrombolysis and classified according to the grade of Mori et al as follows: unchanged, grade 0; movement of thrombus not associated with any improvement in perfusion, grade 1; partial recanalization with perfusion in <50% of the ischemic area, grade 2; complete recanalization, grade 4. Mori grades 0, 1, and 2 were considered poor recanalization; grades 3 and 4 were considered good recanalization.

All patients underwent nonenhanced CT scans immediately and 24 hours after treatment. The presence of contrast enhancement and contrast extravasation was evaluated by 2 radiologists with consensus review after reviewing the CT scans. Contrast enhancement was defined as a hyperdense lesion that disappeared on a 24-hour follow-up CT scan without leaving a hematoma cavity or mass effect. Contrast extravasation was defined as a hyperdense lesion with a maximum Hounsfield unit (HU) measurement >90 that persisted on a 24-hour follow-up CT scan. A hyperdense lesion with maximum HU <90 that persisted on the 24-hour follow-up CT scans was considered hemorrhagic lesion.

The National Institutes of Health Stroke Scale (NIHSS) score was recorded before treatment, at 24 hours after treatment, and on day 7. Clinical outcomes were measured 90 days after the procedure. Outcomes were defined in terms of the modified Rankin Scale; scores of 0 to 3 were defined as good, and scores of 4 or 5 and death as were considered poor outcomes.

Hemorrhagic transformation was defined as any area of petechial or confluent hemorrhage within regions of hypodense ischemic lesion present on follow-up CT obtained >24 hours after therapy. Symptomatic hemorrhage was defined as parenchymatous hematoma with substantial space-occupying effect within the infarcted tissue that related to neurological deterioration, the guideline for which was a ≥4-point increase in NIHSS score or a 1-point deterioration in level of consciousness.

Statistical analyses were performed with SPSS, version 10.0. To determine differences between the 3 groups, ie, contrast enhancement, contrast extravasation, and control groups (patients without contrast enhancement or contrast extravasation), univariate analyses were performed with χ² tests for categorical and dichotomous data, and the Kruskal-Wallis test statistics was performed for continuous data. To determine each difference between 2 groups, Fisher’s exact test and the Kruskal-Wallis test were applied. Independent associations of clinical outcome with other clinical and radiological factors were determined with a stepwise logistic regression model. Continuous data are expressed as either the mean or median±SD. A value of P<0.05 was considered significant.

Results

Baseline characteristics of each group are shown in Table 1. Of all 62 patients treated with intra-arterial thrombolysis, contrast enhancement was found on CT scanning performed immediately after the procedure in 14 patients (22.6%). Contrast enhancement developed in the posterior portion of the lentiform nucleus in 10 patients (see Figure 1), in the entire lentiform nucleus in 3 patients and in the posterior limb of the internal capsule in 1 patient. Thus, all cases of contrast enhancement occurred in the basal ganglia.

In all 62 study patients, contrast extravasation was noted on immediate CT scans in 7 patients (11.3%). Contrast extravasation developed in the entire lentiform nucleus in 3 patients (see Figure 2), in the posterolateral lentiform nucleus in 2 patients, in the entire basal ganglia in 1 patient, and in the frontal cortex in 1 patient. Thus, 86% of the contrast extravasation (6 of 7) occurred in the basal ganglia.

The median baseline NIHSS score was 15.8 in the contrast enhancement group, 17.7 in the contrast extravasation group, and 16.4 in the control group. The median times from onset to beginning of the thrombolysis were 4.8, 5.1, and 4.7 hours in the contrast enhancement, contrast extravasation, and control groups, respectively. Urokinase doses used were 76.7×10³, 63.5×10³, and 69.0×10³ in the contrast enhancement, in contrast extravasation, in control groups. There were no significant differences in baseline NIHSS score, duration of ischemia, and urokinase doses.

Although there were no significant differences in the occlusion site and recanalization grade, both the contrast enhancement and extravasation groups had more proximal occlusion and worse recanalization than the control group. Comparison of the 3 groups showed significant differences in hemorrhagic transformation, symptomatic hemorrhage, and clinical outcome (P=0.001, P<0.001, P=0.012, respectively).

With the use of a stepwise logistic regression analysis, variables independently associated with clinical outcomes were recanalization grade and symptomatic hemorrhage (Ta-
TABLE 1. Baseline Characteristics in the Contrast Enhancement, Contrast Extravasation, and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Contrast Enhancement (n=14)</th>
<th>Contrast Extravasation (n=7)</th>
<th>Control (n=41)</th>
<th>Enhancement vs Control*</th>
<th>Extravasation vs Control*</th>
<th>Enhancement vs Extravasation*</th>
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<tr>
<td>Age, y</td>
<td>60.2±16.2</td>
<td>62.2±14.1</td>
<td>61.9±13.2</td>
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<tr>
<td>Men</td>
<td>5</td>
<td>3</td>
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<tr>
<td>Women</td>
<td>9</td>
<td>4</td>
<td>14</td>
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<tr>
<td>NIHSS score</td>
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<td>16.4±3.3</td>
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<td>Time to reperfusion, h</td>
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</tbody>
</table>

*Fisher’s exact test, Kruskal-Wallis test.

UK indicates urokinase; CTO, carotid T occlusion; and MCA, middle cerebral artery.

Contrast Enhancement Versus Control

The rates of poor recanalization were 64.3% (9 of 14) and 34.1% (14 of 41) in the contrast enhancement and control groups, respectively. There was a significant difference in the recanalization grade between these 2 groups ($P=0.048$).

The rates of hemorrhagic transformation were 14.3% (2 of 14) and 43.9% (18 of 41) in the contrast enhancement and control groups, respectively. There was a significant difference in the hemorrhagic transformation between these 2 groups ($P=0.047$).

Figure 1. A 68-year-old woman presented with acute ischemic stroke. A, Nonenhanced CT scan just after intra-arterial thrombolytic therapy shows hyperdense lesion (arrow) in posterior part of lentiform nucleus. B, Follow-up CT scan obtained 24 hours after completion of intra-arterial thrombolytic therapy shows disappearance of hyperdense lesion and development of acute infarction involving right basal ganglia (arrows).

Figure 2. A 69-year-old woman presented with acute ischemic stroke. A, Posttherapeutic CT scan shows hyperdense lesion in entire lentiform nucleus. Maximum HU measurement was 255, indicating extravasated contrast materials. B, Follow-up CT scan obtained 24 hours after completion of intra-arterial thrombolytic therapy shows that hyperdense area developed into parenchymal hematoma with persistent extremely high density in its posterior portion.
Of contrast medium could be defined as a hyperdensity with the following day. Mericle et al\textsuperscript{12} suggested that extravasation extremely high density or a hyperdensity that had cleared by thrombolytic therapy. It has been described as either an intra-arterial thrombolytic therapy, the appearance of a new hyperdensity that behaves differently from the hemorrhage on CT scans obtained just after thrombolytic procedure. This may be analogous to the technique of delayed high-dose contrast CT by Hayman et al.\textsuperscript{17} Symptomatic hemorrhage did not occur in patients with contrast enhancement. Of the patients with contrast enhancement, 7 had a good outcome and 7 had a poor outcome.

\section*{Contrast Extravasation Versus Control}

Six of 7 patients with contrast extravasation had concomitant hemorrhage on CT scans obtained just after thrombolytic therapy. On the 24-hour CT scans, all patients with contrast extravasation showed persistence of extravasated contrast medium within the hematoma cavity that increased in size and caused considerable mass effect. All of these patients showed neurological deterioration 24 hours after the procedure. Six of 41 control patients (14.6\%) showed symptomatic hemorrhagic transformation. There were significant differences in the rates of hemorrhagic transformation and symptomatic hemorrhage between the contrast extravasation and control groups (\(P=0.006, P<0.001\), respectively).

All patients with contrast extravasation had poor outcomes at 90 days. Among these patients, 5 died <7 days after the thrombolytic therapy. Poor outcomes were significantly more frequent in the contrast extravasation group than in the control group (100\% versus 39\%, \(P=0.003\)). Seven of 18 control patients (38.9\%) with hemorrhagic transformation and 5 of 6 control patients (83.3\%) with symptomatic hemorrhage had poor outcomes. Poor outcomes were more frequent in patients with hemorrhagic transformation in the extravasation than in the control group (100\% versus 38.9\%, \(P=0.003\)).

\section*{Contrast Enhancement Versus Contrast Extravasation}

There were significant differences in the rates of hemorrhagic transformation (14.2\% versus 100\%, \(P<0.001\)) and symptomatic hemorrhage (0\% versus 100\%, \(P<0.001\)) between the contrast enhancement and extravasation groups. Poor outcomes were significantly more frequent in the contrast extravasation group (100\% versus 50\%, \(P=0.047\)).

\section*{Discussion}

On a nonenhanced CT scan obtained immediately after the intra-arterial thrombolytic therapy, the appearance of a new hyperdensity that behaves differently from the hemorrhage has been called extravasation of contrast medium injected during angiographic procedures performed during thrombolytic therapy. It has been described as either an extremely high density or a hyperdensity that had cleared by the following day. Mericle et al\textsuperscript{12} suggested that extravasation of contrast medium could be defined as a hyperdensity with a maximal HU measurement >90 and/or disappearance of the hyperdensity on a repeated CT taken within 24 hours. Recently, Nakano et al\textsuperscript{7} considered only rapidly clearing hyperdense areas to consist of the extravasation of contrast medium.

In this study, the CT findings and the progress of the 2 phenomena clearly differ. In patients with contrast enhancement, a hyperdense lesion that cleared by the next day, only 2 (14.2\%) developed hemorrhage without neurological deterioration on follow-up CT scans; 12 patients (85.7\%) never experienced a hemorrhagic event during their hospital admission. In contrast, all 7 patients with contrast extravasation, a hyperdense lesion with maximum HU >90 that persisted on follow-up CT scan, developed parenchymal hematoma with clinical deterioration. Nakano et al\textsuperscript{7} reported that the rapid disappearance of hyperdense areas, which is analogous to contrast enhancement in this study, on early posttherapeutic CT scans was never associated with symptomatic hemorrhage.

In the present study, 7 patients with contrast enhancement had good outcomes and 7 had poor outcomes. In contrast, contrast extravasation was clearly associated with poor outcome. All 7 patients with contrast extravasation had poor outcomes, and 5 of these 7 patients (71.4\%) died within 1 week of thrombolytic therapy. Therefore, we assume that contrast enhancement may be differentiated from contrast extravasation in that the CT findings and clinical consequences are quite different.

We infer that these differences may be due to dissimilar pathological changes in the cerebral microvascular barriers between the 2 phenomena. Both contrast enhancement and contrast extravasation may result from pathological changes in the integrity of the cerebral microvascular permeability barriers. It is known that the integrity of the cerebral microvasculature is provided mainly by 2 differing anatomical and functional barriers, ie, the blood-brain barrier (BBB) and basal lamina.\textsuperscript{15} The BBB is represented by the interendothelial cell tight junctions. The basal lamina consists of a network of type IV collagen and laminin polymer connected by entactin and serves as a structural barrier to the extravasation of cellular blood elements.\textsuperscript{15,16}

It is well known that contrast enhancement of brain tissue on CT or MR is caused by leakage of contrast medium from vessels into the extracellular spaces as a result of increased permeability of the BBB.\textsuperscript{17,18} Contrast enhancement of brain tissue on nonenhanced CT scans taken immediately after intra-arterial thrombolysis may occur over a prolonged period, with contrast leaking through the BBB of the microvessels supplying the basal ganglia during thrombolysis. When intra-arterial thrombolysis is performed, multiple angiographic injections of contrast medium through either a guiding catheter or a microcatheter is done around the lenticulostriate arteries to assess the response of thrombolytic therapy. This can lead to a gradual accumulation of contrast medium in the basal ganglia and is manifested as contrast enhancement on nonenhanced CT scans obtained just after the thrombolytic procedure. This may be analogous to the technique of delayed high-dose contrast CT by Hayman et al.\textsuperscript{17} They performed CT scans before, immediately after, and 3

\begin{table}
\centering
\caption{Multivariate Associations With Clinical Outcomes}
\begin{tabular}{lll}
\hline
Variable & OR (95\% CI) & \(P\) \\
\hline
Recanalization grade & 9.44 (2.55–34.97) & 0.001 \\
Symptomatic HT & 28.94 (3.01–277.97) & 0.004 \\
\hline
\end{tabular}
\end{table}

\textit{OR} indicates odds ratio; \textit{CI}, confidence interval; and \textit{HT}, hemorrhagic transformation.
hours after a high dose of intravenous contrast medium was administered to patients with acute ischemic stroke. They observed that the delayed scan demonstrated persistent contrast enhancement in areas of infarction in 7 patients. They explained that this contrast enhancement on delayed high-dose contrast CT resulted from the vasogenic edema caused by damage to the BBB. In the present study, the recanalization grade in patients with contrast enhancement group was significantly lower than that in the control group. This finding supports the idea that a prolonged angiographic procedure is responsible for the contrast enhancement in the basal ganglia.

On the other hand, contrast extravasation may be caused by degradation of the basal lamina, a structural barrier associated with disruption of the BBB. It may be postulated that contrast extravasation is easily associated with parenchymal hemorrhage because the basal lamina is the structural barrier preventing the cellular blood elements from extravasating from microvessels. In our study, 6 of the 7 patients with contrast extravasation had concurrent hemorrhage on a post-therapeutic CT scan. The limitation of this study is that histopathological study was not performed. Further experimental and pathological studies are needed to clarify our hypothesis that dissimilar pathological changes in the cerebral microvascular barriers may exist in patients with contrast enhancement and extravasation.

Several pathological mechanisms could disrupt the cerebral microvascular permeability barriers. A number of studies have demonstrated that intravascular injection of iodinated contrast media can disrupt the BBB. Postulates for the mechanism of contrast neurotoxicity include hyperosmolality, increased pinocytosis, and inherent chemotoxicity of the contrast agents. Several studies have shown that even nonionic, dimeric contrast media such as ioxidanol or iotrolan, with osmolality approximating that of plasma, causes BBB damage. In addition, it might be anticipated that the risk of BBB damage by contrast media would be increased in patients receiving intra-arterial thrombolysis because prolonged injection of large volumes of contrast could not be avoided during procedure and BBB damage is already initiated by ischemia. Thus, every effort to reduce contrast neurotoxicity against ischemic brain should be made during thrombolysis. Thrombolytic agents themselves could provoke injury to the microvascular permeability barrier, and exogenous plasminogen activators might accelerate dissolution of the BBB, microvascular basal lamina/extracellular matrix, and platelet-fibrin plugs, thereby increasing edema formation and the risk of hemorrhage. In addition, reperfusion of ischemic brain tissue after thrombolytic therapy may involve the risk of reperfusion injury through enhanced formation of reactive oxygen species and metalloproteinase activation.

In the present study, all cases of contrast enhancement and 86% of the contrast extravasation developed in the basal ganglia. Komiyama et al reported 2 cases of extravasation of contrast medium that occurred in the region of the basal ganglia. Urbach et al reported that 6 of 24 patients who received intra-arterial thrombolytic therapy showed extravasation of contrast medium on CT scans obtained within 24 hours after thrombolytic therapy, all of which occurred within the striatocapsular area. This area, the so-called basal ganglia, is supplied by a variety of arteries, including the recurrent artery of Heubner, the anterior choroidal artery, and the medial and lateral lenticulostriate arteries. These fragile vessels are end arteries with a poor collateral network. Because of this selective regional vulnerability, the microvascular permeability of the vessels in the basal ganglia is more easily disrupted than in other parts of the brain. As a result, contrast enhancement and contrast extravasation may occur primarily in the basal ganglia.

In addition, we have observed that contrast extravasation occurred in accordance with specific vascular territories in the basal ganglia. In our study, 10 patients with contrast enhancement and 2 patients with contrast extravasation showed contrast accumulation localized to the posterior part of the putamen that is supplied by the posteromedial branches of the lateral lenticulostriate artery. One patient with contrast enhancement showed contrast accumulation localized to the posterior limb of the internal capsule, which is the anterior choroidal artery territory. From these observations, it can be postulated that contrast enhancement and extravasation develop from disruption of the microvascular permeability barrier of specific arteries supplying the striatocapsular area.

In conclusion, both contrast enhancement and contrast extravasation develop primarily in the region of the basal ganglia in accordance with the specific vascular territory. Contrast enhancement on CT scans obtained after intra-arterial thrombolysis usually is not associated with hemorrhagic complications and should not be considered a poor prognostic sign. On the contrary, contrast extravasation is usually associated with parenchymatous hematoma and should therefore be considered a negative prognostic sign.

References
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