

Spot sign as a predictor of rebleeding after endoscopic surgery for intracerebral hemorrhage

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Abstract

Objective In patients with spontaneous intracerebral hemorrhage (sICH), postoperative recurrent hemorrhage (PRH) is one of the most severe complications after endoscopic evacuation of hematoma (EEH). However, no predictors of this complication have been identified. In the present study, the authors retrospectively investigated whether PRH can be preoperatively predicted by the presence of the spot sign on CT scans.

Methods In total, 143 patients with sICH were treated by EEH between June 2009 and March 2017, and 127 patients who underwent preoperative CT angiography were included in this study. Significant correlations of PRH with the patients' baseline, clinical, and radiographic characteristics, including the spot sign, were evaluated using multivariable logistic regression models.

Results The incidence of and risk factors for PRH were assessed in 127 patients with available data. PRH occurred in 9 (7.1%) patients. Five (21.7%) cases of PRH were observed among 23 patients with the spot sign, whereas only 4 (3.8%) cases of PRH occurred among 104 patients without the spot sign. The spot sign was the only independent predictor of PRH (OR 5.81, 95% CI 1.26–26.88; $p = 0.02$). The following factors were not independently associated with PRH: age, hypertension, poor consciousness, antihemostatic factors (thrombocytopenia, coagulopathy, and use of antithrombotic drugs), the location and size of the sICH, other radiographic findings (black hole sign and blend sign), surgical duration and procedures, and early surgery.

Conclusions The spot sign is likely to be a strong predictor of PRH after EEH among patients with sICH. Complete and careful control of bleeding in the operative field

should be ensured when surgically treating such patients. New surgical strategies and procedures might be needed to improve these patients' outcomes.

Introduction

Spontaneous intracerebral hemorrhage (sICH) is one of the most devastating forms of cerebrovascular disease. sICH accounts for about 15% of all strokes in the United States and Europe and 20% to 30% of strokes in Asian populations.²⁰ Surgical treatment may prevent secondary neuronal injury due to formation of hematomas and perihematoma edema, which result in a poor prognosis, although surgery via craniotomy has failed to improve patient outcomes in several randomized trials.²⁴ The effectiveness of surgery is controversial.^{4,24} Reduction in surgical complications or the performance of less invasive surgery is considered to improve the patients' prognosis.

Minimally invasive endoscopic surgery has recently been applied to treat patients with sICH and is expected to improve patients' prognosis.^{2,13,26} Although postoperative recurrent hemorrhage (PRH) is one of the most severe complications after endoscopic evacuation of hematoma (EEH), the risk factors for this complication have not been identified. The spot sign on CT is considered to be a significant predictor of spontaneous expansion of sICH and has been reported as a risk factor for PRH after craniotomy.^{4,9,25} However, the relationship of the spot sign with PRH after EEH is unknown. In the present study, we investigated whether the spot sign predicts PRH after EEH.^{4,20,24}

Methods

In this retrospective cohort study, we investigated the relationship between the spot sign and PRH after EEH. The study population comprised patients who underwent

endoscopic surgery to evacuate parenchymal sICH and in whom preoperative CT angiography was performed. sICH was defined as hemorrhage not associated with traumatic brain injury, aneurysms, arteriovenous malformations, arteriovenous fistulas, moyamoya disease, or tumors. The protocol for this retrospective study was approved by the ethics committee at our institution, and the board waived the need for patient consent. In total, 164 patients with sICH were treated by endoscopic surgery at our institution between June 2009 and March 2017. Of these, 143 patients had significant parenchymal sICH and were treated by EEH. Twenty-one patients with a massive intraventricular hematoma (IVH) in whom the endoscopic surgery was applied only for treatment of the IVH and not for treatment of the parenchymal hematoma were excluded from the study. Most of the patients underwent routine CT angiography to rule out secondary hemorrhage before the surgery. Of the 143 patients, 127 underwent preoperative CT angiography, and the data were available to assess the presence of the spot sign. These patients comprised the study population (Fig. 1). The other 16 patients were excluded because CT angiography was not performed due to renal dysfunction, contrast agent allergy, or urgent surgery with no time for the examination. The patients' baseline and clinical characteristics and radiographic findings are shown in Table 1.

The surgical indications were as follows: 1) sICH with a significant mass effect and neurological deterioration, 2) a basal ganglia hematoma of > 10 ml and associated with a massive IVH and hydrocephalus, and 3) a cerebellar hematoma of > 3 cm in diameter. sICH was evacuated via a transcortical or transventricular approach. EEH was performed via a burr hole or small craniotomy under general anesthesia. In patients with

sICH that was associated with significant acute hydrocephalus or a massive IVH, the IVH was simultaneously removed endoscopically with evacuation of the parenchymal hematoma. EEH performed within 8 hours posthemorrhage was defined as early surgery. If information regarding the volume and location of the residual hematoma was not obtained during the surgery, the surgeon stopped the procedure and performed a second EEH after confirming the volume and location. The treat was defined as intraoperative hemorrhage from a vessel requiring electrosurgical coagulation. The surgeons were recorded as Surgeons A, B, C, and others. The details of the surgical procedures are shown in the Online Supplement.

A CT scan was performed before the EEH (132 ± 121 minutes before surgery). The hematoma volume and location were recorded. sICH was classified according to presence of the black hole sign or blend sign on the CT scan (details are shown in the Online Supplement). Briefly, the black hole sign is defined as a hypoattenuated round area encapsulated within the hyperattenuating hematoma.¹⁵ The blend sign is defined as blending of a hypoattenuating area with an adjacent hypoattenuating region.¹⁴

CT angiography was also performed 143 ± 239 minutes before the EEH by using a bolus-tracking method in which 80–100 ml of nonionic iodinated contrast was injected. The presence of the spot sign on CT angiography images was recorded. Briefly, the spot sign was defined as a hyperdense spot within a hematoma without connection to an outside vessel. These details are also shown in the Online Supplement.

The patients routinely underwent repeat CT scans immediately after, 12–36 hours after, and 3–7 days after the surgery. They also underwent a CT scan when their

neurological state deteriorated remarkably. The occurrence of PRH was recorded during the first 3 days following the surgery. PRH was defined as a different appearance of sICH compared with the preoperative appearance on the CT scan, and a mass effect causing neurological deterioration. A residual hematoma was distinguished from PRH based on the intraoperative record and consistency of the sICH appearance between the preoperative and postoperative CT scans (i.e., the same shape and density) and no trace of having performed the endoscopic procedure, such as the presence of air or water bubbles. All radiographic evaluations of the preoperative and postoperative CT scans were independently performed by 2 experienced neurosurgeons in a blinded manner. When the assessments differed, interrater agreement was achieved by discussion.

Preoperative thrombocytopenia was defined as a platelet count of $< 100 \times 10^3/\text{ml}$. Coagulopathy was defined as or a prothrombin time–international normalized ratio of >1.4 . Patients undergoing oral antiplatelet or anticoagulant therapy were recorded. Anticoagulant therapy involved the use of warfarin ($n = 11$). Ten of these patients underwent preoperative administration of prothrombin complex concentrates or vitamin K to neutralize the effect of the anticoagulants, whereas 1 was not given such medication because of a normal activated partial thromboplastin time and prothrombin time–international normalized ratio. The definitions of the patients' other background factors are shown in the Online Supplement.

Statistical analyses were performed with SPSS version 24 software (IBM Corp.). Continuous variables are expressed as the mean \pm SD or median and interquartile range ([IQR], 25th–75th percentile), and categorical variables are expressed as number

(percentage). Predictors of PRH were first assessed using a univariable logistic regression model, and age and possible predictors with a p value of < 0.20 were then included in the multivariable logistic regression analyses for assessment of independent predictors. A p value of < 0.05 was considered statistically significant.

Results

Of the 127 patients, 9 (7.1%) died (6 died directly of sICH-induced brain damage, and 3 died of other causes, such as mesenteric artery occlusion or remote cerebral infarction). The parenchymal hematoma was mostly removed ($> 80\%$ of its volume) in 107 (84.3%) patients.

Of the 127 patients, 9 (7.1%) developed PRH, and it occurred within 1 day after EEH. However, no other hemorrhagic complications occurred, such as a remote ICH or acute subdural or epidural hematoma. PRH was associated with a high mortality rate of 66.7%; 5 patients died directly of PRH, and 1 patient died of a mesenteric artery occlusion.

Five (21.7%) cases of PRH were observed among 23 patients with the spot sign, whereas only 4 (3.8%) cases of PRH were observed among 104 patients without the spot sign. The baseline and clinical characteristics and radiographic findings were compared between the patients with and without PRH (Table 2). Only an increased surgical duration (OR 1.68, 95% CI 1.07–2.63; $p = 0.03$) and presence of the spot sign (OR 6.94, 95% CI 1.70–28.37; $p = 0.007$) were significant risk factors in the univariate regression analyses. Next, a multivariate analysis involving age and all variables with a

p value of < 0.20 in the univariate analyses was performed. The spot sign was the only independent predictor of PRH (OR 5.81, 95% CI 1.26–26.88; $p = 0.02$).

The association of the spot sign with intraoperative active bleeding was evaluated. The spot sign was a significant risk factor for intraoperative active bleeding (OR 3.64, 95% CI 1.43–9.28; $p = 0.007$). The association of the spot sign with early surgery was also assessed. Although our surgical indication did not consider the presence versus absence of the spot sign, we found that the spot sign was significantly associated with early surgery (OR 11.16, 95% CI 1.44–86.24; $p = 0.02$).

Discussion

Endoscopic surgery for sICH is reportedly associated with less invasion, a shorter operative duration, a higher hematoma evacuation rate, a lower frequency of complications, and a better prognosis than traditional craniotomy.^{6,13,26} PRH reportedly occurs in up to 9.5% of patients after EEH;^{2,13,26} this is consistent with the findings of our study. The risk factors for PRH in patients undergoing endoscopic surgery are not well understood, but we have herein demonstrated that the spot sign is an independent risk factor for PRH after EEH.

In previous studies, the spot sign on CT was identified at admission in 30%–37% of patients with sICH.^{4,9,10,25} It is considered a significant predictor of spontaneous expansion of sICH, with a high sensitivity of 51%–91% and specificity of 85%–89% under conservative treatment.^{9,25} Moreover, the spot sign was recently reported as an independent risk factor of PRH after craniotomy for sICH.⁴ Several risk factors are

reportedly associated with the spot sign: a large hematoma volume, anticoagulation, early presentation, a low Glasgow Coma Scale (GCS) score on presentation, a mean arterial blood pressure of > 120 mm Hg, the presence of IVH, and the APOE e2 allele.³ Recent studies using dynamic CT angiography have suggested that the spot sign signifies active extravasation in the hematoma.^{7,10} Extravasation of contrast medium may be attributed to continuous bleeding or a pseudoaneurysm at an injured small vessel. Consistent with a previous study of craniotomy for sICH, the present study showed that the spot sign was a significant risk factor for intraoperative active bleeding.⁴ We consider that the fragile vessel illustrated by the spot sign contributed to PRH as well as spontaneous hematoma expansion under conservative treatment, although the location of the spot sign was not accurately identified intraoperatively, and the active bleeding might not have been associated with a spot sign related vessel.

An antithrombotic state such as that induced by thrombocytopenia, coagulopathy, and the use of antiplatelet and anticoagulant agents has been reported to increase the risk of intracranial hemorrhagic complications after craniotomy for sICH, tumors, aneurysms, and trauma.^{1,5,21-23} Hemostasis is considered important to help prevent PRH. In the present study, however, factors associated with an antithrombotic state were not risk factors for PRH, although a shortage of power in the analyses may have contributed to this lack of an association. In addition, most of the patients undergoing anticoagulant therapy were preoperatively given vitamin K or prothrombin complex, which may also have contributed to the suppression of PRH by neutralizing the hemorrhagic effect of anticoagulant therapy.

The optimal timing of surgery for sICH has not been established. In a meta-analysis, early surgery within 8 hours posthemorrhage reportedly improved the patients' prognosis.¹¹ Surgical evacuation of sICH might suppress secondary brain injury by improving regional blood flow and restricting the release of toxic breakdown products by the clot.¹² In contrast, early surgery within 4 hours posthemorrhage is a reported risk factor for PRH.¹⁷ In the present study, early surgery (< 8 hours from onset) was not associated with PRH. Further studies are needed to establish the best timing of EEH.

A treatment strategy for spot sign–positive sICH with a high risk of expansion has not been established. Urgent surgery may prevent spontaneous expansion of sICH by treating the point of vessel rupture illustrated by the spot sign in patients with a high risk of sICH expansion. In addition, spot sign–positive sICH tends to be larger in size and theoretically provides further rationale for decompression.⁴ However, the performance of surgery should be carefully considered because of the high risk of PRH, which results in a poor outcome. We believe that the benefit of surgery outweighs the risk in patients with the spot sign. The reported in-hospital mortality rate among spot sign–positive patients was 41% under conservative treatment in a previous large study.⁸ The in-hospital mortality rate was higher than 28% in patients who underwent craniotomy,^{4,8} and it was 7.1% in those who had endoscopic surgery in the present study.

When surgically treating sICH in patients with the spot sign, extra effort and new treatments are needed to prevent PRH. For this purpose, we suggest the following. Complete and careful control of bleeding in the operative field is important. Irrigating

and inflating the hematoma cavity with saline or artificial CSF is a useful method of identifying bleeding points.¹⁹ Identifying a ruptured small vessel illustrated by the spot sign under the guidance of a navigation system and direct coagulation of the rupture point may suppress the development of PRH. Administration of coagulant factors also has the potential to inhibit PRH. In a trial of activated factor VII for ICH, recombinant activated factor VII suppressed hematoma expansion in patients undergoing conservative treatment.¹⁶ Close and careful postoperative neurological and radiographic monitoring is necessary in such patients. An early repeated CT scan is recommended to identify PRH for which reoperation is needed. Intensive control of blood pressure may suppress the incidence of PRH, although its effect did not inhibit spontaneous expansion of sICH in patients with the spot sign in a secondary analysis of the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-II) trial.¹⁸

This study has several limitations. The first is its retrospective, single-center design. Second, all patients were not included in the study because in some preoperative CT angiography examinations were lacking. Third, the surgeons may have been aware of the presence of the spot sign. In fact, patients with the spot sign more frequently underwent early surgery, although whether the spot sign was present or absent was not included in our surgical indication. Finally, the statistical power of this study is somewhat limited, although this is one of the largest studies to have investigated the association between the spot sign and PRH. A prospective multicenter study with a sufficient number of patients is needed to confirm our findings regarding the spot sign and PRH. Furthermore, a new treatment strategy should be established to improve the

surgical outcomes in patients with unstable sICH with the spot sign.

Conclusions

The spot sign is likely to be a strong predictor of PRH after EEH among patients with sICH. When surgically treating sICH in patients with the spot sign, complete and careful control of bleeding in the operative field should be ensured. Furthermore, new surgical strategies and procedures might be needed to improve these patients' outcomes.

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Figure Legend

Figure 1. Flowchart of inclusion and exclusion criteria for patients with sICH.

Table 1

Baseline, clinical, and radiographic characteristics

	Patients who underwent EEH n = 127
Age	66.6 ± 11.5
Female sex	51 (40.2)
Hypertension	80 (63.0)
Diabetes mellitus	24 (18.9)
Smoking	48 (37.8)
Daily alcohol consumption	45 (35.4)
Thrombocytopenia	8 (6.3)
Coagulopathy	6 (4.7)
Antiplatelet therapy	24 (18.9)
Anticoagulant therapy	11 (8.7)
Glasgow Coma Scale score	10 (7–12)
Hematoma volume (ml)	51.1 ± 36.9
Location	
Basal ganglia	92 (72.4)
Lobar	16 (12.6)
Cerebellum	19 (15.0)
Radiographic findings	
Black hole sign	15 (11.8)
Blend sign	11 (8.7)
Spot sign	23 (18.1)

EEH, endoscopic evacuation of a hematoma

Data are presented as mean ± standard deviation, n (%), or median and interquartile range (25th–75th percentile).

Table 2. Effects of predictors of rebleeding after endoscopic surgery in patients with spontaneous intracerebral hemorrhage

	Crude model			Multivariable model		
	OR	95%CI	<i>p</i> -value	OR	95%CI	<i>p</i> -value
Age (per 10-year increase)	0.87	0.49–1.55	.63	0.71	0.35–1.46	.35
Female sex	1.21	0.31–4.73	.79			
Hypertension	0.72	0.18–2.81	.63			
Diabetes mellitus	0.52	0.06–4.34	.67			
Smoking	1.35	0.34–5.28	.67			
Daily alcohol consumption	0.91	0.22–3.80	.89			
Thrombocytopenia	1.98	0.22–18.15	.55			
Coagulopathy	Not calculable					
Antiplatelet drug	1.25	0.24–6.42	.79			
Anticoagulant drug	Not calculable					
Glasgow Coma Scale score of <9	3.36	0.80–14.13	.10	3.17	0.61–16.57	.17
Hematoma volume (per 5-ml increase)	1.03	0.96–1.11	.44			
Location						
Basal ganglia	Reference					
Lobar	0.81	0.09–7.06	.85			
Cerebellum	0.68	0.08–5.83	.72			
Radiographic findings						
Black hole sign	0.93	0.11–7.99	.95			
Blend sign	1.35	0.15–11.91	.79			
Spot sign	6.94	1.70–28.37	0.007	5.81	1.26–26.88	.02
Early surgery	3.37	0.41–27.99	.26			
Duration of surgery (per 1-hour increase)	1.68	1.07–2.63	.03	1.39	0.81–2.39	.24
Transventricular approach	2.83	0.71–11.31	.14	1.31	0.19–9.00	.78
Removal of IVH	3.24	0.77–13.62	.11	1.05	0.13–8.89	.96
Staged surgery	Not calculable					
Surgeon						
A	Reference					
B	1.30	0.17–10.05	.80			
C	1.24	0.16–9.55	.84			
Others	0.77	0.12–4.87	.78			

IVH, intraventricular hematoma; OR, odds ratio; CI, confidence interval

