Hemorrhagic Risk of Emergent Endovascular Treatment Plus Stenting in Patients with Acute Ischemic Stroke

Laura Dorado, PhD,* Carlos Castaño, PhD,† Mònica Millán, PhD,* Aitziber Aleu, MD,† Natàlia Pérez de la Ossa, MD,* Meritxell Gomis, PhD,* Elena López-Cancio, PhD,* Elio Vivas, MD,‡ Ana Rodriguez-Campello, MD,§ Mar Castellanos, PhD,‖ and Antoni Dávalos, PhD*

Background: Several endovascular revascularization strategies have been described for the treatment of acute ischemic stroke (AIS). One of them is stenting when a very narrow stenosis with high reocclusion risk remains after recanalization. This study describes the risk of symptomatic intracerebral hemorrhage (SICH) after emergent stenting in patients with AIS treated with endovascular therapies. *Methods:* Consecutive patients who underwent endovascular treatment over a 37-month period were retrospectively analyzed. Patients were classified in 2 groups: (1) patients in whom a stent was deployed; and (2) patients without stenting. Double antiplatelet treatment with aspirin and clopidogrel was administered at the time of stenting. SICH was defined as any hemorrhagic transformation with National Institutes of Health Stroke Scale (NIHSS) score worsening 4 points or more (European-Australasian Acute Stroke Study II criteria). *Results:* A total of 143 patients were included (mean age: 66.1 ± 11.7 years, median NIHSS score: 18). Acute phase stenting was performed in 24 subjects (16.8%): 4 intracranial (3 in basilar artery, 1 in middle cerebral artery) and 20 extracranial (internal carotid artery). SICH occurred in 11 patients, 5 of 24 (20.8%) in patients with stenting and in 3 of 119 (2.5%) without ($P = .008$). No differences were found with respect to baseline NIHSS score or intravenous tissue plasminogen activator administration. Acute phase stenting emerged as an independent predictor of SICH after adjustment for potential confounders and procedure duration: odds ratio 7.3 (confidence interval 1.4-36.8, $P = .016$). *Conclusions:* Our findings suggest that emergent stenting in endovascular treatment of AIS is associated with SICH. **Key Words:** Acute ischemic stroke—endovascular stroke therapy—emergent stenting—intracranial hemorrhage.

Several endovascular mechanical techniques for clot removal or lysis in patients with acute ischemic stroke (AIS) have been developed.[1] In the setting of an underlying high-grade stenosis, the benefit of emergent intracranial/extracranial stenting as adjunctive therapy to revascularization is not well established. The use of emergent stenting in patients with tandem occlusion (extracranial internal carotid artery [ICA], origin and intracranial

From the *Stroke Unit; †Unit of Interventional Neuroradiology, Department of Neurosciences, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona (Barcelona), Spain; ‡Unit of Interventional Neuroradiology; §Stroke Unit, Department of Neurosciences, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain; and ‖Stroke Unit, Department of Neurosciences, Hospital Dr Josep Trueta, Girona, Spain.

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Address correspondence to Laura Dorado, PhD, Stroke Unit, Department of Neurosciences, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Carretera de Canyet, s/n, 08916 Badalona (Barcelona), Spain. E-mail: lauritadb@yahoo.es.

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ICA, or middle cerebral artery [MCA]) has been reported. Different approaches have been described that propose treating either the proximal or the distal occlusion first.[2] Regarding intracranial occlusions, several case series have shown good outcomes with self-expanding stents in patients with acute intracranial occlusion in whom other recanalization methods have failed.[3–5]

The combination of mechanical and pharmacologic endovascular approaches in addition to antithrombotic drugs administered to prevent acute stent thrombosis might increase the risk of postischemic intracerebral hemorrhage after acute revascularization.

Therefore, we conducted a retrospective review of the experience in a single comprehensive stroke center to determine the safety of emergent stent placement in individuals who underwent endovascular treatment for AIS.

Methods

We retrospectively reviewed a prospective register of patients who underwent endovascular therapy for AIS at the Hospital Universitari Germans Trias i Pujol in Badalona (Barcelona), Spain, from March 2008 to April 2011.

Patients were admitted to our comprehensive stroke center covering an area of 1.5 million inhabitants and connected with a stroke network of a primary stroke center and 4 community hospitals. Criteria for endovascular treatment were predefined and approved by the ethics committee. In summary, endovascular treatment was indicated when the patient had salvageable tissue on neuroimaging and a terminal ICA occlusion, a basilar artery occlusion, or an MCA occlusion refractory to intravenous (IV) tissue plasminogen activator (tPA), or when the patient had contraindications for systemic thrombolysis.

All eligible patients met the following criteria: age 18 years or older, brain computed tomography (CT) or magnetic resonance (MR) imaging excluding hemorrhage, duration of stroke symptoms inferior to 8 hours, and an angiographically proved occlusion of the main anterior or posterior cerebral artery. Informed consent was signed by patients or direct family members. Exclusion criteria were current pregnancy, oral anticoagulant therapy with international normalized ratio greater than 3.0, partial thromboplastin time greater than 2 times normal, platelet count less than 30,000/μL, sustained systolic blood pressure greater than 185 mm Hg or diastolic blood pressure greater than 110 mm Hg despite treatment, and life expectancy less than 3 months.

The National Institutes of Health Stroke Scale (NIHSS) score was obtained at baseline, daily for the first 3 days, and then at day 7 and 90. All patients were initially evaluated with a non-contrast CT scan, followed by additional imaging using a new CT scan or MR diffusion-weighted imaging studies to assess the amount of tissue presumably irreversibly compromised immediately before endovascular therapy. A hypodensity area in non-contrast CT scan involving greater than one-third MCA territory, an Alberta Stroke Program Early CT Score of less than 7, or diffusion lesion greater than 50% of MCA territory on MR imaging excluded any acute stroke treatment. Vessel status at baseline was assessed by using MR angiography or transcranial color-coded duplex sonography.

Patients arriving at the hospital within 4.5 hours from symptoms' onset were treated with IV tPA in a standard 0.9-mg/kg dose. The vessel patency was monitored by transcranial color-coded duplex sonography during tPA infusion following Thrombolysis In Brain Ischemia (TIBI) transcranial Doppler flow grades. The angiosuite was prepared for rescue therapy after 30 minutes of unsuccessful recanalization (lack of recanalization was considered when TIBI grades IV or V were not achieved). Patients who arrived beyond 4.5 hours from symptoms' onset or had contraindications for systemic thrombolysis were directly transferred to the angiosuite.

Endovascular stroke treatment was performed using a variety of endovascular recanalization techniques: (1) pharmacological intra-arterial (IA) treatments: infusion of tPA or abciximab boluses; (2) mechanical IA treatments: mechanical embolectomy with the Merci clot retriever device (Concentric Medical, Mountain View, CA), manual aspiration thrombectomy with the distal access catheters or Stentrievers thrombectomy (Solitaire FR revascularization device, ev3-Covidien, Irvine, CA, or Trevo stent-like retriever, Concentric Medical, Mountain View, CA); and (3) stenting was performed as a salvage technique in patients with intracranial occlusions in whom other recanalization methods had failed or in patients with tandem occlusions with a remaining extracranial high-grade stenosis after the procedure.

Patients were admitted in the acute stroke or intensive care departments after the procedure and treated following the European Stroke Organization guidelines. Antiplatelet drugs and anticoagulants were not allowed during the first 24 hours in any patients except for those with emergent stent placement in whom, immediately before stenting, aspirin (300 mg) or IV lysine acetylsalicylate (450-900 mg) and clopidogrel (300 mg) were administered through a nasogastric tube.

A CT scan was routinely performed at 24-36 hours after treatment (or earlier in case of any neurological worsening ≥4 points in NIHSS score). Then the appropriate secondary prevention treatment was started in all patients. Patients who underwent stenting were discharged on a maintenance dose of aspirin (300 mg daily) and clopidogrel (75 mg daily) for 3-6 months. After this period, the patient continued treatment with aspirin or clopidogrel according to physician decision.

Stenting Procedure

Treatment protocols at our center initially included general anesthesia as the standard modality of sedation.

However, due to the theoretical advantages of conscious sedation, we changed our standard protocols of sedation for acute stroke IA treatment from preprocedural intubation and general anesthesia to conscious sedation without intubation when feasible.

Extracranial Stenting

An 8F guide catheter was placed into the ipsilateral distal common carotid artery. A 0.014-in wire was then passed through the proximal occlusion, and a microcatheter was advanced over this wire into the petrous portion of the ICA. A microcatheter injection was performed to explore the vessel distally.

If the patient had a tandem occlusion, we performed an ICA angioplasty before mechanical thrombectomy followed by stenting of the ICA after thrombectomy without embolic protection.

Intracranial Stenting

An 8F guide catheter (Merci balloon guide catheter concentric) was placed in the ICA for anterior circulation stenosis, or a 6F guide catheter (Neuron delivery catheter, Penumbra Inc, San Leandro, CA; or Envoy Guiding Catheter, DePuy) was placed in the vertebral artery, for vertebrobasilar stenosis.

Then, the Wingspan stent system (Boston-Scientific) was advanced and deployed covering the entire lesion. In those cases where the stent was not able to dilate the vessel itself, an angioplasty was performed using a balloon (Gateway percutaneous transluminal angioplasty balloon catheter, Boston-Scientific), always smaller than the healthy artery. We used an IA abciximab bolus during stent implantation (2-3 mg locally).

Outcome Variables

The following variables were recorded: time from stroke onset to groin puncture, time from groin puncture to recanalization, the use of IA thrombolytic treatment, and postprocedural recanalization classified according to thrombolysis in cerebral infarction grading system.[6] Successful recanalization was considered when thrombolysis in cerebral infarction grades 2a, 2b, or 3 were achieved at the end of the procedure. Major procedure-related complications (including vascular perforation, distal embolism in a different arterial territory, and intramural arterial dissection) were recorded.

Cerebral bleeding was classified in hemorrhagic infarction types 1 and 2 and parenchymal hemorrhage (PH) types 1 and 2[7] and subarachnoid hemorrhage. Symptomatic intracerebral hemorrhage (SICH) was defined following: (1) the European-Australasian Acute Stroke Study II as any hemorrhage with neurological deterioration of 4 or more points in the NIHSS score compared to baseline score or any hemorrhage leading to death[8]; and (2) according to Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria as PH type 2 on the 24- to 36-hour CT combined with neurological deterioration of 4 points or greater.[9] An asymptomatic hemorrhage was defined in the presence of blood on the 24- to 36-hour CT or MR scan with no more than a 3-point decline in the NIHSS score. All 24-hour CT scans were reviewed by a neuroradiologist blinded to clinical evolution of the patient.

Functional independence was defined as modified Rankin scale score of 2 or less evaluated at day 90. Mortality was also recorded at 90 days.

Results

A total of 157 AIS patients underwent cerebral angiography for revascularization purposes in a 37-month period. Fourteen of them were excluded from revascularization approaches due to physician decision after baseline angiography (n = 6) or to unsuccessful access to the occlusion given a high-grade stenosis or tortuosity of the artery proximal to the target vessel (n = 8).

Stenting was performed in 24 patients (16.8%) of the 143 patients who received endovascular therapy. Stenting sites were: basilar artery (n = 3), MCA (n = 1), and extracranial carotid artery (n = 20). Table 1 summarizes clinical characteristics in the overall sample (n = 143) and in the group of patients in whom recanalization was stent-assisted (n = 24) or not (n = 119).

Procedure-related complications were recorded in 5 patients: 1 vascular perforation, 3 distal embolisms, and 1 intramural arterial dissection.

In total, 69 patients (48.3%) were treated with IV tPA before the neurointerventional approach. The use of systemic thrombolysis was similar between both groups as was antiplatelet pretreatment. No significant differences were found with respect to vital signs, baseline stroke severity, or time from symptoms' onset to groin puncture. Patients in the stenting group had a higher rate of tandem ICA/MCA and proximal isolated ICA occlusions. In line with this finding, Trial of Org 10172 in Acute Stroke Treatment (TOAST) etiology was more frequently atherothrombotic in stenting group and cardioembolic in the non-stenting group.

Successful recanalization of treated vessels was achieved in 86% in the total series with no significant differences between groups. The time from groin puncture to recanalization was significantly longer in the stenting group (97 [61-130] versus 55 [37-100] minutes, $P = .003$).

Table 2 summarizes the outcome variables. Higher parenchymal hematoma and SICH rates were observed in patients with emergent stenting when compared with patients without. This association might have led to a higher mortality rate in the stenting group. No other variables were associated with SICH (European-Australasian Acute Stroke Study II criteria), but female gender ($P = .058$) and

Table 1. *Baseline and procedure characteristics associated with emergent stenting*

	All patients (n = 143)	No stent (n = 119)	Stent (n = 24)	*P*
Age, y	66.1 ± 11.7	66.2 ± 12.2	65.1 ± 9.5	.668
Gender (male)	62.9%	59.7%	79.2%	.011
Smoking habit	22%	18.8%	37.5%	.044
Hypertension	62.9%	59.7%	79.2%	.011
Diabetes mellitus	24.5%	22.7%	33.3%	.269
Dyslipemia	44.8%	42%	58.3%	.143
Ischemic heart disease	14.4%	16%	12.5%	.668
Oral anticoagulant treatment	18.4%	22.2%	0%	.011
INR	1.10 [1.00-1.50]	1.12 [1.02-1.56]	1 [0.98-1.10]	.022
Antiplatelet pretreatment	33.8%	33.9%	33.3%	.941
IV tPA	48.3%	47.9%	50%	.851
Baseline systolic BP, mm Hg	144.8 ± 24.9	143.9 ± 25.7	149.3 ± 21.1	.143
Baseline diastolic BP, mm Hg	77.4 ± 15.0	76.7 ± 14.3	80.5 ± 17.9	.264
Baseline glucose, mg/dL	126 [109-149]	126 [109-149]	125 [109-150]	.749
Baseline NIHSS score	18 [14-22]	18 [14-22]	17 [14-23]	.849
TOAST classification				.000
Atherothrombotic	25.9%	16.8%	70.8%	
Cardioembolic	51%	60.5%	4.2%	
Lacunar	21%	22.7%	12.5%	
Undetermined	2.1%	0%	12.5%	
ASPECTS on CT (n = 127)	10 [9-10]	10 [9-10]	9 [9-10]	.393
OTT, min	315 [225-415]	315 [220-410]	319 [237-252]	.501
Baseline occluded artery				.000
Terminal carotid	14%	16.0%	4.2%	
Middle cerebral	53.9%	61.3%	16.7%	
Basilar	12.6%	12.6%	12.5%	
Posterior cerebral	1.4%	1.7%	0%	
Extracranial carotid	4.2%	2.5%	12.5%	
Tandem occlusion	14%	5.9%	54.2%	
Intra-arterial tPA use	25.2%	22.4%	29.2%	.621
Thrombectomy device use*	81.8%	83.2%	75%	.949
GRT, min	63 [40-120]	55 [37-100]	97 [61-130]	.003

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; BP, blood pressure; CT, computed tomography; GRT, time from groin puncture to recanalization; INR, international normalized ratio; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; TOAST, Trial of Org 10172 in Acute Stroke Treatment; tPA, tissue plasminogen activator.

Table cells express results in mean ± SD, number (%), and median [interquartile range] as appropriate.

*Use of thrombectomy devices (Merci Retriever, Trevo, or Solitaire) alone or in combination.

higher systolic ($P = .063$) and diastolic ($P = .087$) blood pressure at baseline showed a non-significant trend.

In multivariate analysis with adjustment for covariates with *P* less than .1 in univariate analysis (gender, baseline systolic and diastolic blood pressure) and procedure duration, the odds ratio of SICH for patients with emergent stenting was 7.307 (95% confidence interval 1.45-36.84, $P = .016$) Table 3. When using the Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria for defining SICH, similar results were found (odds ratio 15.194, 95% confidence interval 1.01-228.72, $P = .049$).

Discussion

The present study shows that emergent stenting in endovascular treatment of AIS is independently associated with an increased risk of SICH. In addition PH was also more frequent in the stenting group.

The chief goal in treating AIS is to restore cerebral blood flow as rapidly and safely as possible. IV tPA achieves early recanalization in only 30%-50% of patients, with even lower recanalization rates in proximal large-vessel occlusions (MCA, basilar artery, and carotid terminus),[10] and reocclusion of the vascular segment occurs frequently,[11,12] particularly in tandem occlusion.[13] The endovascular techniques such as IA thrombolysis[14] or mechanical thrombectomy[15] are feasible and may produce better vascular patency and improve clinical outcomes compared with IV tPA.[16] Moreover, other endovascular approaches in the setting of acute stroke have been reported. A large multicenter retrospective study shows that stent deployment in patients with AIS

Table 2. *Distribution of hemorrhage subtypes and outcome variables according to emergent stenting in acute ischemic stroke*

	All patients (n = 143)	No stent (n = 119)	Stent (n = 24)	*P*
Hemorrhage subtypes				
No ICH	92 (64.3)	79 (66.4)	13 (54.2)	
ICH	51 (35.7)	40 (33.6)	11 (45.8)	.007
HI1	12 (8.4)	10 (8.4)	2 (8.3)	
HI2	16 (11.2)	15 (12.6)	1 (4.2)	
PH1	10 (7)	7 (5.9)	3 (12.5)	
PH2	8 (5.6)	3 (2.5)	5 (20.8)	
SAH	5 (3.5)	5 (4.2)	0 (0)	
Outcome variables				
Recanalization	86%	84%	95.8%	.128
SICH (SITS-MOST)	8 (5.6)	3 (2.5)	5 (20.8)	.000
SICH (ECASS II)	11 (7.7)	6 (5)	5 (20.8)	.008
Mortality (7 d)	10 (7)	6 (5)	4 (16.7)	.042
mRS score > 2 (90 d)	75 (53.2)n = 141	59 (50)n = 118	16 (69.6)n = 23	.085

Abbreviations: ECASS, European-Australasian Acute Stroke Study; HI, hemorrhagic infarction; ICH, intracerebral hemorrhage; mRS, modified Rankin scale; PH, parenchymal hemorrhage; SAH, subarachnoid hemorrhage; SICH, symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

Values in parentheses are percentages.

involving the anterior circulation within 8 hours of symptoms' onset increases the chance of recanalization.[17]

However, the use of emergent stenting is not well established. Its main use seems to be when a tandem occlusion is found in angiography performed with the intent to revascularize. Recently, Malik et al[2] reported the largest case series of proximal and distal recanalization of anterior circulation tandem occlusion in patients with AIS. Proximal revascularization was performed with carotid stenting in all patients. A total of 77 patients were included with a high recanalization rate and low postprocedure PH rates (8 of 77, 10.4%). No data about SICH were given. In that series, initially, patients received an IV bolus of eptifibatide (180 μg/kg) at the time of stenting followed by an oral load of clopidogrel and aspirin if hemorrhage was absent on postprocedure neuroimaging. After a number of patients not reported in the paper, they changed their approach in favor of administrating oral aspirin (325 mg) and clopidogrel (600 mg) loading doses through a nasogastric tube before stenting and stopped administrating gycoprotein IIb/IIIa inhibitors. This study also differs from ours in the endovascular strategy chosen, as the first step is angioplasty and stenting of the proximal occlusion followed by intracranial intervention.

Table 3. *Logistic regression model for prediction of symptomatic intracerebral hemorrhage according to European-Australasian Acute Stroke Study II criteria*

Variable	OR	CI	*P*
Gender (female)	3.959	1.31-27.16	.021
Acute phase stenting	7.307	1.45-36.84	.016
Baseline systolic BP	1.025	0.99-1.05	.084
Procedure duration	1.003	0.992-1.01	.559

Abbreviations: BP, blood pressure; CI, confidence interval; OR, odds ratio.

Intracranial stenting with self-expanding stents seems to be a good salvage technique in patients with recalcitrant occlusions in whom other recanalization methods have failed. Several case series have reported excellent outcomes and low intracranial hemorrhage rates.[3–5] However, antithrombotic drug protocol varies highly from one series to another, the main differences being the type of combined antithrombotic drugs, the route of administration, and the doses administered.

The first Food and Drug Administration–approved prospective study on intracranial stenting in a sample of 20 patients with an acute stroke treated within 8 hours of symptoms' onset, showed low rates of symptomatic (5%) and asymptomatic (10%) intracranial hemorrhages in postprocedure CT scan.[18] Clopidogrel (600 mg) and aspirin (650 mg orally/600 mg rectally) were administered preprocedurally to all patients. In contrast, in our series, the overall rate of PH and SICH was much higher in the group of patients with emergent stenting compared with the group of patients without. No significant association was found between SICH and the use of systemic or IA thrombolytics as well as the previous use of antithrombotic drugs. It seems reasonable to think that longer procedure duration resulted in a more delayed reperfusion in the setting of an ischemic brain once the blood-brain barrier integrity was disrupted. And this fact, added to combined use of antithrombotic drugs, could lead to the development of bigger parenchymal hematoma with higher risk of clinical deterioration.

We recognize that our study has 2 main limitations. Firstly, the study was not controlled and derives from

a single-center retrospective design. Secondly, the sample size is small in emergent stenting group, so the results should be cautiously interpreted.

In summary, the present findings suggest that emergent stenting in endovascular treatment of AIS might be associated with SICH. Taking into account the impact of this feared complication, larger studies are warranted to know whether stenting in the setting of AIS should be avoided.

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