CT angiography spot sign in intracerebral hemorrhage predicts active bleeding during surgery

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ABSTRACT

Objective: To determine whether the CT angiography (CTA) spot sign marks bleeding complications during and after surgery for spontaneous intracerebral hemorrhage (ICH).

Methods: In a 2-center study of consecutive spontaneous ICH patients who underwent CTA followed by surgical hematoma evacuation, 2 experienced readers (blinded to clinical and surgical data) reviewed CTAs for spot sign presence. Blinded raters assessed active intraoperative and postoperative bleeding. The association between spot sign and active intraoperative bleeding, postoperative rebleeding, and residual ICH volumes was evaluated using univariable and multivariable logistic regression.

Results: A total of 95 patients met inclusion criteria: 44 lobar, 17 deep, 33 cerebellar, and 1 brainstem ICH; ≥ 1 spot sign was identified in 32 patients (34%). The spot sign was the only independent marker of active bleeding during surgery (odds ratio [OR] 3.4; 95% confidence interval [CI] 1.3–9.0). Spot sign (OR 4.1; 95% CI 1.1–17), female sex (OR 6.9; 95% CI 1.7–37), and antiplatelet use (OR 4.6; 95% CI 1.2–21) were predictive of postoperative rebleeding. Larger residual hematomas and postoperative rebleeding were associated with higher discharge case fatality (OR 3.4; 95% CI 1.1–11) and a trend toward increased case fatality at 3 months (OR 2.9; 95% CI 0.9–8.8).

Conclusions: The CTA spot sign is associated with more intraoperative bleeding, more postoperative rebleeding, and larger residual ICH volumes in patients undergoing hematoma evacuation for spontaneous ICH. The spot sign may therefore be useful to select patients for future surgical trials. *Neurology*® 2014;83:883–889

GLOSSARY

CI = confidence interval; CTA = CT angiography; ICH = intracerebral hemorrhage; MGH = Massachusetts General Hospital; OR = odds ratio; UMCU = Utrecht University Medical Center.

Intracerebral hemorrhage (ICH) remains the most lethal form of stroke, with 1-month mortality rates of 40%.¹ Clinical trials assessing surgical therapy for ICH have not shown an effect on functional outcome, although benefit has been shown for cerebellar hematomas larger than 3 cm in observational studies.^{2,3} Systematic reviews also suggest a beneficial effect for specific subgroups in supratentorial ICH.^{4,5} Based on those results, STICH II evaluated surgery for patients with superficial hematomas (≤ 1 cm of the cortex) without intraventricular extension. The results showed a neutral effect on functional outcome. Yet the updated meta-analysis, published in the same article, suggested a beneficial effect for surgical intervention for spontaneous ICH (odds ratio [OR] 0.74; 95% confidence interval [95% CI] 0.64–0.86).⁶

Thus, a tool to identify patients who may benefit from surgery is warranted. A robust marker of ongoing bleeding, studied extensively over the last 10 years, is the CT angiography (CTA) spot sign (figure 1B).⁷ The spot sign is commonly assumed to represent continued bleeding (e.g., contrast extravasation visualized on CTA after contrast bolus injection) from ruptured

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Figure 1 Case example

A 77-year-old woman had acute onset of nausea, vomiting, slurred speech, and ataxia. Her initial noncontrast CT showed a 21 mL cerebellar intracerebral hemorrhage (A). The CT angiography source images revealed 2 spot signs in the medial aspect of the hematoma (B). The postoperative CT demonstrated a fresh hematoma in the surgical bed (C). After the CT, the patient was emergently taken for repeated surgery. The patient was scored as having active intraoperative bleeding, given the extended hemostatic measures applied during the initial surgery. Given the fresh blood on the postoperative CT and the need for an additional surgical procedure, this patient was considered to have had unsuccessful hematoma removal.

vessels surrounding the initial hematoma. The spot sign has been associated with both hematoma expansion and poor clinical outcome.^{7–10}

We investigated whether the spot sign is also associated with active bleeding during surgery and postoperative rebleeding in patients undergoing craniotomy for spontaneous ICH.

METHODS Study design. We studied a consecutive series of patients with spontaneous ICH who underwent surgical evacuation from Massachusetts General Hospital (MGH), Boston, and Utrecht University Medical Center (UMCU), Utrecht, the Netherlands.

Standard protocol approvals, registrations, and patient consents. The local institutional review boards at both hospitals approved all parts of the study. Informed consent was obtained from all study participants (or their legally authorized health care proxies), or consent was waived by a protocol-specific allowance. Data exchange and analysis was completed using de-identified data.

Study subjects. Consecutive patients undergoing surgery for spontaneous ICH between August 2003 and August 2012 were reviewed for study inclusion at the 2 centers. Indications for surgery included clinical deterioration (decline in Glasgow Coma Scale by ≥ 2 points), expansion of the hematoma (increase in ICH volume of $>33\%$), significant mass effect (midline shift >10 mm or obliteration of basal cisterns), and cerebellar hematomas larger than 3 cm. Inclusion criteria for this study were (1) spontaneous ICH; (2) baseline CTA of sufficient quality for spot sign reading; and (3) craniotomy for surgical hematoma evacuation within 24 hours of the qualifying CTA. Exclusion criteria were (1) known or suspected secondary ICH, including aneurysmal subarachnoid hemorrhage, other vascular malformations, neoplasms, hemorrhagic transformation of an acute ischemic stroke, and trauma; (2) primary intraventricular hemorrhage; and (3) enrollment in a randomized controlled treatment trial. All patients enrolled were treated according to a standard institutional protocol (available for

MGH online at <http://www2.massgeneral.org/stopstroke/>), and none of the patients received recombinant factor VIIa.

Clinical data. Clinical covariables were collected through review of clinical and research records at both centers and comprised age, sex, previous medical history, and medication use including anticoagulation use and antiplatelet therapy. Upon admission, the following variables had been collected prospectively: systolic blood pressure, Glasgow Coma Scale, time from emergency department admission to surgery, time from CTA to surgery, and the duration of the procedure. Case fatality at discharge and 3 months was assessed by trained study staff via telephone interview and complemented by the Social Security Death Index (MGH only), if no contact could be established with the patient or the family. The Social Security Death Index is a publicly available database with information regarding deaths reported to the United States Social Security Administration.¹¹

CT analysis. Trained neurologists or neuroradiologists ascertained ICH locations, blinded to clinical, surgical, and outcome data. Hematoma volumes for baseline (prior to surgery) and follow-up CTs were outlined and measured by trained study staff, using Analyze 10.0 (Mayo Clinic, Rochester, MN) software, according to previously published protocols.^{9,12} The same imaging sequence for diagnosis of spot sign was used at each site and CTAs were reviewed for spot sign presence by 2 experienced readers (authors H.B.B. and K.A.M.), blinded to clinical and surgical data, following standard methods with high interrater agreement.¹²

Intraoperative and postoperative bleeding. Intraoperative bleeding was assessed by evaluation of the operative notes at the individual centers by 2 reviewers (authors M.R.R. and K.M.v.N.), blinded to all clinical and imaging data. Active intraoperative bleeding was operationally defined as a dichotomous outcome: standard surgical hemostasis applied (e.g., including Surgicel, cotton balls) vs active bleeding in need of extended hemostasis including electrosurgical coagulation or abortion of the procedure. Postoperative rebleeding was defined as a composite endpoint of the presence of fresh blood on the postoperative CT, $<50\%$ removal of the initial hematoma (i.e., unsuccessful surgery), or the need for repeated surgery. Percentage hematoma removed was calculated using the follow-up (postoperative) ICH volume divided by the baseline ICH volume $\times 100\%$.^{13,14} An example case is shown in figure 1.

Statistical analysis. Continuous variables are summarized using mean (SD) or—when appropriate—median (interquartile range). Discrete variables are shown as number (%). As described, intraoperative and postoperative bleeding were analyzed as dichotomous outcomes. The CTA spot sign was modeled as a dichotomous variable (absent or present). Association testing between the CTA spot sign and active intraoperative and postoperative bleeding was completed using univariable and multivariable logistic regression. Age, sex, time from CTA to surgery, anticoagulation use, and variables with a $p < 0.20$ in univariable analyses were included in multivariable models. Of note, time from symptom onset to CTA was considered as a covariate in the multivariate models, but this data point was not available for all patients (missing $n = 27$, 28%) and model performance was superior using time from CTA to surgery. Therefore, time from CTA to surgery was used in the final multivariable models. Collinear variables were removed when appropriate, as measured by the variance inflation factor. In addition, we tested intraoperative and postoperative bleeding for association with in-hospital and 3-month case fatality. All statistical analyses were performed using

JMP Pro version 9.0 (SAS Institute Inc., Cary, NC) and statistical significance was declared at $p < 0.05$ (2-tailed).

RESULTS Study population. Based on inclusion/exclusion criteria, 95 patients were included at MGH (n = 75) and UMCU (n = 20). A total of 186 patients underwent surgery for hematoma evacuation at both sites combined. A total of 113 of these patients had a CTA available, 95 of which were of quality to diagnose spot sign presence and within

the specified 24 hours between CTA and time of surgery (figure e-1 on the *Neurology*[®] Web site at Neurology.org). Indications for surgery were clinical deterioration (n = 33, 35%), expansion of the hematoma (n = 15, 16%), significant mass effect (n = 10, 10%), cerebellar hematomas larger than 3 cm (n = 33, 35%), and other (n = 4, 4%). One or more spot signs were present in 32 patients (34%). Clinical and imaging baseline characteristics are given in table 1.

Table 1 Cohort characteristics

Variable	All patients, n (%) or median (IQR)	Spot sign-negative, n (%) or median (IQR)	Spot sign-positive, n (%) or median (IQR)
No. of patients	95 (100)	63 (66)	32 (34)
Age, y, mean (SD)	61 (13)	59 (13)	66 (13)
Female sex	42 (44)	24 (38)	18 (56)
Hypertension	63 (67)	43 (68)	20 (65)
Diabetes	11 (12)	8 (13)	3 (10)
Antiplatelets	34 (37)	21 (34)	13 (42)
Warfarin	19 (20)	9 (14)	10 (31)
INR ^a			
1.2–1.9	0 (0)	0 (0)	0 (0)
2.0–3.0	9 (47)	2 (22)	7 (70)
>3.0	10 (53)	7 (78)	3 (30)
GCS	9 (5–14)	11 (5–14)	8 (4–15)
SBP	180 (149–198)	185 (151–207)	176 (143–190)
ICH location			
Lobar	44 (46)	25 (40)	19 (59)
Deep	17 (18)	12 (19)	5 (16)
Brainstem	1 (1)	0 (0)	1 (3)
Cerebellar	33 (35)	26 (41)	7 (22)
Baseline ICH volume, mL	53 (27–75)	44 (25–69)	65 (38–82)
Intraventricular extension	46 (52)	29 (51)	17 (53)
Baseline IVH volume, mL ^b	10 (3–24)	11 (3–22)	7 (4–27)
Time symptoms to surgery, h	7.2 (5.1–11.2)	7.8 (5.6–13.5)	6.1 (4.7–8.8)
Time ED to surgery, h	3.3 (2.2–5.2)	3.3 (2.2–6.8)	2.8 (2.1–4.3)
Time CTA to surgery, h	2.3 (1.5–4.4)	2.4 (1.5–6.0)	2.2 (1.5–3.9)
Procedure time, h	2.8 (2.0–3.5)	3.0 (2.0–3.4)	2.6 (2.0–3.7)
Intraoperative bleeding	38 (40)	19 (30)	19 (59)
Postoperative bleeding	16 (18)	6 (10)	10 (31)
Repeated surgery	5 (5)	1 (2)	4 (13)
Discharge case fatality	24 (25)	15 (24)	9 (28)
90-day case fatality	30 (32)	16 (26)	14 (44)

Abbreviations: CTA = CT angiography; ED = emergency department; ICH = intracerebral hemorrhage; INR = international normalized ratio; IQR = interquartile range; IVH = intraventricular hemorrhage; GCS = Glasgow Coma Scale; SBP = systolic blood pressure.

^aData refer only to patients using warfarin at time of hospital presentation (n = 19).

^bData refer to patients with intraventricular extension only (n = 46).

Active intraoperative and postoperative bleeding. Active intraoperative bleeding occurred in 38 patients (40%) and was more common in patients with a spot sign (59% vs 30%; $p = 0.01$). A total of 16 patients (18%) met the composite endpoint of postoperative rebleeding or unsuccessful surgery, which was also more common in spot sign–positive patients (31% vs 10%; $p = 0.02$). On follow-up CT, postoperative rebleeding in need of repeated surgery was identified in 5 patients (5%); 4 were spot sign–positive (13%) and 1 spot sign–negative (2%; $p = 0.03$) (table 1).

Predictors of intraoperative and postoperative bleeding. In univariable analysis, only the spot sign was associated with intraoperative bleeding (OR 3.4; 95% CI 1.4–8.2; table 2). After adjustment for age, sex, warfarin use, and time from CTA to surgery in multivariable analysis, the spot sign remained independently associated with intraoperative bleeding: OR 3.4 (95% CI 1.3–9.0; table 3). Of note, time from arrival to surgery was collinear with time from CTA to surgery and was therefore removed from the analysis. Similarly, international normalized ratio was collinear with warfarin use and the latter was used for the analysis because of superior model fit.

The spot sign ($p = 0.02$), female sex ($p = 0.002$), and antiplatelet use ($p = 0.04$) were associated with larger residual hematomas and postoperative rebleeding in univariable analysis (table 2). In multivariable analysis, all 3 associations remained statistically significant (table 3).

Active bleeding and case fatality. Intraoperative bleeding was not associated with in-hospital (OR 0.9;

95% CI 0.3–2.3) or 3-month case fatality (OR 0.8; 95% CI 0.3–1.9). Unsuccessful hematoma removal and postoperative rebleeding were associated with discharge case fatality (OR 3.4; 95% CI 1.1–11) and a trend toward significance was found for the association with 3-month case fatality (OR 2.9; 95% CI 0.9–8.8).

DISCUSSION This study demonstrates that the CTA spot sign marks active bleeding in patients with spontaneous ICH. Patients with a spot sign have more intraoperative bleeding, more postoperative rebleeding, and larger residual ICH volumes. Our results may therefore help select patients for future clinical trials of surgical evacuation in patients with spontaneous ICH.

Multiple studies published over the past decade demonstrate that the spot sign is a robust radiographic marker of hematoma expansion and poor clinical outcome.^{7,10} Its frequency in our cohort (34%) is in line with previous observations, as the spot sign is more commonly seen in individuals with larger hematomas.^{9,10,12,15} Those are also the very patients who are more likely to undergo hematoma evacuation. Its frequent appearance and strong correlation with intraoperative and postoperative bleeding highlight its potential not only for diagnosis and prognosis, but also as a tool for treatment stratification. This could open a path for clinical trial design with guided interventions based on neuroimaging. Currently, the spot sign is already in use to select patients for treatment with recombinant factor VIIa in 2 ongoing trials (SPOTLIGHT [ClinicalTrials.gov #NCT01359202] and STOP-IT [ClinicalTrials.gov #NCT00810888]),

Table 2 Univariable analyses: Intraoperative and postoperative bleeding

Variable	Intraoperative bleeding		Postoperative bleeding	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.0 (0.9–1.0)	0.63	1.0 (0.9–1.1)	0.19
Female sex	2.1 (0.9–4.9)	0.09	7.7 (2.0–30)	0.002
Hypertension	1.1 (0.5–2.7)	1.00	0.8 (0.2–2.3)	0.77
Antiplatelet	1.4 (0.6–3.3)	0.51	3.4 (1.1–10)	0.04
Warfarin	1.1 (0.4–3.1)	1.00	0.9 (0.2–3.7)	1.00
GCS	1.0 (0.9–1.1)	0.86	1.0 (0.9–1.2)	0.74
SBP	1.0 (0.9–1.0)	0.86	1.0 (0.9–1.0)	0.29
Baseline ICH volume, mL	1.0 (0.9–1.0)	0.62	1.0 (0.9–1.0)	0.81
Baseline IVH volume, mL	1.0 (0.9–1.0)	0.66	1.0 (0.9–1.0)	0.98
Spot sign	3.4 (1.4–8.2)	0.01	4.0 (1.3–12)	0.02
Time CTA to surgery, h	1.0 (0.9–1.0)	0.83	0.9 (0.8–1.0)	0.41
Procedure time, h	0.8 (0.5–1.2)	0.26	1.1 (0.6–1.8)	0.83

Abbreviations: CI = confidence interval; CTA = CT angiography; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; OR = odds ratio; SBP = systolic blood pressure.

Table 3 Multivariable analysis: Intraoperative and postoperative bleeding

Variable	Intraoperative bleeding		Postoperative bleeding	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.0 (0.9–1.0)	0.93	1.0 (0.9–1.1)	0.56
Female sex	1.7 (0.7–4.2)	0.25	6.9 (1.7–37)	0.01
Antiplatelet	NA	—	4.6 (1.2–21)	0.04
Warfarin	0.8 (0.2–2.7)	0.76	NA	—
Time CTA to surgery, h	1.0 (0.9–1.0)	0.94	1.0 (0.7–1.0)	0.70
Spot sign	3.4 (1.3–9.0)	0.01	4.1 (1.1–17)	0.04

Abbreviations: CI = confidence interval; CTA = CT angiography; NA = not applicable; OR = odds ratio.

and is the subject of an ancillary study of ATACH–II, a clinical trial of intensive blood pressure reduction.¹⁶

The spot sign is generally assumed to represent contrast leakage from small vessels within and surrounding the hematoma, but little is known about its biological underpinnings.⁷ The mechanism proposed is active extravasation of contrast following peripheral bolus injection, visualizing active—continued—bleeding.¹⁷ This is supported by the observations that anticoagulation use and possession of the *APOE* ε2 allele are associated with spot sign presence, linking it to longer bleeding times and increased vasculopathic changes leading to vessel fragility and rupture.^{12,18,19} Other theories include pseudoaneurysms, microdissections, and Charcot-Bouchard aneurysms.^{8,20} Our results provide pathologic support for the hypothesis that the spot sign indeed represents active bleeding.

The 2 negative STICH trials add to the continuing debate regarding which patients—if any—to select for early hematoma evacuation.^{6,21} A possible explanation for the neutral results comes from the numerous crossovers from conservative treatment to surgery (21% in STICH II), as treatment effect was analyzed according to an intention-to-treat design.⁶ In addition, 2 large meta-analyses have shown a positive effect in favor of surgery in specific subgroups, even with the inclusion of STICH II.^{4–6} Informed patient selection may therefore be of pivotal importance, and the spot sign offers the promise of providing a novel selection tool for future surgical trials.

Our results raise the concern that patients with a spot sign have more intraoperative and postoperative bleeding and larger residual ICH volumes compared to those without a spot sign. This suggests that such patients are at higher risk of sustaining a complication from surgery. Although the absolute difference is 21% for the composite endpoint, it significantly impacts discharge case fatality. Consequently, those without a spot sign may be the optimal surgical

candidates who achieved hemostasis, and for whom evacuation will be least complicated. On the other hand, patients with a spot sign have worse prognosis and higher risk of hematoma expansion.^{8–10,22} Indeed, in-hospital case fatality among spot sign–positive patients was 41% in a large retrospective study of ICH patients who did not undergo hematoma evacuation (compared to 28% in our cohort).²² It may therefore be that the benefits of surgery outweigh the risks in patients with a spot sign. That ICH patients with spot signs tend to have larger ICH volumes^{9,10,12,15} theoretically provides further rationale for decompression of the hematoma, given the strong relationship between ICH volume and outcome.²³ Finally, it may simply be that spot sign presence can alert the neurosurgical team to those patients requiring extra effort to ensure meticulous hemostasis before concluding the procedure. Therefore, patients with a spot sign may benefit most from surgical intervention but simultaneously they are also at higher risk of intraoperative and postoperative bleeding. Intraoperative administration of antifibrinolytic drugs or recombinant factor VIIa combined with meticulous hemostasis before finalizing the procedure may reduce these bleeding complications. Future clinical trials are warranted to test this hypothesis.

The robustness of our results is driven by its 2-center design, the relatively large sample size for a surgical study, and the blinded assessment of CTA and outcome measures. Yet our study is limited by the number of missing CTAs in patients undergoing surgery and the fact that the surgeons may have been aware of the presence of the spot sign on CTA at the time of surgery. Given that most patients underwent surgery before the spot sign became routinely described in the radiology reports at our 2 centers, we suspect it is unlikely that the surgical teams used it in any way for clinical decision-making at the time of surgery.

In the current study, we show that the CTA spot sign is a common finding in patients who undergo

hematoma evacuation for spontaneous ICH. The spot sign is associated with more intraoperative bleeding, more postoperative rebleeding, and larger residual ICH volumes in these patients, consistent with its representation of active bleeding. Our results may help select patients for future surgical trials in ICH.

AUTHOR CONTRIBUTIONS

Study design: H.B.B., J.N.G., J.R. Data acquisition: H.B.B., M.R.R., K.M.v.N., A.M.A., K.A.M. Data analysis: H.B.B., G.J.F. Study management: K.S., S.M.G., G.J.E.R., J.N.G., C.J.M.K., J.R. Manuscript preparation: H.B.B., J.N.G., J.R. Manuscript Review: M.R.R., K.M.v.N., G.J.F., A.M.A., K.A.M., K.S., J.M.R., B.K.V., A.V., S.M.G., C.S.O., A.v.d.Z., G.J.E.R., J.N.G., C.J.M.K., J.R. Drs. Brouwers, Goldstein, and Rosand had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have seen and approved the submitted version of the manuscript.

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DISCLOSURE

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This Week's *Neurology*[®] Podcast

Current practices in feeding tube placement for US acute ischemic stroke inpatients (See p. 874)

This podcast begins and closes with Dr. Ted Burns, Section Editor Podcasts, briefly discussing highlighted articles from the September 2, 2014, issue of *Neurology*. In the second segment, Dr. Kevin Barrett talks with Drs. Ben George and Adam Kelly about their paper on current practices in feeding tube placement for acute ischemic stroke inpatients in the US. Dr. James Addington then reads the e-Pearl of the week about childhood stroke and “thinking metabolic.” In the next part of the podcast,

Dr. Stephen Donahue focuses his interview with Dr. Michael Jaffee on the definition of concussion and how the grading has evolved over recent years.

Disclosures can be found at Neurology.org.

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