Risk Factors of Ischemic Lesions Related to Cerebral Angiography and Neuro-interventional Procedures

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Abstract

Embolism after cerebral angiography is not a rare complication of cerebral angiography. The risk factors for incidental embolism after cerebral angiography were retrospectively examined using diffusion-weighted magnetic resonance imaging (DWI) in 180 patients who underwent 247 angiography procedures, consisting of 174 diagnostic angiography and 73 interventional procedures, and magnetic resonance imaging including DWI within 72 hours after angiography. The two neuroradiologists in our hospital detected embolism after cerebral angiography as high-intensity lesions (HIL) on DWI. The relationships between HIL on DWI and procedural factors were evaluated. DWI after cerebral angiography revealed HIL related to the procedure in 72 of 247 angiographies. In all procedures, age ($p < 0.01$), past history of cerebral infarction ($p < 0.05$), anti-platelet therapy ($p < 0.05$), neuro-intervention ($p < 0.01$), and total amount of contrast medium (odds ratio [OR] 2.125, 95% confidence interval [CI] 1.045–4.321) were significantly correlated with HIL. In diagnostic angiography, the performance of the procedure by a resident operator (OR 2.526, 95% CI 1.214–5.254) was significantly correlated with HIL. Age, past history of cerebral infarction, and previous anti-platelet therapy determined the risk of atherosclerotic changes in patients. The neuro-intervention and total amount of contrast medium used could predict the risk of time limitations for angiography. Resident operator is also a risk factor. This study demonstrates the importance of improving the risk of time limitations for angiography and the risk due to operator inexperience. Further training of residents may be needed to reduce the occurrence of embolic complications.

Key words: cerebral angiography, diffusion-weighted magnetic resonance imaging, cerebral embolism, complication

Introduction

Neuroimaging techniques, such as magnetic resonance (MR) imaging and multi-detector computed tomography, have been improving in recent years. However, cerebral angiography is still an important tool for examining cerebral vascular diseases and performing neuro-interventional procedures. This technique carries a small but defined risk for neurological complications with incidental embolism. Previous reports have indicated that incidental embolism is not rare, and past history of vasculopathy, amount of contrast medium used, fluoroscopy time, use of additional catheters, procedures of the occlusion test, and performance of endovascular surgery for cerebrovascular disease are

risk factors for embolism.^{1,4,5,8,9,11,13,16,17,20,21} Angiography of the coronary arteries also carries a risk for cerebral embolism due to the duration of the procedure.^{4,15} Diffusion-weighted MR imaging (DWI) allows for the most sensitive early detection of cerebral ischemia within minutes of onset.²² The present study tried to examine the risk factors for cerebral embolism after cerebral angiography and neuro-interventional procedures using DWI.

Methods

From October 2008 to March 2010, 180 patients (73 men and 107 women, mean age 56.0 years [range 5–92 years]) underwent 247 cerebral angiography procedures in our university hospital. These patients were enrolled in this study retrospectively. Of these patients, 174 belonged to the diagnostic angiography group, and 73 belonged to the neuro-inter-

Table 1 Comparison of baseline clinical characteristics and subsequent disease diagnosis

	All cases (n = 247)	DWI		p Value
		Yes (n = 72)	No (n = 175)	
Clinical characteristic:				
Age*, yrs	56.6 ± 19.8	63.1 ± 17.3	54.3 ± 20.4	< 0.05
Female (%)	153 (61.9)	43 (59.8)	110 (62.9)	NS
Myocardial infarction (%)	20 (8.1)	10 (13.9)	10 (5.7)	NS
Cerebral infarction (%)	66 (26.7)	26 (36.1)	40 (22.9)	< 0.05
Diabetes (%)	40 (16.2)	14 (19.4)	26 (14.9)	NS
Hypertension (%)	124 (50.2)	42 (58.3)	82 (46.9)	NS
Hypercholesterolemia (%)	48 (19.4)	10 (13.9)	38 (21.7)	NS
Uric acid abnormality (%)	3 (1.2)	0 (0)	3 (1.7)	NS
Chronic renal failure (%)	9 (3.6)	3 (4.2)	6 (3.4)	NS
Obesity (%)	8 (3.2)	1 (1.4)	7 (4.0)	NS
Smoking (%)	70 (28.3)	25 (34.7)	45 (25.7)	NS
Anti-platelet therapy (%)	84 (34.0)	32 (44.4)	52 (29.7)	< 0.05
Subsequent diagnosis:				
Unruptured aneurysm (%)	61 (24.7)	19 (26.4)	42 (24.0)	NS
Arteriovenous malformation (%)	30 (12.1)	6 (8.3)	24 (13.7)	NS
Cervical artery stenosis (%)	58 (23.5)	19 (26.4)	29 (16.6)	NS
Dural arteriovenous fistula (%)	21 (8.5)	7 (9.7)	14 (8.0)	NS
Infarction (%)	8 (3.2)	1 (1.4)	7 (4.0)	NS
Moyamoya disease (%)	16 (6.5)	5 (6.9)	11 (6.3)	NS
Tumor (%)	34 (13.8)	7 (9.7)	27 (15.4)	NS
Others (%)	29 (11.7)	8 (11.1)	21 (12.0)	NS

*Values are mean ± standard deviation. DWI: diffusion-weighted magnetic resonance imaging, NS: not significant.

ventional procedure group. The patients had the following diagnoses: unruptured cerebral aneurysm (n = 61), arteriovenous malformation (n = 30), cervical artery stenosis (n = 58), dural arteriovenous fistula (n = 21), infarction (n = 8), moyamoya disease (n = 16), brain tumor (n = 34), and others (n = 29) (Table 1). Informed consent was obtained from each subject. We identified a subgroup of patients with vascular risk factors, listed as follows: age, sex, previous myocardial infarction and cerebral infarction, diabetes, hypertension, hypercholesterolemia, uric acid abnormality, chronic renal failure, obesity (body mass index ≥ 30), smoking, and previous anti-platelet therapy. These risk factors included both well controlled and not controlled cases. The Institutional Ethics Committee at our university hospital approved this study.

Cerebral angiography was performed through a trans-femoral artery approach (n = 229) or a trans-radial artery approach (n = 18). Diagnostic angiography was performed with a 4 Fr catheter and a standard guide wire (Radifocus, 0.035 inch diameter; Terumo, Tokyo). Neuro-interventional procedures were performed with appropriately sized catheters and guide wires for each case. We used nonionic contrast medium (OMNIPAQUE 300;

Daiichi Sankyo, Tokyo) in all cases. During the neuro-interventional procedure, the catheters were continuously flushed with heparin and additional saline unless a guide wire was used. The flushing system consisted of a high-pressure infusion system with a drop catheter (permanent pressure > 300 mmHg), which was permanently attached to the catheter.

The following factors were recorded in each case: total procedure time; total amount of contrast medium used; total number of examinations; whether an additional catheter was needed; whether the patient underwent three-dimensional rotation angiography; and the anti-coagulation therapy used during angiography (Table 2). In our university hospital, neurosurgeons and neuroradiologists always perform angiography together and discuss the findings at the time. Cerebral angiography was performed by more than two operators who are resident operators with senior operators or two senior operators.

The senior operators were two neurosurgeons or one neuroradiologist with licenses from the Japanese Society for Neuroendovascular Therapy or the Japanese Radiological Society, which guarantees that the operator has performed more than 300 cerebral angiographies in the last 5 years. The resident operators were physicians who had held medi-

Table 2 Comparison of three magnetic resonance (MR) imaging scanners and the procedural factor

	All cases (n = 247)	DWI	
		Yes (n = 72)	No (n = 175)
MR imaging scanner:			
Gyrosan NT 1.5T (%)	78 (31.6)	16 (22.2)	62 (35.4)
Achieva 1.5T (%)	83 (34.0)	27 (37.5)	36 (20.6)
Achieva 3.0T (%)	86 (34.8)	29 (40.3)	57 (32.6)
Procedural factor:			
Total time*, min	88.0 ± 62.9	97.2 ± 54.6	84.2 ± 65.7
Amount of contrast medium*, ml	124.0 ± 58.3	142.9 ± 58.3	116.2 ± 56.6
Number of examinations*	13.0 ± 8.0	14.2 ± 6.0	12.4 ± 8.7
Resident operator (%)	74 (30.0)	24 (33.3)	50 (28.6)
Additional catheter (%)	42 (17.0)	12 (16.7)	30 (17.1)
3D rotation angiography (%)	109 (44.1)	35 (48.6)	74 (42.3)
Interventional procedure (%)	73 (29.6)	31 (43.1)	42 (24.0)
Anti-coagulation therapy (%)	70 (28.3)	31 (43.1)	39 (22.3)

*Values are mean ± standard deviation. 3D: three-dimensional, DWI: diffusion-weighted magnetic resonance imaging.

cal licenses for up to 6 years and had performed fewer than 100 diagnostic cerebral angiographies in their career.

All patients underwent MR imaging including DWI within 72 hours after angiography using three MR imaging scanners, as follows: Gyrosan NT 1.5T (Phillips Medical Systems, Eindhoven, the Netherlands), Achieva 1.5T (Phillips Medical Systems), and Achieva 3.0T (Phillips Medical Systems). DWI was obtained using a single-shot echo-planar spin-echo sequence. The protocol of each scanner was as follows: Gyrosan NT 1.5T, repetition time (TR) = 4070.2 msec, echo time (TE) = 88.0 msec, slice thickness (ST) = 5.0 mm, matrix = 256×256 , b = 1000 sec/mm²; Achieva 1.5T, TR = 3500 msec, TE = 67.1 msec, ST = 5.0 mm, matrix = 256×256 , b = 1000 sec/mm²; and Achieva 3.0T, TR = 5000 msec, TE = 57.5 msec, ST = 5.0 mm, matrix = 288×288 , b = 1000 sec/mm². According to the Acute Stroke Imaging Standardization Group-Japan (ASIST-Japan) for standardization of DWI, the two neuroradiologists in our university hospital set the window width equal to the signal intensity in the b0 images of the normal-appearing thalamus and then set the window level,¹⁹⁾ and evaluated the DWI findings after cerebral angiography. The patient distribution was as follows: Gyrosan NT 1.5T (78 cases, 16 DWI positive), Achieva 1.5T (83 cases, 27 DWI positive), and Achieva 3.0T (86 cases, 29 DWI positive) (Table 2). We statistically compared the historical differentiation between these three MR imaging scanners. We referred to the recommended protocol of ASIST-Japan and standardized the DWI by setting the window width and window level. The DWI obtained from the three MR imaging scanners showed

no significant differences in the background distribution, frequency of HIL on DWI, or operator distribution. The histories of patients and the types of procedures (diagnosis or neuro-intervention) were concealed during the image analysis.

Absence of high-intensity lesions (HIL) on DWI was not confirmed before angiography in all patients. Usually, small HIL on DWI vanish within 2 weeks. We excluded patients who suffered cerebral infarction or transient ischemic attack within 1 month before angiography,^{3,15)} so that we could consider small HIL on DWI to be related to the present angiographic procedure and as indicators of cerebral microembolism.

Continuous variables are expressed as the mean value ± standard deviation, and comparisons of these variables between groups were performed using the Student's t-test. Categorical variables are expressed as counts and percentage frequencies, and were compared using the chi-square test. A multivariate logistic regression test was used to identify independent predictors of risk for cerebral embolism from procedural factors. A p value of <0.05 was considered to be significant. The differences between the MR imaging scanners were analyzed statistically by one-way analysis of variance (ANOVA) and Tukey's post-hoc tests ($\alpha = 0.05$). SPSS ver.19 for Windows (IBM, Armonk, New York, USA) was used for all statistical analyses.

Results

DWI after cerebral angiography revealed HIL related to the procedure in 72 of 247 angiographies (Fig. 1). The baseline patient clinical characteristics and

Fig. 1 Typical cases of high intensity lesions on diffusion-weighted magnetic resonance imaging indicating silent embolism after cerebral angiography. **A:** A 72-year-old man with cervical artery stenosis (Gyroscan NT 1.5T), **B:** a 32-year-old woman with an unruptured cerebral aneurysm (Gyroscan NT 1.5T), **C:** a 72-year-old man with an unruptured cerebral aneurysm (Achieva 1.5T), **D:** a 75-year-old woman with an unruptured cerebral aneurysm (Achieva 1.5T), **E:** a 65-year-old woman with an unruptured cerebral aneurysm (Achieva 3.0T), **F:** a 52-year-old woman with an unruptured cerebral aneurysm (Achieva 3.0T).

the diagnosis by angiography are shown in Table 1. Age ($p < 0.05$), past history of cerebral infarction ($p < 0.05$), and previous anti-platelet therapy ($p < 0.05$) were significantly different between the two groups. Sex, preceding myocardial infarction, diabetes, hypertension, hypercholesterolemia, uric acid abnormality, chronic renal failure, obesity, and smoking were not significantly different. Six of the 72 patients in the HIL group had symptomatic neu-

rological deficits after angiography. Of these, four patients had transient symptoms and two patients had permanent neurological deficit. The frequency of disease diagnosis by angiography was similar in both groups. For procedural factors, univariate analysis showed that total time ≥ 80 minutes (odds ratio [OR] 2.057, 95% confidence interval [CI] 1.167–3.626), amount of contrast medium ≥ 100 ml (OR 2.833, 95% CI 1.539–5.216), ≥ 12 examinations (OR 2.101, 95% CI 1.204–3.667), neuro-intervention (OR 2.394, 95% CI 1.339–4.282), and anti-coagulation therapy (OR 1.804, 95% CI 1.260–2.581) were risk factors (Table 3). Additionally, multivariate analysis indicated that amount of contrast medium ≥ 100 ml (OR 2.125, 95% CI 1.045–4.321) was a significant risk factor. The mean procedure duration was 97.2 ± 54.6 minutes in patients with HIL on DWI and 84.2 ± 65.7 minutes in patients without HIL (Table 2). There was no significant difference in total procedure time.

A senior operator performed most neuro-interventional procedures. Therefore, we analyzed the subgroup receiving only diagnostic cerebral angiography, which represented 174 diagnostic cerebral angiographies. Of these, 41 patients had HIL on DWI. Univariate analysis identified the following risk factors: total amount of contrast medium ≥ 100 ml (OR 2.383, 95% CI 1.157–4.910), ≥ 10 examinations (OR 2.054, 95% CI 1.011–4.174), and performance of the procedure by a resident operator (OR 2.417, 95% CI 1.185–4.929) (Table 4). Additionally, multivariate analysis indicated that performance of the procedure by a resident operator (OR 2.526, 95% CI 1.214–5.254) was the only significant risk factor. The mean procedure duration was 64.1 ± 20.2 minutes in patients with HIL on DWI and 60.0 ± 21.5 minutes in patients without HIL. There was no significant difference in the total procedure time. Analysis by one-way ANOVA and Tukey's post-hoc tests revealed no significant difference between the three MR imaging scanners.

Discussion

Previous articles have reported that the risk of HIL on DWI after cerebral angiography ranges from 9% to 26%.^{1,2,14} The amount of contrast medium used, fluoroscopic time, and use of additional catheters were risk factors for the detection of HIL on DWI after cerebral angiography.¹ The results of occlusion tests of the internal carotid arteries were significantly correlated with the appearance of HIL on DWI.¹⁴ Additionally, a history of stroke and transient ischemic attack were more highly correlated with neurological complication after angiogra-

Table 3 Univariate and multivariate analysis of risk factors for all cases

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	p Value	Odds ratio	95% CI	p Value
Total time $\geq$ 80 min	2.057	1.167–3.626	0.013	0.976	0.427–2.232	0.954
Amount of contrast medium $\geq$ 100 ml	2.833	1.539–5.216	0.001	2.125	1.045–4.321	0.037
Number of examinations $\geq$ 12	2.101	1.204–3.667	0.009	1.273	0.662–2.445	0.469
Resident operator	1.25	0.693–2.254	0.458			
Additional catheter	0.967	0.467–2.014	0.928			
3D rotation angiography	1.291	0.744–2.240	0.363			
Interventional procedure	2.394	1.339–4.282	0.003	1.745	0.767–3.971	0.185
Anti-coagulation therapy	1.804	1.260–2.581	0.01	1.469	0.557–3.874	0.437

3D: three-dimensional, CI: confidence interval.

Table 4 Univariate and multivariate analysis of risk factors in diagnostic cerebral angiography

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	p Value	Odds ratio	95% CI	p Value
Total time $\geq$ 60 min	1.167	0.562–2.424	0.679			
Amount of contrast medium $\geq$ 100 ml	2.383	1.157–4.910	0.019	2.038	0.840–4.943	0.115
Number of examinations $\geq$ 10	2.054	1.011–4.174	0.047	1.599	0.665–3.841	0.58
Resident operator	2.417	1.185–4.929	0.015	2.526	1.214–5.254	0.013
Additional catheter	0.671	0.183–2.461	0.547			
3D rotation angiography	0.936	0.457–1.917	0.857			

3D: three-dimensional, CI: confidence interval.

phy.^{10,12)} In our study, 72 (29.1%) of 247 cerebral angiography procedures resulted in HIL on DWI. Age, past history of cerebral infarction, and previous anti-platelet therapy were significantly correlated with HIL on DWI. The findings demonstrate that arteriosclerosis or vasculopathy might be risk factors for incidental embolism after angiography. Patients with symptomatic carotid artery stenosis had a neurological complication rate as high as 10%.⁷⁾ However, there was no significant difference between subsequent diseases in this study.

Previous articles have reported that patients who undergo neuro-interventional procedures carry a greater risk of presentation of HIL on DWI, which ranges from 51.3% to 61%.^{17,18,21)} In the present study, HIL on DWI were detected after 31 (43%) of 73 interventional procedures. Neuro-interventional procedures usually take longer, require more contrast medium, and involve increased procedural complexity, which could explain the higher risk of embolisms in an interventional procedure than in diagnostic cerebral angiography.

The use of higher amounts of contrast medium was also a risk factor for embolism in our study, although the total procedure time and the total num-

ber of examinations were not significantly different. Evaluation of the frequency of embolic events during cerebral angiography by continuous transcranial Doppler monitoring found that embolic phenomena were detected in all procedure phases, but were more frequent during catheter flushing and injection of the contrast medium than during catheter and guide wire manipulation.⁶⁾ We speculate that the usage of contrast medium for checking vessels or catheter position may frequently cause embolic sources, such as blood clots and micro bubbles, during exchange from guide wire to syringe. The performance of diagnostic angiography by resident operators was significantly associated with HIL on DWI. The difference in experience might have affected the frequency of embolism. Therefore, we propose that additional angiography training should be provided to inexperienced operators, possibly using a simulator.

The present study has several limitations. Not all HIL might have been infarctions, because we did not perform DWI before angiography. This study was a retrospective study, so there will be substantial selective bias. Specifically, our university hospital treats no emergency patients. We need a prospective

study to prove this result for future recommendations.

Cerebral embolism is not a rare complication of cerebral angiography. Age, past history of cerebral infarction, and previous anti-platelet therapies determine the risk for atherosclerotic changes in patients. Neuro-intervention and total amount of contrast medium determine the risk of time limitation for angiography. Moreover, the present study indicated that senior operators administered diagnostic cerebral angiography more safely than resident operators. This study indicates the necessity of lessening the risk of time limitations for angiography and the risk related to operator inexperience. As such, we recommend reducing the occurrence of embolic complications by providing further training. Furthermore, experience with angiography simulation training devices will help us to reduce the occurrence of procedural complications.

Acknowledgment

This work was partly supported by a Grant-in-Aid for Scientific Research (C), No.23592085 and the Ministry of Education, Culture, Sports, Science, and Technology-Japan.

Department of Biostatistics in University of Tsukuba at Critical Path Research and Education Integrated Leading Center supported us in statistical analysis.

Conflicts of Interest Disclosure

We declare no conflicts of interest. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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