Prior Intravenous Stroke Thrombolysis Does Not Increase Complications of Carotid Endarterectomy

Petra Ijäs, MD, PhD, MSc; Ellinoora Aro, MD, PhD; Henrietta Eriksson, MD; Pirkka Vikatmaa, MD, PhD; Lauri Soinne, MD, PhD; Maarit Venermo, MD, PhD

Background and Purpose—Carotid endarterectomy (CEA) is recommended within 14 days after carotid artery stroke to prevent recurrence. However, the optimal timing of CEA after intravenous thrombolysis (IVT) remains unclear. We studied the safety of CEA after IVT while taking into account both stroke recurrence and CEA-related complications.

Methods—Patients who underwent IVT followed by CEA in Helsinki University Hospital 2005 to 2016 were withdrawn from prospectively collected registers. The incidence of stroke recurrence during the time between IVT and CEA, peri/postoperative stroke, hyperperfusion syndrome or drug-resistant high blood pressure, and 3-month outcome measured by modified Rankin Scale was recorded. Stroke patients treated with CEA without preceding IVT were used as controls.

Results—Altogether 128 CEAs with preceding IVT and 777 CEAs for stroke without IVT were identified. The median time from IVT to CEA was 9 days (range, 0–349 days; interquartile range, 16). Seven patients (5.5%) underwent CEA within 24 hours, 20 (15.6%) within 48 hours and 87 (68.0%) within 2 weeks from IVT. Stroke recurrence in IVT-CEA patients was 5.5% at median 4 days after IVT (range, 0–8 days). Outcome from CEAs performed within 48 hours from IVT did not differ from CEAs performed later with respect to peri/postoperative ischemic strokes (5.0% and 3.7%), hemorrhagic strokes (5.0% and 1.9%), neck hematomas (5.0% and 8.3%), myocardial infarctions (0.0% and 0.9%), or 3-month modified Rankin Scale. There was a tendency toward higher incidence of hyperperfusion syndrome in the patients operated within 48 hours from IVT (20.0% versus 6.5%; P=0.070). The CEA-related stroke rate was similar to that of the operation without thrombolysis. Only smoking was significantly associated with peri/postoperative stroke (odds ratio, 21.82; 95% confidence interval, 1.08–439.58).

Conclusions—Time between IVT and CEA was not associated with CEA-related complications. The high rate of stroke recurrence during the waiting time for CEA underscores the importance of shortening surgery delays. **(*Stroke*. 2018;49:1843-1849. DOI: 10.1161/STROKEAHA.118.021517.)**

Key Words: hematoma ■ hypertension ■ incidence ■ myocardial infarction ■ smoking

To prevent a recurrent stroke, carotid endarterectomy (CEA) is recommended within 14 days after transient ischemic attack or minor stroke caused by 50% to 99% ipsilateral carotid stenosis[1–3]; the incidence of recurrent stroke is reported as high as 5% to 8% within the first 48 hours and 11% to 25% within 2 weeks.[1] In the case of 70% to 99% stenosis, recurrent stroke can be efficiently prevented by CEA with the number-needed-to-treat of 5 to prevent 1 stroke when surgery is performed within 2 weeks.[4] However, it remains controversial whether CEA is safe within 48 hours from the most recent cerebrovascular symptom.[5] National audit data from Sweden (SwedVasc) reported a 30-day stroke/death rate of 11.1% in those operated within 48 hours of symptom onset compared with 3.6% to 5.4% in those operated later.[6] Subsequently, UK register also reported small but significantly increased risk related to performing CEA within 48 hours of symptom onset (odds ratio, 1.64; 95% confidence interval [CI], 1.04–2.59).[7] However, German register did not find association between the time from index symptom to CEA and the risk of any in-hospital stroke or death.[8] The recent American Heart/Stroke Association guidelines recommend revascularization between 48 hours and 7 days after nondisabling stroke (modified Rankin Scale [mRS] score of 0–2),[2] whereas other guidelines do not take as clear opinion on the earliest timing of revascularization.

Many acute stroke patients are treated with intravenous thrombolysis (IVT), most often intravenous r-tPA (recombinant tissue-type plasminogen activator) which increases the risk of bleeding both intracranially and locally. Furthermore, carotid stenosis patients often have impaired cerebral vasomotor autoregulation because of exhausted vasomotor reserve, which lends them susceptible to hyperperfusion and intracranial hemorrhage after CEA.[9,10] Therefore, CEA is often postponed after IVT at the risk of stroke recurrence. Several

Received March 18, 2018; final revision received June 12, 2018; accepted June 14, 2018.
From the Department of Neurology (P.I., H.E., L.S.) and Department of Vascular Surgery (E.A., P.V., M.V.), Helsinki University Hospital, Finland; and Department of Clinical Neurosciences, Clinicum, University of Helsinki, Finland (P.I., L.S.).
Presented in part at the European Stroke Conference, Barcelona, Spain, May 10–12, 2016.
Correspondence to Petra Ijäs, MD, PhD, MSc, Department of Neurology, Helsinki University Hospital, PO Box 340, 00029 Helsinki, Finland. Email petra.ijas@hus.fi

case series reporting outcome of CEA after IVT have been published. A meta-analysis of studies published until 2014[11] and a Scandinavian multicentre case series of 202 IVT-treated patients found no evidence for an increased rate of complications within 30-day follow-up period after CEA.[12] However, recent case series including patients operated within 24 to 72 hours after CEA found a small and insignificant increase in 30-day complication rate in IVT group when compared with non-IVT group.[13,14]

Reason behind the slightly increased complication rate of CEA performed within the first 48 hours after cerebrovascular symptoms is not fully elucidated; it is not known whether it is because of excess in bleeding complications as a result from hyperperfusion syndrome or embolic events from unstable carotid plaque. Furthermore, none of the earlier studies have taken into account the recurrent stroke rates during the waiting time for CEA, most probably because the data deriving from national registers often miss detailed clinical data on that time period. If the recurrence rate is higher than the perioperative risk, then the early operation may still be justified. The objective of our study was to investigate the safety and optimal timing of CEA after IVT by taking into consideration both the recurrent symptoms while waiting for CEA and the ischemic and bleeding complications peri/postoperatively.

Methods

The study was performed in Helsinki University Hospital (HUH), a tertiary hospital in southern part of Finland with a catchment population of 1.6 million. During the year 2015, 250 CEAs and 330 IVTs were performed. Patients who underwent IVT because of a carotid territory stroke and a subsequent ipsilateral CEA between January 2005 and December 2016 were identified from our hospital-based prospective registers, HUSVASC and Helsinki Stroke Thrombolysis Registry (Figure). The prospective databases for quality control have been maintained from 1995 for IVT and from 1990 for vascular surgery procedures.

The HUSVASC register contains data on all the vascular procedures performed in HUH. With respect to CEAs, the register includes demographic factors (the stenosis grade, sex, comorbidities, smoking status, preoperative medication, and postoperative medication), type of the index symptom (ie, symptom that led to consultation and CEA: transient ischemic attack, amaurosis fugax, stroke or no symptom), date of the index symptom, operation date, and stroke and death within the 30 days from CEA.

The Helsinki Stroke Thrombolysis Registry contains data on all patients who received IVT because of acute stroke in HUH. Data are collected on multiple variables including the time of stroke and IVT, stroke severity (National Institutes of Health Stroke Scale), imaging results, comorbidities, and 3-month outcome measured by mRS.

The patients were identified by linking the registers by personal identity code. The side of the symptomatic vessel (right or left carotid artery) was verified from medical records to ensure that the symptoms of acute stroke treated with IVT matched with the carotid artery operated. Data on recurrent cerebrovascular symptoms during the waiting time for CEA, peri- and postoperative ischemic and hemorrhagic stroke within 30 days after CEA, bleeding complications, the signs of hyperperfusion syndrome, and myocardial infarction within 30 days from CEA were reviewed from medical records. Hyperperfusion syndrome was defined as follows: criterion A, a triad of high blood pressure, headache, and confusion and neurological symptoms resembling previous stroke without other cause and occurring within 1 month after CEA; or criterion B, 2× higher mean blood flow velocity in the ipsilateral middle cerebral artery when compared with the contralateral middle cerebral artery in transcranial Doppler examination in combination with one of the symptoms listed above. In this study, all patients fulfilled the clinical criteria for the hyperperfusion syndrome (the A criterion). In addition, patients with elevated drug-resistant postoperative blood pressure (above individually set target, usually systolic blood pressure >120–150 mm Hg for at least the first 24 hours) requiring constant or repeated intravenous blood pressure medication and treatment in the intensive care unit were recorded. All patients who received IVT were either seen or contacted by telephone by a neurologist at 3 months after stroke.

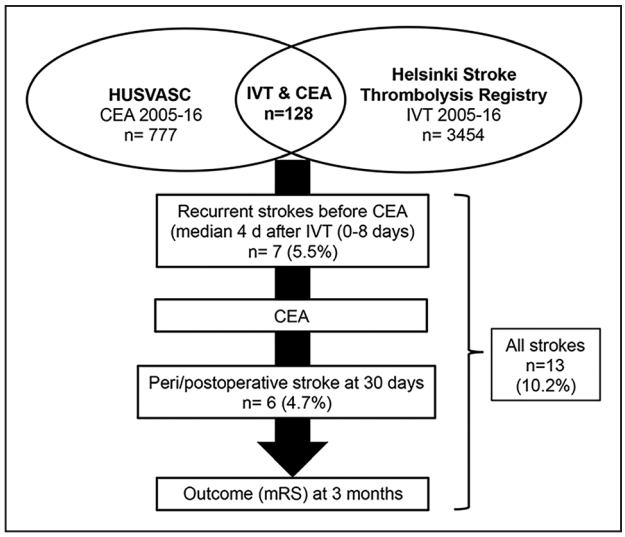

Figure. Flowchart of the study. CEA indicates carotid endarterectomy; IVT, intravenous thrombolysis; and mRS, modified Rankin Scale.

Decision on IVT was made by a stroke neurologist according to the international guidelines.[2,3] After IVT, the patients were monitored at the stroke unit for at least 24 hours, after which brain computed tomography (CT) or magnetic resonance imaging was performed. Antiplatelet therapy after IVT was designed individually taking into consideration previous medications, comorbidities (eg, atrial fibrillation or other cause for anticoagulation), and vessel pathology (eg, intraluminal thrombus). Most patients received aspirin 100 mg daily (or clopidogrel 75 mg daily if there existed a contraindication for aspirin) until CEA if there was no large infarct and hemorrhage in the control CT. If there was a high suspicion of intraluminal thrombus in the carotid artery, a combination of aspirin and low–molecular weight heparin was commonly used until surgery. A few patients did not receive any antiplatelet regimen because of emergency CEA.

Five patients received IVT in rural community hospitals via teleconsultation of a neurologist in HUH and were transferred to HUH for follow-up and CEA. Relevant information on IVT was included in our hospital-based register and could be withdrawn from the medical records. Patients were included in this case series because these patients have been shown to have similar outcome with those treated at the emergency department of HUH.[15]

A consecutive series of 38 patients treated during 2008 to 2012 were included earlier in the Scandinavian multicenter case series.[12]

As a control population, we used patients that underwent CEA because of stroke in 2008 to 2016 in HUH but were not treated with IVT before surgery (Figure). All patients were evaluated by a neurologist and vascular surgeon before CEA. One month after CEA, they were met or contacted by a vascular surgeon or nurse. They were not routinely seen by a neurologist unless in need of rehabilitation evaluation or management.

Statistical analysis was performed with SPSS 22.0 statistical software (IBM SPSS Inc, Chicago, IL). Continuous variables are expressed as mean (95% CI) and dichotomous variables as percentage. Comparison between groups was performed with Student *t* test for continuous variables and χ^2 for discrete variables. Logistic regression was used to model the effects of age, sex, vascular risk factors (smoking, hyperlipidemia), comorbidities, and medications on CEA-related stroke as outcome. In the second model, only age, sex, and

Table 1. Patient Characteristics and Outcomes by Sex

	All	Males	Females	*P* Value*
Characteristics				
No. of patients	128	94 (73.4%)	34 (26.5%)	
Age	68.9 (±9.2)	67.9 (±9.1)	71.7 (±8.9)	0.039†
Current smoker	38 (29.7)	25 (26.6)	13 (38.2)	0.273
Hypertension	99 (77.3)	73 (77.7)	26 (76.5)	1.000
Diabetes mellitus (type I/II)	36 (28.1)	27 (28.7)	9 (26.5)	1.000
Dyslipidemia	74 (57.8)	51 (54.3)	23 (67.6)	0.225
Coronary heart disease	35 (27.3)	25 (26.6)	10 (29.4)	0.823
Atrial fibrillation	9 (7.0)	7 (7.4)	2 (5.9)	1.000
Previous stroke or TIA	37 (28.9)	28 (29.8)	9 (26.5)	0.827
Medications				
Antihypertensive	80 (62.5)	56 (59.6)	24 (70.6)	0.305
Statin	58 (45.3)	44 (46.8)	14 (41.2)	0.688
Antithrombotic	31 (24.2)	22 (23.4)	9 (26.5)	0.816
Stroke onset and IVT				
Median NIHSS at stroke onset	6 (0–20)	6 (1–20)	6 (0–19)	0.834
Time (min) from symptom-onset to IVT	120 (±54)	115 (±55)	131 (±52)	0.142
Systolic BP before IVT	160 (±20)	158 (±20)	166 (±20)	0.046†
Diastolic BP before IVT	82 (±14)	83 (±13)	78 (±15)	0.107
Median NIHSS at 24 h	2 (0–22)	2 (0–22)	2 (0–15)	0.349
ICH related to IVT	5 (3.9)	5 (5.3)	0 (0)	0.324
Time between symptom onset and CEA				
Recurrent preoperative stroke/TIA	7 (5.5)	6 (6.4)	1 (2.9)	0.674
Time (days) to recurrence	4 (0–8)	4 (2–8)	0	0.117
CEA				
Time (days) from IVT to CEA	9 (0–349)	9.0 (0–349)	8.5 (0–182)	
CEA within 24 h	7 (5.5)	4 (4.3)	3 (8.8)	0.381
CEA within 48 h	20 (15.6)	13 (13.8)	7 (20.6)	0.410
CEA within 72 h	28 (21.9)	20 (21.3)	8 (23.5)	0.811
CEA within 2 wk	87 (68.0)	62 (66.0)	25 (73.5)	0.522
Peri/postoperative ischemic stroke within 30 days	5 (3.9)	2 (2.1)	3 (8.8)	0.116
Time (days) from CEA to peri/postoperative stroke	2 (0–16)	1	3 (0–16)	0.642
Hyperperfusion or drug-resistant hypertension	21 (16.4)	15 (16.0)	6 (17.6)	0.792
Hyperperfusion syndrome	11 (8.6)	8 (8.5)	3 (8.8)	1.000
ICH/hemorrhagic transformation	3 (2.3)	2 (2.1)	1 (2.9)	1.000
Time (days) from CEA to ICH	4 (2–16)	9 (2–16)	4	
CEA-related stroke	6 (4.7)	2 (2.1)	4 (11.8)	0.042†
Exploration because of neck hematoma	11 (8.6)	11 (11.7)	0 (0.0)	0.036†
Myocardial infarction	1 (0.8)	1 (1.1)	0 (0.0)	1.000
Outcome				
All stroke	13 (10.2)	8 (8.5)	5 (14.7)	0.328
Median mRS at 3 mo	1 (0–5)	1 (0–5)	2 (0–5)	0.231
0–2	94 (73.4)	71 (75.5)	23 (67.6)	0.374
3–5	34 (26.6)	23 (24.4)	11 (32.4)	0.374
Mortality within 90 days	0 (0.0)	0 (0.0)	0 (0.0)	

Data given in number (%), mean (±SD), or median (range). BP indicates blood pressure; CEA, carotid endarterectomy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

*Statistical test: χ^2 or Fisher exact test for dichotomous or categorical variables, Mann-Whitney test for ordinal, and *t* test for continuous variables.

†$P<0.05$.

variables having a significant effect on CEA-related stroke (ie, smoking) were included.

The HUSVASC and the Helsinki Stroke Thrombolysis Registries have been approved by institutional authorities. According to Finnish legislation, no patient consent is required for registration in quality registries.

The authors declare that all supporting data are available within the article.

Results

Patient Characteristics and Stroke Onset in IVT-CEA Patients

During the years 2005 to 2016, 3454 IVT for acute stroke and altogether 2314 CEAs, of which 777 (33.6%) because of preceding hemispheric stroke, were performed in HUH (Figure). One hundred twenty-eight patients had both IVT and ipsilateral CEA, comprising 3.7% of all IVT-treated patients and 16.5% of the patients that underwent CEA because of stroke.

Of the IVT-treated patients, 73.4% were male (Table 1). Women were somewhat older (71.7 versus 67.9; P=0.039), but no other differences between genders were noted. On stroke onset, women had higher systolic blood pressure at admission (171±27 mm Hg in women and 159±23 mm Hg in men; P=0.029) and before IVT (Table 1).

Median National Institutes of Health Stroke Scale at stroke onset was 6 (range, 0–20; interquartile range, 6). Mean time from symptom onset to IVT was 120 minutes (95% CI, 110–129). Median National Institutes of Health Stroke Scale at 24 hours was 2 (range, 0–22; interquartile range, 5). The rate of any ICH related to IVT (from hemorrhagic infarction to parenchymal hemorrhage) was 3.9%.

Recurrent Cerebrovascular Symptoms Before CEA in IVT-CEA Patients

Seven patients suffered a recurrent stroke or progression of symptoms (crescendo transient ischemic attack or stroke-in-evolution) while waiting for CEA (incidence 5.5%, Table 1). These occurred at median 4 days from symptom onset (range, 0–8 days). In most cases, recurrent symptom led to expedited surgery (median, 2 days; range, 0–5 days).

Table 2. Complications and Outcomes According to the Timing of CEA

	All	CEA≤48 h	CEA>48 h	P Value*
No. of patients	128	20	108	
Stroke onset				
Median NIHSS at stroke onset	6 (0–20)	5 (1–20)	6 (0–20)	0.519
Median NIHSS at 24 h	2 (0–22)	2.5 (0–11)	2 (0–22)	0.878
ICH related to IVT	5 (3.9%)	0 (0.0)	5 (4.6)	1.000
Time between symptom onset and CEA				
Recurrent preoperative stroke/TIA*	7 (5.5)	1 (5.0)	6 (5.6)	1.000
Time (days) to recurrence	4 (0–8)	0	4 (2–8)	
CEA				
Peri/postoperative ischemic stroke within 30 days	5 (3.9)	1 (5.0)	4 (3.7)	0.579
Time (days) from CEA to peri/postoperative stroke	2 (0–16)	1	3 (0–16)	
Hyperperfusion or drug-resistant hypertension	21 (16.4)	6 (30.0)	15 (13.9)	0.098
Hyperperfusion syndrome	11 (8.6)	4 (20.0)	7 (6.5)	0.070
ICH/hemorrhagic transformation	3 (2.3)	1 (5.0)	2 (1.9)	0.402
Time (days) from CEA to ICH	4 (2–16)	2	10 (4–16)	
CEA-related stroke	6 (4.7)	1 (5.0)	5 (4.6)	1.000
Exploration because of neck hematoma	11 (8.6)	2 (10.0)	9 (8.3)	0.682
AMI	1 (0.8)	0 (0.0)	1 (0.9)	1.000
Outcome				
All stroke	13 (10.2)	2 (10.0)	11 (10.2)	1.000
Median mRS at 3 mo	1 (0–5)	1 (0–3)	1 (0–5)	0.561
0–2	94 (73.4)	16 (80.0)	78 (72.2)	0.588
3–5	34 (26.6)	4 (20.0)	30 (27.8)	0.588
Mortality within 90 days	0 (0.0)	0 (0.0)	0 (0.0)	

Data given in number (%), mean (±SD), or median (range). CEA indicates carotid endarterectomy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

*Statistical test: χ^2 or Fisher exact test for dichotomous or categorical variables, Mann-Whitney test for ordinal, and t test for continuous variables.

CEA and Peri/Postoperative Complications in IVT-CEA Patients

CEA was performed median 9 days after IVT (range, 0–349 days; interquartile range, 16; Table 1). There was a declining trend in the delay between IVT and CEA over the 10 years study period: between 2005 and 2007, the median time was 25 days; during 2008 to 2010, 10 days; during 2011 to 2013, 5 days; and between 2013 and 2016, 8 days. Seven patients (5.5%) had CEA within 24 hours from stroke onset, 20 patients (15.6%) within 48 hours, and 87 patients (68.0%) within 14 days from stroke onset (Table 1.).

The incidence of peri/postoperative ischemic stroke was 3.9% (n=5, Table 1). Strokes occurred in patients operated at median 12 days (range, 2–32 days) after IVT. There was no association between peri/postoperative ischemic stroke and the time between IVT and CEA (P=0.656). Furthermore, the incidence was not significantly increased in patients operated within 48 hours from IVT: 5.0% (n=1) in patients operated within 48 hours and 3.7% (n=4) in patients operated later (P=0.579; Table 2).

The incidence of hyperperfusion syndrome after IVT and CEA was 8.6%. In addition, 16% of patients had drug-resistant hypertension requiring frequent/continuous intravenous medication or treatment in an intensive care unit. Hyperperfusion was slightly but not significantly more common among patients operated within 48 hours after stroke onset than in patients operated with longer delay (20.0% versus 6.5%; P=0.070, respectively). In line, drug-resistant hypertension was twice as common in patients operated within 48 hours compared with later-operated patients (30.0% versus 13.9%; P=0.098). Altogether 3 patients suffered ICH or hemorrhagic transformation of ischemic infarct (incidence 2.3%), 1 had been operated within 48 hours and 2 with longer delay (5.0% versus 1.9%; P=0.402).

There were no obvious other complications in early-operated patients. Early- and later-operated patients did not differ in the incidence of neck hematomas requiring exploration or in the rate of myocardial infarctions (Table 2).

Overall, there were no differences in the incidence of CEA-related stroke (peri- and postoperative ischemic stroke or hemorrhagic stroke) in early-operated compared with later-operated patients (5.0% versus 4.6%; P=1.000). With preoperative recurrences included, the incidence of all CEA-related strokes was 10.2% in patients operated within 48 hours and 10.0% in patients with more delayed operation (P=1.000). None of the patients died within the 3-month follow-up period. Outcome measured by mRS was comparable (1 meaning no significant disability) in early- and later-operated patients (P=0.561).

Acute Thrombectomy/Endarterectomy Within 24 Hours From Stroke Onset in IVT-CEA Patients

Six patients had emergency surgery within 24 hours from the stroke onset because of an acute occlusion of carotid artery (CCA or ICA, n=4) or progressing symptoms (stroke-in-evolution, n=2) and no clinical response to IVT. Four patients had evidence of penumbra in CT perfusion imaging, whereas 2 patients were operated based on brain CT and CT angiography. In 1 patient, mechanical thrombectomy of M1 and balloon angioplasty of ICA was performed after IVT and before CEA. In an additional seventh patient, CEA was performed within 24 hours from IVT and aspiration thrombectomy of

Table 3. Logistic Regression Models With CEA-Related Stroke as Outcome

	β	Significance	OR	95% CI
Model A				
Sex	–1.693	0.167	0.184	0.017–2.030
Age	0.149	0.052	1.160	0.999–1.348
Smoking	3.083	0.044	21.820	1.083–439.576
Diabetes mellitus type I or II	–1.327	0.462	0.265	0.008–9.079
Hypertension	1.684	0.270	5.387	0.271–107.093
Hyperlipidemia	0.467	0.687	1.596	0.164–15.509
Previous stroke or TIA	0.344	0.795	1.410	0.106–18.722
Medications at stroke onset				
Statin	–2.302	0.244	0.100	0.002–4.797
Antithrombotic	2.003	0.308	7.414	0.158–347.807
Antihypertensive	–2.201	0.129	0.111	0.006–1.893
Time between IVT and CEA	0.015	0.299	1.015	0.987–1.043
Model B				
Sex	–1.156	0.239	0.315	0.046–2.152
Age	0.114	0.086	1.121	0.984–1.276
Smoking	2.756	0.022	15.740	1.492–166.003
Time between IVT and CEA	0.005	0.701	1.005	0.980–1.031

CEA indicates carotid endarterectomy; CI, confidence interval; IVT, intravenous thrombolysis; OR, odds ratio; and TIA, transient ischemic attack.

M1 occlusion. There were no perioperative ischemic or hemorrhagic strokes and none of these 7 patients died within 3 months. One patient needed evacuation of a neck hematoma. The median 3-month mRS was 2 (range, 0–3).

Predictors for CEA-Related Stroke in IVT-CEA Patients

In multivariate analysis, the risk of CEA-related stroke (peri- or postoperative ischemic stroke or ICH related to hyperperfusion syndrome) was not associated with the time between IVT and CEA (hazard ratio, 1.02; 95% CI, 0.99–1.04; Table 3). The only factor significantly associated with CEA-related stroke was smoking at time of stroke onset (odds ratio, 21.82; 95% CI, 1.08–439.58). In bivariate analysis, women had more CEA-related strokes mainly because of higher incidence of peri/postoperative stroke (Table 1). However, after adjustment of other risk factors such as age and smoking, sex did not remain a significant predictive factor.

IVT-Treated Compared With Non-IVT-Treated CEA Patients

Compared with controls (the patients who underwent CEA because of stroke but did not receive IVT), there was no difference in the rate of perioperative ischemic or hemorrhagic stroke (5.2% in non-IVT group and 4.7% in IVT group; P=1.000) or mortality within 30 days (0.6% in non-IVT group and 0.0% in IVT group; P=1.000).

Discussion

In this large and clinically comprehensive single-center study, we found no association between the time from IVT to CEA and the occurrence of peri/postoperative stroke or other CEA-related complications (neck hematoma or myocardial infarction). Moreover, none of these complications was over-represented among the patients operated within 48 hours from IVT. The perioperative stroke rate and mortality among 128 patients treated with thrombolysis before surgery was similar to that of the 777 stroke patients who underwent CEA with no prior IVT. Smoking status at the stroke onset was the only independent factor associated with the overall risk of stroke during the 30-day follow-up (odds ratio, 21.82; 95% CI, 1.08–439.58). To our knowledge, the present study reports the largest single-center data on CEAs after IVT published to date.

Drug-resistant hypertension and hyperperfusion syndrome tended to be more common in patients operated within 48 hours; however, these did not lead to complications. This may be because of high level of suspicion and successful treatment of hypertension. One patient operated on the second day after stroke onset suffered contralateral stroke and small ipsilateral ICH within the ischemic brain region considered to result from hyperperfusion, but eventually recovered well (mRS score of 1 at 3 months). However, the 2 other hyperperfusion-related ICHs occurred in patients that had been operated late, 19 and 54 days after stroke onset. Both suffered severe hyperperfusion syndrome with ICH and status epilepticus and the other patient died 5 months later because of stroke and severe epileptic sequelae.

It is postulated that acute stroke particularly with underlying carotid stenosis is characterized by impaired cerebral autoregulation which in turn predisposes the patient to hyperperfusion syndrome after CEA.[9,16] Our data seem to support this hypothesis, but there are also other factors that may explain the finding. In our hospital, patients are treated in a semi-intensive stroke unit at least 24 hours after IVT and if early operated on, they commonly return to the stroke unit after surgery and are continuously monitored. Therefore, early symptoms of hyperperfusion and resistant hypertension are more often registered and treated than in patients recovering from surgery in conventional ward, rehabilitation institute, or at home. Thus, the relatively high frequency of hyperperfusion and drug-resistant hypertension in early-operated IVT patients may also reflect detection bias. This aspect is further supported by the fact that the 2 most severe cases of hyperperfusion syndrome in our cohort were seen in patients which were operated very late, 19 and 54 days after stroke onset and IVT. Thus, hyperperfusion may be more common and appear later that is generally considered.

Assuming the risk of hyperperfusion is truly increased after early CEA after IVT, the incidence of hyperperfusion-related ICH could be higher also and explain the increased risk of complications associated with early surgery in some studies.[6,7] According to our institutional guidelines, blood pressure of CEA patients is carefully controlled before and after CEA. The systolic blood pressure is kept <120 or 150 depending on patients' risk factors for hyperperfusion (severe stenosis, contralateral occlusion, high blood pressure before surgery or after CEA, increased intraoperative ICA flow measured with transit time flowmeter after clamp release). The optimal timing of the CEA is also decided in close collaboration between vascular surgeons and neurologists. Without these precautions, the rate of ICH might be higher.

During the study period, our hospital practice for CEA changed and patients underwent CEA earlier after IVT: the median time decreased from 25 days in 2005 to 2007 to 8 days in 2013 to 2016. In the beginning of our study period, most patients (68%) underwent CEA during the same index hospitalization within 2 weeks from stroke onset. From 2011 onward, CEA was usually performed at first available urgent surgery slot if the patient was stable and no ICH was visible in the control CT at 24 hours after IVT. The most common causes to postpone surgery were a large infarct, IVT-related hemorrhagic transformation or ICH, or other complication (most commonly infection). When we analyzed our data in 3-year time intervals (2005–2007, 2008–2010, 2011–2013 and 2013–2016), we did not detect any increase in peri/postoperative stroke rate. We noticed a slight increase in the incidence of drug-resistant hypertension and hyperperfusion (4.3% in 2005–2007, 12.5% in 2008–2010, 24.3% in 2011–2013, and 19.4% in 2013–2016) but whether this represents a true phenomenon or detection bias discussed earlier is uncertain.

Limitations of the Study

Even though our hospital is a large tertiary hospital and we have gathered data on 11-year period, the number of patients is still limited and study is underpowered to detect small risk

increase related to early CEA. However, there was only 1 ischemic and hemorrhagic stroke among patients operated within 48 hours supporting a true low risk.

Our results are limited to patients with relatively minor stroke because the median National Institutes of Health Stroke Scale was 6 at stroke onset and 2 at 24 hours in our cohort. Furthermore, CEA was not performed in patients with large infarcts, hemorrhagic transformation or ICH, or other serious complication but was postponed until the patient was stabilized.

Our study design may underestimate the risk of recurrent stroke while waiting for CEA. Seven patients (5.5%) had recurrent stroke or progressing symptoms in the form of crescendo transient ischemic attacks or stroke-in-evolution between IVT and CEA, and in most of the cases, this led to expedited surgery. The number of patients with stroke while waiting for the operation (n=7) was similar to the number of patients with peri/postoperative stroke (n=6). Furthermore, 4 patients got their index stroke while waiting for CEA, but these were not included as recurrent strokes in our analyses. Also a patient who would suffer a major stroke while waiting could be excluded from operation and so would not be included in our data. Thus, the overall incidence of recurrent strokes while waiting for CEA possibly exceeds that of peri/postoperative strokes. This underscores the importance of shortening the delay from IVT to CEA to decrease the total risk of stroke.

Conclusions

We found no association between the time from IVT to CEA and CEA-related complications. Furthermore, the complication risk of the IVT-CEA patients was not increased compared with patients who underwent CEA alone. On the other hand, there were several recurrent strokes during the first week after stroke onset in the patients waiting for CEA. For patients who recover well with only minor deficits after IVT and with no IVT-related intracerebral hemorrhage, early CEA seems to be safe provided that blood pressure and the symptoms of hyperperfusion are carefully monitored and treated.

Sources of Funding

This work supported by The Paulo Foundation.

Disclosures

None.

References

1. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, et al; Esvs Guidelines Committee; Esvs Guideline Reviewers. Editor's choice - management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2018;55:3–81.
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al; American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110. doi: 10.1161/STR.0000000000000158.
3. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457–507. doi: 10.1159/000131083.
4. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915–924. doi: 10.1016/S0140-6736(04)15785-1.
5. Eckstein HH. Editorial on "Delays to Surgery and Procedural Risks Following Carotid Endarterectomy in the UK National Vascular Registry". *Eur J Vasc Endovasc Surg*. 2016;52:425–426. doi: 10.1016/j.ejvs.2016.07.085.
6. Strömberg S, Gelin J, Osterberg T, Bergström GM, Karlström L, Osterberg K; Swedish Vascular Registry (Swedvasc) Steering Committee. Very urgent carotid endarterectomy confers increased procedural risk. *Stroke*. 2012;43:1331–1335. doi: 10.1161/STROKEAHA.111.639344.
7. Loftus IM, Paraskevas KI, Johal A, Waton S, Heikkila K, Naylor AR, et al. Editor's choice - delays to surgery and procedural risks following carotid endarterectomy in the UK National Vascular Registry. *Eur J Vasc Endovasc Surg*. 2016;52:438–443.
8. Tsantilas P, Kuehnl A, König T, Breitkreuz T, Kallmayer M, Knappich C, et al. Short time interval between neurologic event and carotid surgery is not associated with an increased procedural risk. *Stroke*. 2016;47:2783–2790. doi: 10.1161/STROKEAHA.116.014058.
9. van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA, et al. Cerebral hyperperfusion syndrome. *Lancet Neurol*. 2005;4:877–888. doi: 10.1016/S1474-4422(05)70251-9.
10. Abreu P, Nogueira J, Rodrigues FB, Nascimento A, Carvalho M, Marreiros A, et al. Intracerebral hemorrhage as a manifestation of cerebral hyperperfusion syndrome after carotid revascularization: systematic review and meta-analysis. *Acta Neurochir (Wien)*. 2017;159:2089–2097. doi: 10.1007/s00701-017-3328-4.
11. Mandavia R, Qureshi MI, Dharmarajah B, Head K, Davies AH. Safety of carotid intervention following thrombolysis in acute ischaemic stroke. *Eur J Vasc Endovasc Surg*. 2014;48:505–512. doi: 10.1016/j.ejvs.2014.08.012.
12. Rathenborg LK, Venermo M, Troeng T, Jensen LP, Vikatmaa P, Wahlgren C, et al. Editor's choice - safety of carotid endarterectomy after intravenous thrombolysis for acute ischaemic stroke: a case-controlled multicentre registry study. *Eur J Vasc Endovasc Surg*. 2014;48:620–625.
13. Bazan HA, Zea N, Jennings B, Smith TA, Vidal G, Sternbergh WC III. Urgent carotid intervention is safe after thrombolysis for minor to moderate acute ischemic stroke. *J Vasc Surg*. 2015;62:1529–1538. doi: 10.1016/j.jvs.2015.07.082.
14. Gunka I, Krajickova D, Lesko M, Renc O, Raupach J, Jiska S, et al. Safety of early carotid endarterectomy after intravenous thrombolysis in acute ischemic stroke. *Ann Vasc Surg*. 2017;44:353–360. doi: 10.1016/j.avsg.2017.03.195.
15. Sairanen T, Soinila S, Nikkanen M, Rantanen K, Mustanoja S, Färkkilä M, et al; Finnish Telestroke Task Force. Two years of Finnish Telestroke: thrombolysis at spokes equal to that at the hub. *Neurology*. 2011;76:1145–1152. doi: 10.1212/WNL.0b013e318212a8d4.
16. Xiong L, Liu X, Shang T, Smielewski P, Donnelly J, Guo ZN, et al. Impaired cerebral autoregulation: measurement and application to stroke. *J Neurol Neurosurg Psychiatry*. 2017;88:520–531. doi: 10.1136/jnnp-2016-314385.