ORIGINAL ARTICLE

The cortical contrast accumulation from brain computed tomography after endovascular treatment predicts symptomatic hemorrhage

J.-M. Kim[a], K.-Y. Park[a], W. J. Lee[b], J. S. Byun[b], J. K. Kim[b], M.-S. Park[a], S.-W. Ahn[a] and H.-W. Shin[a]

[a]*Department of Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul; and* [b]*Department of Neuroradiology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea*

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Background and purpose: The prognostic value of contrast accumulation from non-contrast brain computed tomography taken immediately after endovascular reperfusion treatment in acute ischaemic stroke patients to predict symptomatic hemorrhage was studied.

Methods: Between July 2007 and August 2014, acute anterior circulation ischaemic stroke patients who were treated by intra-arterial thrombolysis or thrombectomy were included. Contrast accumulation was defined as a high attenuation area from non-contrast brain computed tomography immediately taken after endovascular reperfusion treatment, and patients were categorized into three groups according to the presence and location of contrast: (i) negative, (ii) cortical involvement and (iii) non-cortical involvement. The rates of symptomatic hemorrhage after 24 h and functional outcome at discharge were compared between patients with and without cortical involvement.

Results: Of 64 patients who were treated by endovascular intervention, contrast accumulation was detected in 56, including 33 patients with cortical involvement and 23 patients without cortical involvement. The cortical involvement pattern was more frequently associated with symptomatic hemorrhage (13 vs. 1 patient, $P = 0.003$) and with grave outcome at discharge with modified Rankin Scale 5 or 6 (14 vs. 4, $P = 0.048$) than the non-cortical involvement group. Multivariate logistic regression analysis including initial collateral status and occlusion site disclosed that cortical involvement pattern independently predicted symptomatic hemorrhage after endovascular treatment (odds ratio 19.0, confidence interval 1.6–227.6, $P = 0.020$).

Conclusion: Our study provides evidence that the cortical involvement of contrast accumulation is associated with symptomatic hemorrhage after endovascular reperfusion treatment.

Introduction

Intra-arterial thrombolytic therapy is an effective reperfusion treatment modality for acute ischaemic stroke patients, but is associated with symptomatic hemorrhage risk. Early detection of symptomatic hemorrhage is important because it is associated with neurological deterioration after reperfusion treatment. Non-contrast brain computed tomography (CT) is usually done immediately after intra-arterial reperfusion treatment to detect hemorrhagic complication. Contrast accumulation from non-contrast brain CT is frequently observed after intra-arterial intervention and can be either hemorrhagic or transient contrast extravasation [1]. Although initial studies implicated the relationship of contrast enhancement with symptomatic hemorrhagic complication [1,2], recent studies have reported low specificity and positive predictive value of contrast accumulation to predict hemorrhagic

Correspondence: K.-Y. Park, Department of Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, 224-1, Heukseok-dong, Dongjak-gu, Seoul 156-755, Korea (tel.: +82 2 6299 1502; fax: +82 2 6299 1493; e-mail: kwangyeol.park@gmail.com).

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complication [3,4]. The conflicting study results seem to be derived from different study populations, inclusion time, outcome parameters and, most importantly, the heterogeneous nature of contrast accumulation.

If contrast accumulation reflects blood–brain barrier disruption [2], the extent/location of contrast accumulation may be different between patients with symptomatic hemorrhage and those without. In this study the prognostic value of contrast accumulation from brain CT taken immediately after intra-arterial intervention was studied, focusing on its location, to predict symptomatic hemorrhagic complication.

Materials and methods

Patient selection

Between June 2007 and May 2013, acute ischaemic stroke patients who were treated by intra-arterial reperfusion therapy were eligible to be included. When acute ischaemic stroke patients were admitted to the emergency department, endovascular treatment was considered when the symptom onset was within 6 h but either the patient was not eligible for intravenous thrombolysis or neurological status was not restored after intravenous thrombolysis. All the patients underwent multidetector CT angiography using a Brilliance 256-channel CT v 2.2 (Philips Medical System, Best, The Netherlands) with the following parameters: 120 kVp, 140 mA, 0.9 mm section thickness, 0.9 mm slice acquisition interval, and intravenous administration of 80 ml iohexol (GE Healthcare, Milwaukee, WI, USA) at a rate of 4.0–4.5 ml/s. Endovascular recanalization treatment using a stent retriever (Solitaire™ FR: ev3, Irvine, CA, USA) or aspiration thrombectomy (Penumbra system, Alameda, CA, USA) with or without intra-arterial urokinase infusion was performed, and the treatment strategy was determined after discussion with the attending neurologist and neuro-interventionist. This study was reviewed and approved by the institutional review board of Chung-Ang University Hospital (IRB number C2013110-1070) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was exempted due to the retrospective design.

Since our main objective was to predict symptomatic hemorrhage by the extent and location of contrast enhancement from brain CT, stroke patients with middle cerebral artery or internal carotid artery occlusion were included and basic demographic data as well as clinical information were reviewed. Vascular risk factor profile, blood test results, initial stroke severity in terms of the National Institutes of Health Stroke Scale (NIHSS) and reperfusion treatment modalities were reviewed. The occluded vessel and collateral status were determined by initial brain CT angiography, and, as previously reported, collateralization was graded as good when contrast-enhanced vessels existed in more than 50% of the total vascular territory supplied by the occluded arterial segment [5]. Angiographic successful recanalization was defined as complete or partial recanalization with perfusion of more than a half of the previously occluded target artery territory [6]. The stroke mechanism was defined according to the Trial of ORG 10172 in Acute Stroke Treatment criteria [7].

Brain image analysis

Non-contrast brain CT (120 kVp, 140 mA, 5.0 mm section thickness) was performed immediately after the intra-arterial procedure and before transferring the patient to the stroke unit. All the patients took follow-up brain imaging 24 h after intervention, by either brain CT or brain magnetic resonance imaging (MRI) including susceptibility-weighted imaging depending on the patient's status and the attending physician's decision.

The contrast accumulation was defined as a high attenuation region with a Hounsfield unit >90 from post-intervention brain CT and was classified into one of three groups according to its presence and location: (i) negative, when contrast accumulation was absent; (ii) cortical involvement (CO), when contrast accumulation involved the cortex with or without basal ganglia and subarachnoid space; (iii) non-cortical involvement (NC), when contrast accumulation presented but not involving the cortex. Two neurologists independently performed imaging analysis, and any discrepancy between the two was solved by a neuroradiologist (Fig. 1).

Outcome assessment

Symptomatic hemorrhage was defined as a local or remote type 2 parenchymal hemorrhage with mass effect from follow-up brain imaging with neurological worsening of 4 or more NIHSS deterioration [8], and asymptomatic hemorrhage was defined as any hemorrhagic transformation other than symptomatic hemorrhage detected from follow-up brain imaging. Grave functional outcome was defined as a modified Rankin Scale between 5 and 6 at discharge.

Statistical analysis

The inter-rater agreement for discrimination between CO and NC was calculated with the multirater κ

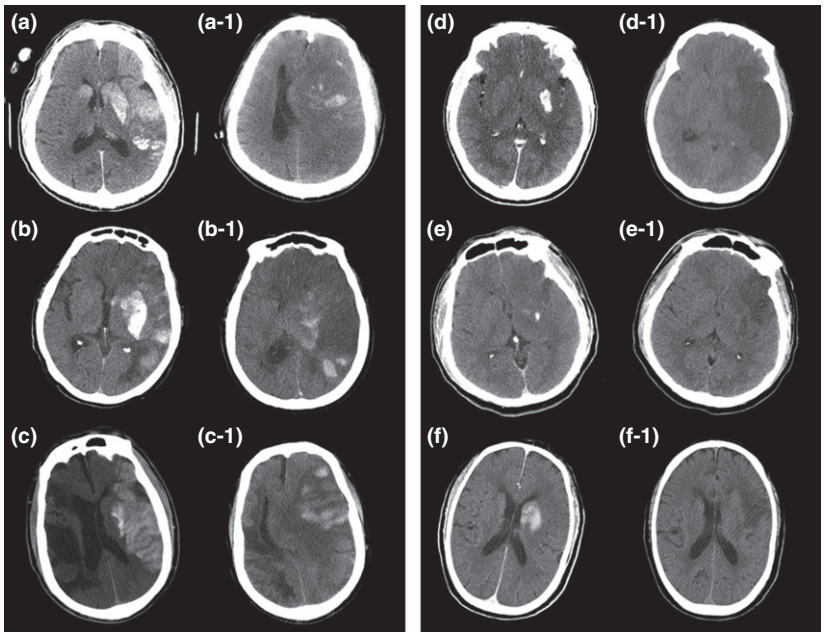

Figure 1 Representative brain CT findings of patients with contrast accumulation. The patients with contrast accumulation involving the cortex from brain CT after intra-arterial intervention (a, b, c) displayed symptomatic hemorrhagic transformation in brain imaging taken 24 h after treatment (a-1, b-1, c-1). The patients with contrast accumulation confined within the basal ganglia (d, e, f) were more likely to be free from hemorrhage (d-1, e-1, f-1). In each patient, the left image (a–e) was taken immediately after intra-arterial reperfusion treatment and the right image (a-1–e-1) was taken 24 h after endovascular treatment.

statistic. Statistical analyses between CO and NC groups were performed by the Mann–Whitney U test for continuous variables and Pearson's chi-squared test for dichotomous variables. Bivariate analyses were used to assess the dependence of symptomatic hemorrhagic transformation on clinical and radiological variables, followed by multivariable logistic regression analysis to find independent variables to predict symptomatic hemorrhagic transformation by including biologically relevant variables with $P < 0.05$ derived from bivariate analysis. Diagnostic performance of cortical contrast accumulation was calculated. All the statistical analyses were performed with SPSS version 19.0 (SPSS, Chicago, IL, USA) and a P value < 0.05 was determined as statistically significant.

Results

A total of 89 patients were treated by intra-arterial interventional treatment and 64 of those patients with anterior circulation stroke were included in this study. All the patients were followed by non-contrast brain CT immediately after intra-arterial reperfusion treatment and by either brain CT or MRI 24 h after treatment. Contrast accumulation was detected in 56 patients (87.5%), including 33 patients with CO pattern (51.6%) and 23 patients with NC pattern (35.9%) in terms of the contrast accumulation location. Amongst the patients displaying CO pattern, 23/33 patients (69.7%) had basal ganglia involvement. Sixteen patients with NC pattern had contrast accumulation restricted to basal ganglia, whilst the other seven patients had contrast accumulated in the subarachnoid space. The inter-rater agreement for discrimination between CO and NC was adequate ($\kappa = 0.77$). Of all the patients involved, symptomatic hemorrhage occurred in 14 patients (21.8%) and asymptomatic hemorrhage in 13 patients (23.4%).

Basic demographic and clinical data of the two groups are illustrated in Table 1. The patients with CO were more likely to have poor baseline collateral and successful arterial recanalization than the NC group. The intravenous thrombolysis treatment, occluded vessel, initial NIHSS and laboratory variables were not significantly different. Symptomatic hemorrhage after reperfusion treatment was more frequent in the CO group than in the NC group (13 vs. 1 patient, $P = 0.026$, Table 1). Sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio for symptomatic hemorrhage (with 95% confidence interval) were 93% (69–99), 52% (38–67), 39% (25–56), 96% (79–99) and 2.0% (1.7–2.2). The proportion of asymptomatic hemorrhage was not different between the two groups. Grave functional outcome at discharge was more prevalent in the CO group than in the NC group (14 vs. 4 patients, $P = 0.048$, Table 1). The analysis of factors associated with symptomatic hemorrhagic transformation after endovascular treatment is illustrated in Table 2, and CO pattern independently predicted symptomatic hemorrhage with an odds ratio of 19 (95% confidence interval 1.6–227.6, $P = 0.020$) after adjusting for initial collateral status and occlusion site (Table 3, Fig. 2).

Discussion

This study shows that non-contrast brain CT taken immediately after intra-arterial reperfusion treatment for acute anterior circulation cerebral infarction can predict symptomatic hemorrhage when the location of contrast accumulation is considered. The patients with cortical contrast accumulation were more likely to have symptomatic hemorrhage than those without. Consequently, the proportion of patients with poor neurological outcome at discharge was higher in the CO pattern group than in the NC pattern group.

The presence of contrast accumulation has been reported with a wide variation of between 20% and 80% of the study populations [1,3,9]. Contrast accumulation was observed in 87.5% of patients, and its presence was not always related to grave consequence because half of them disappeared without hemorrhagic transformation after 24 h. However, contrast accumulation with cortical involvement increased the likelihood of symptomatic hemorrhage, suggesting that the location of contrast accumulation is a more important factor than simply its presence in prediction of symptomatic hemorrhage. No patient without contrast accumulation suffered from symptomatic hemorrhage, which correlated with previous studies [1].

The pathophysiology of contrast accumulation after intra-arterial reperfusion therapy is a disruption of the blood–brain barrier and basal lamina by initial ischaemic insult, reperfusion injury and toxic effect of contrast media or thrombolytic agent [2,10]. Since the fate of contrast accumulation is diverse ranging from spontaneous resolution to massive symptomatic hemorrhage, several attempts have been reported to increase its prognostic value, such as with serial follow-up of brain CT, by measuring the Hounsfield unit of enhanced area, and by applying dual energy CT [2,3,11]. 'Malignant' contrast accumulation was differentiated from 'benign' by simply considering its location. Studies have consistently reported that the basal ganglia were the most frequently enhanced location because most contrast media injection to evaluate endovascular treatment response is done around the origin of the lenticulostriate arteries. Therefore it is speculated that contrast accumulation restricted to basal ganglia might not predict symptomatic hemorrhage. When contrast accumulation involves the cortex beyond the basal ganglia, symptomatic hemorrhagic risk increases, reflecting more widespread blood–brain barrier disruption and reperfusion injury. The majority of the NC pattern group had good initial collateral (95.7%) and less symptomatic hemorrhage, suggesting that the CO pattern is associated with widespread initial ischaemic insult due to insufficient collateral. There has been a recent study showing that initial poor collateral status predicts symptomatic hemorrhage after endovascular reperfusion treatment [12]. The blood–brain barrier damage might be more pronounced after restoration of blood flow [13]. The CO pattern was associated more commonly with successful recanalization than the NC pattern (87.9% vs. 60.9%), suggesting that widespread contrast accumulation could be related to extensive reperfusion injury.

Several limitations exist in our study. First, the study was performed by retrospective data review from a single center with a relatively small number of patients, which might result in selection bias. The reperfusion

Table 1 Comparison of the patients with non-cortical contrast accumulation versus cortical contrast accumulation

	Cortical	Non-cortical	*P*
Number of patients	33	23	
Age, years	68.5 ± 12.2	61.8 ± 14.1	0.087
Female patients, *n* (%)	16 (48.5)	12 (52.2)	0.786
Diabetes mellitus, *n* (%)	8 (24.2)	5 (21.7)	1.000
Hypertension, *n* (%)	18 (54.5)	13 (56.5)	0.770
Cardioembolic source, *n* (%)	24 (72.7)	14 (60.9)	0.347
Previous stroke, *n* (%)	9 (27.3)	1 (4.3)	0.030
Systolic blood pressure, mmHg	141 ± 25	144 ± 20	0.622
White blood cell count, per μl	7646 ± 1961	8845 ± 2947	0.073
Initial blood glucose, mg/dl	141 ± 44	137 ± 60	0.771
aPTT, s	31.6 ± 8.4	26.7 ± 11.3	0.087
Intravenous thrombolysis, *n* (%)	20 (60.6)	13 (56.5)	0.222
Onset within 3 h, *n* (%)	23 (69.7)	16 (69.6)	1.000
Initial NIHSS, median	18	16	0.441
Internal carotid artery occlusion, *n* (%)	7 (21.2)	5 (21.7)	0.644
Initial collateral >50%, *n* (%)	15 (45.5)	22 (95.7)	<0.001
Intervention duration, min	162 ± 47	151 ± 57	0.419
Onset to recanalization, min	384 ± 76	301 ± 80	0.896
Successful recanalization, *n* (%)	29 (87.9)	14 (60.9)	0.033
Symptomatic hemorrhage, *n* (%)	13 (39.4)	1 (4.3)	0.003
All types of hemorrhage, *n* (%)	21 (63.6)	8 (34.8)	0.039
Discharge mRS 5 or 6, *n* (%)	14 (42.4)	4 (17.4)	0.048

aPTT, activated partial thromboplastin time; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

Table 2 Analysis of factors associated with symptomatic hemorrhage

	Symptomatic hemorrhage (+)	Symptomatic hemorrhage (−)	*P*
Number of patients	14	42	
Age >70 years	8 (57.1)	13 (31.0)	0.080
Female patients, *n* (%)	6 (42.9)	22 (52.4)	0.537
Diabetes mellitus, *n* (%)	5 (35.7)	8 (19.0)	0.201
Cardioembolic source, *n* (%)	10 (71.4)	28 (66.7)	0.741
Previous stroke, *n* (%)	3 (21.4)	7 (16.7)	0.687
Onset to recanalization time, min	402 ± 79	376 ± 76	0.290
Systolic blood pressure, mmHg	133 ± 26	145 ± 22	0.159
White blood cell count, per μl	7321 ± 47	162 ± 47	0.102
Initial blood glucose, mg/dl	143 ± 37	138 ± 55	0.374
Initial collateral >50%, *n* (%)	6 (42.9)	31 (73.8)	0.034
Internal carotid artery occlusion, *n* (%)	6 (42.9)	6 (14.3)	0.024
Successful recanalization, *n* (%)	11 (78.6)	32 (76.2)	0.855
Initial NIHSS >20	7 (50.0)	10 (23.8)	0.065
Cortical contrast accumulation	13 (92.9)	20 (47.6)	0.003

NIHSS, National Institutes of Health Stroke Scale.

Table 3 Multivariate logistic regression analysis predicting factors related to symptomatic hemorrhagic transformation

	P	Odds ratio	Confidence interval
Cortical contrast enhancement	0.020	19.0	1.6–227.6
Internal carotid artery occlusion	0.026	7.5	1.3–44.3
Initial collateral >50%	0.793	0.8	0.2–3.8

modality was rather heterogeneous, including intra-arterial urokinase infusion, aspiration thrombectomy and most recently stent retriever. However, all the patients had been through homogeneous scheduled imaging follow-up and outcome assessment. Contrast media volume is reported as one of the factors increasing hemorrhagic transformation risk after acute cerebral infarction [10], but contrast media volume was not quantitatively considered because contrast delivery during procedure was not uniformly controlled.

This study shows that cortical contrast accumulation from brain CT is associated with symptomatic hemorrhage and poor functional outcome amongst

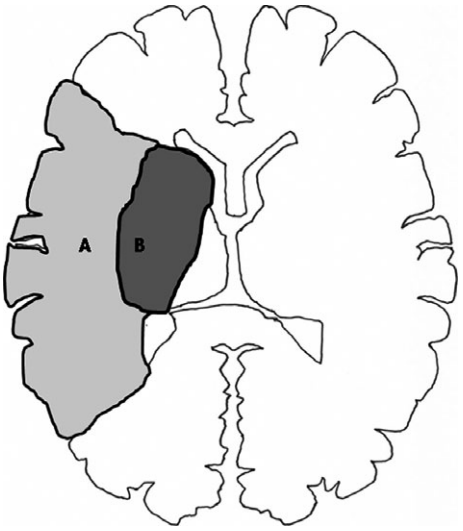

Figure 2 The contrast accumulation location after endovascular treatment and the risk of symptomatic hemorrhage. The location of contrast accumulation from non-contrast brain CT taken immediately after intra-arterial reperfusion treatment is important in the prediction of symptomatic hemorrhage. The patients with cortical contrast accumulation (A) were more likely to have symptomatic hemorrhage than those without cortical involvement (B).

acute ischaemic stroke patients who were treated by intra-arterial reperfusion treatment. Future studies are warranted to evaluate the pathophysiological mechanism of different contrast accumulation patterns which are related to symptomatic hemorrhage. Also, it will be interesting to study whether proactive management such as strict blood pressure control for those patients with high risk of symptomatic hemorrhage after reperfusion treatment can reduce hemorrhagic transformation in the future.

Ethical standards

All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was reviewed and approved by the institutional review board of Chung-Ang University Hospital (IRB number C2013110-1070) and informed consent was exempted due to its retrospective design.

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Disclosure of conflicts of interest

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