The need for emergency surgical treatment in carotid-related stroke in evolution and crescendo transient ischemic attack

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Objective: **The purpose of this study was to examine the safety of emergency carotid endarterectomy (CEA) in patients with carotid stenosis and unstable neurological symptoms.**

Methods: **This prospective, single-center study involved patients with stroke in evolution (SIE) or fluctuating stroke or crescendo transient ischemic attack (cTIA) related to a carotid stenosis ≥50% who underwent emergency surgery. Preoperative workup included National Institute of Health Stroke Scale (NIHSS) neurological assessment on admission, immediately before surgery and at discharge, carotid duplex scan, brain contrast-enhanced head computed tomography (CT) or magnetic resonance imaging (MRI). End points were perioperative (30-day) neurological mortality, NIHSS score variation, and hemorrhagic or ischemic stroke recurrence. Patients were evaluated according to clinical presentation (SIE or cTIA), timing of surgery, and presence of brain infarction on neuroimaging.**

Results: **Between January 2005 and December 2009, 48 patients were submitted to emergency surgery. CEAs were performed from 1 to 24 hours from onset of symptoms (mean, 10.16 ± 7.75). Twenty-six patients presented an SIE with a worsening NIHSS score between admission and surgery, and 22 presented ≥3 cTIAs with a normal NIHSS score (= 0) immediately before surgery. An ischemic brain lesion was detected in four patients with SIE and eight patients with cTIA. All patients with cTIA presented a persistent NIHSS normal score before and after surgery. Twenty-five patients with SIE presented an NIHSS score improvement after surgery. Mean NIHSS score was 5.30 ± 2.81 before surgery and 0.54 ± 0.77 at discharge in the SIE group ($P < .0001$). One patient with SIE had a hemorrhagic transformation of an undetected brain ischemic lesion after surgery, with progressive neurological deterioration and death (2%).**

Conclusions: **Due to the absence of randomized controlled trials of CEA for neurologically unstable patients, data currently available do not support a policy of emergency CEA in those patients. Our results suggest that a fast protocol, including CT scans and carotid duplex ultrasound scans in neurologically unstable patients, could help identify those that can be safely submitted to emergency CEA. (J Vasc Surg 2012;55:1611-7.)**

In previous years, ischemic stroke treatment has gained more and more attention worldwide because of imaging technique improvements and the development of new treatment strategies such as fibrinolytic therapy.

The immediate management of a patient presenting with a suspected acute focal neurological syndrome follows published guidelines for emergency stroke care.[1] Once the diagnosis of acute ischemic stroke is established, the patient has been stabilized, thrombolytic therapy has been administered to an eligible patient, and initial preventive therapy has been implemented, further evaluation is directed toward establishing the vascular territory involved and the cause and pathophysiology of the event.[1-4] Such evaluations must be offered as soon as possible in order to promptly start therapeutic maneuvers.

In patients who display ischemic symptoms in the territory of a carotid artery that has high-grade stenosis, surgical intervention reduces the risk of major neurological events.[5,6]

There is increasing evidence that carotid endarterectomy (CEA) after an ischemic cerebrovascular event can safely be performed within a shorter waiting period than in the past years,[7] with the aim of reducing brain cells loss by promptly restoring blood flow in the ischemic penumbra.[8]

The benefit of CEA in preventing stroke is greatly diminished beyond 2 weeks after the onset of symptoms, in large part because the risk of recurrent ischemic events is highest in this early period. After 4 weeks in women and 12 weeks in men, the benefit of surgery in these symptomatic patients is no more than that observed with surgery for asymptomatic patients, and in some cases surgery may be harmful.[9] Some physicians question the higher perioperative complication rates in those patients when compared to generally called "symptomatic patients." Nevertheless, some protocols have proven to be effective in preventing stroke recurrence in experienced hands.[10,11]

As reported in those studies,[10,11] in neurologically stable patients, CEA has proven to be effective in reducing the risk of recurrent events with low intraoperative stroke

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rates. On the other hand, main concern exists on the risk of hemorrhagic transformation or conversion of the brain lesion in patients presenting with unstable neurological symptoms, such as crescendo transient ischemic attack (cTIA) and stroke in evolution (SIE).

Unstable patients have a higher surgical risk in an emergency setting because of the high carotid plaque instability and the repeated brain insults, thus the increased brain vulnerability. For many years, complication rates detected in unstable patient studies have been the highest reported. Recently, some authors have demonstrated that in unstable patients emergency revascularization complication rates are quite acceptable after a strict patient selection and management protocol.[12-14] Currently, the consensus is lacking if unstable patients could benefit from an emergency revascularization procedure.

This study was undertaken to evaluate the benefit of emergency carotid revascularization by CEA in patients with carotid disease and unstable neurological symptoms (cTIA and SIE) given a predefined management protocol.

METHODS

Patient population and treatment protocol. This prospective, single-center study involved patients with stroke in evolution or fluctuating stroke (SIE) or cTIA related to a carotid stenosis >50% who underwent surgery within 24 hours from the onset of neurological symptoms at our academic center. All patients gave their written informed consent before urgent CEA. The protocol was approved by the local ethical committee. From January 2005 to December 2009, 22,666 patients presented to our emergency department with neurological symptoms and were evaluated by a neurologist who established the initial neurologic severity and stability. All patients followed a standardized evaluation protocol. For each patient, age, sex, body weight, history of hypertension, hypertension on admission (systolic >160 mm Hg or diastolic >90 mm Hg), history of coronary artery disease and/or diabetes mellitus, atrial fibrillation on admission, stroke severity on admission (as assessed by National Institutes of Health Stroke Scale [NIHSS]), level of consciousness on admission, time from onset of symptoms to hospital admission, blood tests, and anticoagulant or antiplatelet treatment were recorded. Whenever an ischemic or hemorrhagic brain insult was suspected, the patient promptly underwent cerebral computed tomography (CT) or magnetic resonance imaging (MRI) to assess the presence, nature, and extent of eventual brain lesions. After exclusion of brain hemorrhage, a carotid duplex ultrasound scan was performed and low-molecular-weight heparin was administered according to body weight. When a carotid plaque causing a ≥70% stenosis or an irregular or ulcerated carotid plaque causing a ≥50% stenosis was encountered, patency of middle cerebral artery (MCA – M1 and M2 portions) was assessed by transcranial Doppler (TCD) scan, whenever possible, or by contrast-enhanced cerebral CT scans. According to inclusion and to clinical and imaging exclusion criteria, as listed in Table I, patients were subsequently submitted to emergency CEA. A cTIA was defined as repeated TIAs within a relatively short period of time. On each occasion, the patient had a full recovery of the neurological deficit before the new event that was more severe than the previous one. SIE was defined as an increasingly worsening or fluctuating neurological deficit with no restoration of the neurologic status between episodes. Forty-eight patients were submitted to CEA of 71 patients presenting to the emergency department with a carotid stenosis ≥50% and unstable neurological symptoms (67% of patients presenting with unstable symptoms and carotid stenosis, 0.2% of those presenting at our emergency department with neurological symptoms). In 23 patients, the presence of a huge ischemic lesion on CT scans (attenuation of density, sulcal effacement, or ventricular compression) prevented an expeditious treatment. All patients submitted to surgery received at least three NIHSS assessments, on admission, immediately before surgery, and at discharge.

Table I. Inclusion and exclusion criteria for patient enrolment

Inclusion criteria
Clear time of onset of symptoms
NIHSS score <22
Recent ischemic hemispheric brain infarct <1/3 of the middle cerebral artery area regardless of BBB disruption at CT or MRI scans
ICA stenosis ≥70% or ≥50% with an ulcerated surface plaque at ultrasound scan evaluation
Patent middle cerebral artery in the detectable portion M1 and M2
Exclusion criteria
According to clinical presentation on admission
Not clear time of onset of symptoms
Severe neurological deficit (NHISS score >22)
Cerebral ischemia onset with seizures
Previous ischemic or hemorrhagic stroke with residual severe deficit (modified Rankin scale ≥2)
History of cerebral hematomas
Any other cerebral disease with residual permanent deficit
According to CT or MRI scans on admission
Recent ischemic hemispheric brain infarct >1/3 of the middle cerebral artery area
Presence of cerebral hemorrhage
Brain tumor
Cerebral arteriovenous malformation
Cerebral aneurysm

BBB, Blood-brain barrier; *CT,* computed tomography; *ICA,* internal carotid artery; *MRI,* magnetic resonance imaging; *NIHSS,* National Institute of Health Stroke Scale.

Perioperative management. Routine physiological monitoring included pulse oximetry, electrocardiogram, and invasive blood pressure measurement via radial artery. Before clamping the internal carotid artery (ICA) a dose of heparin (5000 ± 2000 IU, depending on body weight) was injected intravenously. Neurological status assessment was performed using the near-infrared spectroscopy (NIRS) and TCD whenever possible throughout the entire procedure. CEA was performed by standard surgical protocol in

Table II. Preoperative variables

	cTIA (n = 22)	*Percentage*	*SIE (n = 26)*	*Percentage*	P *value*
Male gender	19	86.4	21	80.8	.45
Age	74.2 ± 6.8		70.7 ± 9.3		.14
Hypertension	14	63.6	16	61.5	.56
Diabetes	4	18.2	6	23.1	.26
Smoker	11	50	15	57.7	.20
Hyperlipemia	4	18.2	6	23.1	.26
Ischemic brain lesion on CT scans	8	36.4	4	15.4	.09
NIHSS before surgery	0		5.30 ± 2.81		—
Stenosis percentage					
51% to 70%	3	13.6	7	26.9	.15
71% to 90%	9	40.9	8	30.8	.33
91% to 99%	10	45.4	10	38.5	.20
Occlusion	0		1	3.8	.54
Carotid plaque composition					
Hyperechoic	8	36.4	10	38.5	.23
Hypo-anechoic	14	63.6	16	61.5	.56

CT, Computed tomography; *cTIA,* crescendo transient ischemic attack; *NIHSS,* National Institute of Health Stroke Scale; *SIE,* stroke in evolution.

all cases. A shunt was used when a >50% reduction in the MCA mean velocity at TCD monitoring or a >20% reduction of regional oxygen saturation at NIRS monitoring was detected.

In the postoperative period, patients were maintained under a low dosage of heparin (4000 IU enoxaparin sodium) together with their scheduled medicaments. Systolic blood pressure was maintained below 140 mm Hg in the immediate postoperative period. At discharge, antiplatelet therapy (acetylsalicylic acid 100 mg daily) was started. All patients were evaluated by an experienced neurologist immediately after surgery and at discharge with recording of any neurological adverse event and NIHSS score assessment. All patients were submitted to CT scans before discharge.

End points and statistical analysis. Perioperative (30-day) neurological mortality, NIHSS score variation (increase or decrease), and hemorrhagic or ischemic stroke recurrence were considered primary end points. Cardiac or pulmonary complications such as wound or cervical nerve injuries were considered secondary end points and recorded for each patient.

Patients were evaluated according to clinical presentation (SIE or cTIA), clinical and demographic characteristics, timing of surgery, and the presence of brain infarction on neuroimaging. Univariate analysis was performed by Mann-Whitney test for continuous variables, and results are expressed as mean ± SD, and the χ^2 and Fisher exact tests were used for categorical variables and are expressed as numbers and percentages. A value of $P < .05$ was considered statistically significant.

RESULTS

Between January 2005 and December 2009, 48 patients presenting to the emergency department with a carotid stenosis >50% and unstable neurological symptoms were submitted to urgent CEA. Surgery was performed from 1 to 24 hours from onset of symptoms (mean, 10.16 ± 7.75 hours). Twenty-six patients presented a worsening NIHSS score between admission and surgery and were classified as SIE, and 22 presented three or more TIAs with a complete recovery before surgery (NIHSS = 0) and were classified as cTIA. Forty patients were men (83.3%) and eight patients were women (16.7%). Mean age was 72.5 ± 8.3 years. Hypertension was detected in 30 patients (62.5%), diabetes in 10 patients (20.8%), hyperlipemia in 10 patients (20.8%), and smoking habitus in 26 patients (54.2%).

An ischemic brain lesion was detected in 12 of these patients (25%), SIE in four patients, and cTIA in eight patients. No significant differences were found in the two clinical groups in carotid plaque composition or stenosis percentage. In one patient with SIE, a complete thrombosis of the ICA was encountered intraoperatively (Table II).

Locoregional anesthesia was used in 14 cases (29.2%) and general anesthesia in 34 (70.8%) with TCD monitoring in 24 (50%) and NIRS monitoring in 24 (50%). In three cases (6.2%), CEA was performed with standard technique and direct closure, in 37 cases (77.1%) with patch closure, in 7 cases (14.6%) with eversion technique, and in one case, a common-internal carotid bypass was implanted (2%). In 12 patients (five patients with cTIA and seven patients with SIE; 25%), a shunt was used during endarterectomy because of TCD and NIRS monitoring in eight and four cases, respectively (Table III). All patients with cTIA presented a persistent NIHSS normal score (= 0) before and after surgery.

Twenty-five patients with SIE presented an NIHSS score improvement after surgery. Mean NIHSS score was 2.23 ± 1.31 on admission, 5.30 ± 2.81 before surgery, and 0.54 ± 0.77 at discharge in the SIE group ($P < .0001$; Fig).

In one patient with SIE, a hemorrhagic transformation of an undetected brain ischemic lesion was noted after surgery with a progressive neurological deterioration in the following 24 hours and death (2%).

Table III. Intraoperative variables

	cTIA (n = 22)	*Percentage*	*SIE (n = 26)*	*Percentage*	P *value*
Cervical block	4	18.2	10	38.5	.08
General anesthesia	18	81.8	16	61.5	
Neurological status monitoring					.19
TCD	10	45.5	14	53.8	
NIRS	12	54.5	12	46.2	
CEA					
Patch closure	16	72.7	21	80.8	.22
Direct closure	1	4.5	2	7.7	.41
CEA-eversion technique	5	22.7	2	7.7	.14
Common-internal carotid bypass	0		1	3.8	.54
Shunt	5	22.7	7	26.9	.25

CEA, Carotid endarterectomy; *cTIA,* crescendo transient ischemic attack; *NIRS,* near-infrared spectroscopy; *SIE,* stroke in evolution; *TCD,* transcranial Doppler.

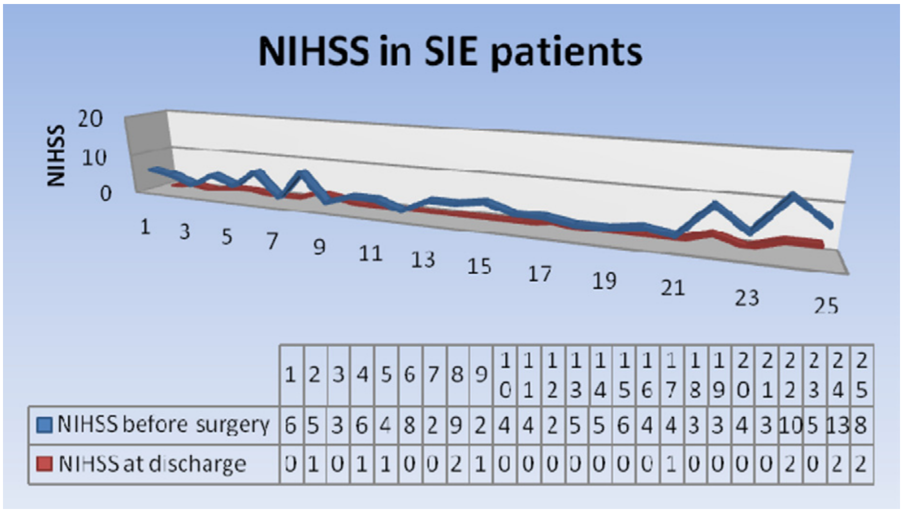

Fig. National Institutes of Health Stroke Scale (*NIHSS*) score in patients with stroke in evolution (*SIE*) before and after surgery (patient died of hemorrhagic brain lesion transformation excluded).

Table IV. Perioperative complications

		Major complications			*Minor complications*	
	Total number	*Stroke recurrence*	*Hemorrhagic conversion*	*Myocardial infarction*	*Wound complications*	*Temporary cervical nerve palsy*
SIE	26	0	1	0	0	0
cTIA	22	0	0	0	0	1

cTIA, Crescendo transient ischemic attack; *SIE,* stroke in evolution.

Logistic regression analysis showed no statistically significant association between NIHSS score decrease and time of intervention or age in patients with SIE (P = .68 and .44, respectively). Major and minor complications are listed in Table IV.

DISCUSSION

In the last 10 years, Rothwell et al[15-17] published different articles on indication to CEA in relation to clinical presentation and timing of surgery.

In a meta-analysis published in 2003, Bond et al[18] reported data on the risk of stroke and death resulting from CEA in subset of asymptomatic and symptomatic patients reported in studies published up to 2000. In the 95 studies reporting the risk of CEA in 36,482 patients for symptomatic stenosis, the absolute risk of stroke and death ranged from 2.8 (95% confidence interval [CI], 2.2-3.4; 18 studies) for CEA for ocular events only to 19.2% (95% CI, 10.7-27.8; 12 studies) for surgery for ongoing cerebral symptoms. The highest operative risks were reported in studies of surgery for SIE, cTIA, and cases that were simply termed "urgent." Thirteen studies reported data on those groups showing a higher operative risk in urgent cases, even if the number of cases reported in each study was small. The combined relative odds of operative stroke and death resulting from surgery for these urgent indications vs nonurgent surgery was 4.9 (95% CI, 3.4-7.1; $P < .001$). So Bond et al[18] concluded that, even if SIE and cTIA have a relatively poor prognosis on medical treatment alone, the number of studies included in the meta-analysis was relatively small and the definitions of urgent surgery varied among studies; in these patients, the available data do not support a policy of CEA in the acute phase.

A systematic review analyzing CEAs in patients with SIE or cTIA in the last 23 years published by Karkos et al[19] in 2009 showed a stroke/death perioperative rate after CEA for cTIA of 6.5% and 9%, respectively, and 16.9% and 20.0% for SIE. The authors concluded that the combined risk of neurological and cardiac complications in those patients is higher than that anticipated after elective surgery for stable symptoms. However, the series analyzed reported on a small number of patients over a long period of time, usually grouping all "urgent" indications together so that a satisfactory meta-analysis was prevented. Moreover, the new diagnostic modalities, the easier access to dedicated stroke units, and the closer collaboration between specialists involved in stroke treatment showed better results in urgent CEAs in the most recent series so they will definitely improve future outcomes.

The preoperative workup seems to be crucial to the outcome of urgent CEAs in patients with unstable neurological symptoms. A fast management of neurologically unstable patients involving early assessment of presence and extension of brain lesions by CT scans, presence and characteristics of carotid plaque by duplex ultrasound scans, and patency of MCA by TCD or contrast-enhanced CT scans, is mandatory in order to offer the earliest treatment. In our study, we were able to maintain a low major complication rate because of a strict collaboration among stroke specialists and a quick protocol that has proven to be effective in previous reports by our group.[10,13] Patients included in this study presented with low-moderate neurological impairment (mean NIHSS score, 2.23 ± 1.31 on admission and 5.30 ± 2.81 before surgery in patients with SIE) and a brain infarction <1/3 of the middle cerebral artery territory.[20] About two thirds of the patients were included in the study and submitted to expedite surgery with a mean time between admission and intervention of 10 hours and treatment within 24 hours in all of them. Excluded patients presented brain infarctions that prevented a safe treatment of the carotid stenosis. The urgent CEAs performed in our patients have rapidly deleted a source of ongoing embolism and rescued flow-impaired brain areas (ischemic penumbra).[21] The key points of our protocols are evident from the exclusion criteria listed in Table I. Neurologically unstable patients are classified and then submitted to surgery according to clinical and anatomical or imaging criteria. The consciousness and the relatively small brain infarction area are basic requirements to offer emergency CEA to patients. Particularly, anatomical criteria concerning the MCA area are derived from previous observational studies and randomized trials on thrombolytic therapy in stroke patients.[22] Moreover, the easiness of use and good reproducibility of NIHSS neurological score have allowed treatment of patients with mild and moderate neurological impairment with good outcomes. In the SIE group, the shorter interval between admission and surgery could explain the lower rate of brain infarcts detected on neuroimaging, with a persistent lower rate in the postoperative period. In the present series, the only major neurological complication occurred in a patient whose brain ischemic lesion remained undetected, and he had hemorrhagic transformation and finally death.

Because of the necessity of a quick diagnosis and the unstable character of neurological symptoms in those patients, CT scans were mainly used instead of the more accurate diffusion-weighted imaging (DWI) to diagnose very early ischemic lesions. Nevertheless, the reported protocol, including mainly CT scans, performed quite well in the emergency setting.

In a recent report by Merwick et al[23] on the validation of the $ABCD^2$ score in patients at early risk of stroke after TIA, the series included for analysis were mainly evaluated by CT scans instead of MRI scans. However, the use of MRIs should be encouraged because of its higher sensitivity in ischemic brain lesions. TIA is associated with high risk of early recurrent stroke, with stroke rates as high as 35% in some subgroups by 7 days.[16,23] The presence of carotid stenosis and acute DWI hyperintensity in patients with a previous TIA are highly sensitive for identification of those at high risk of stroke as early as 2 days after assessment. So every effort in order to prioritize carotid imaging after TIA and urgent CEA,[24-26] whenever possible, should be emphasized as shown by recent guidelines.[23,27,28] In the acute-stroke phase, stroke outcome can be greatly influenced by numerous factors, such as recanalization, evolving stroke, reperfusion injury, and collateral circulation. As reported by Wong et al,[29] different factors could influence outcome in the subacute-stroke phase such as age, presence of previous stroke, DWI lesion volume, and NIHSS score at 7 days, so the possibility to decrease the NIHSS score in the first 7 days after the event can deeply affect long-term outcome in stroke patients. Close collaboration among stroke specialists is mandatory in order to offer the quickest strategy to patients presenting with acute neurologic events. Clinical neurologic assessment is crucial to the application of recommendations for selection of patients for CEA, which includes estimation of perioperative stroke risk. In a meta-analysis of nearly 16,000 symptomatic patients undergoing CEA, the 30-day risk of stroke or death was 7.7% when a neurologist evaluated the patient and 2.3% when a vascular surgeon performed the evaluation.[30] These data show a threefold increase in reported events when independent adjudication is used and support a policy of evaluation by a neurologist for patients undergoing CEA. Furthermore, collaboration among specialists is crucial to develop more and more effective management protocols. The possibility to offer early CEA after intravenous thrombolysis in stroke-eligible patients, as usually performed by our group, further broadens the benefit of treatment and reinforces the need for collaboration.

Results from meta-analysis and systematic reviews on major series reporting on urgent CEA seem quite discouraging, advocating for new randomized controlled trials to prove the efficacy and benefit of urgent treatment in unstable neurological patients. Nevertheless, some management protocols in patients with acute neurological symptoms have proven to be effective with low complication rates when administered by experienced practitioners that had taken the chance to go on and operate on those patients to prevent stroke recurrence and treat brain flow impairment. The timing of the onset of neurological symptoms, the rapid examination with the use of the NIHSS to quantify the deficit, and the eventual detection of a focal area of low density that involves more than one third of the MCA territory seem to be the basic requisites to decide when emergency CEA can be safely performed. Therefore, we need more randomized trials to demonstrate that urgent CEA can avoid more deaths or disabilities, that are in the order of 14% to 18% and 31% to 71%, respectively,[18,31,32] than hundreds of CEAs in asymptomatic patients.[33]

AUTHOR CONTRIBUTIONS

Conception and design: LC, ES
Analysis and interpretation: LC, ES
Data collection: LC, ES, DT
Writing the article: LC
Critical revision of the article: ES, FS, DT, NM, AB
Final approval of the article: FS
Statistical analysis: LC, ES
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Overall responsibility: FS, PF

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INVITED COMMENTARY

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The article by Capoccia et al addresses a critical question in the treatment of carotid-related stroke. Appropriate timing of endarterectomy after an ischemic stroke or transient ischemic attack has not been conclusively established. In the past, endarterectomy has been delayed to avoid the devastating complications of hemorrhage and edema into the pre-existent infarct, thereby extending the stroke.

A waiting period of 6 to 12 weeks has been advocated in the past to decrease the incidence of reperfusion injury or hemorrhage into the area of the ischemic tissue. However, it has been recognized that most recurrent strokes occur shortly after the initial event, thereby decreasing the window for beneficial intervention to actually reduce the risk of a second more disabling stroke.[1]

Reperfusion injury has been minimized as knowledge about the pathogenesis of ischemic stroke has increased. Unfortunately, the landmark prospective trials regarding carotid endarterectomy, the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial, do not shed light on this issue, enrolling patients up to 6 months after presentation without commenting on timing of the intervention in regard to initial symptoms.

Therefore, attempts such as those made by the authors are important to maximize the benefit of endarterectomy to reduce stroke. Guidelines from the American Heart Association and American Stroke Association support rapid intervention after the development of ischemic symptoms.[2] Citing level B evidence, the most recent guidelines state that "benefit from surgery was greatest in men >75 years of age and randomized within 2 weeks after their last ischemic event; benefit fell rapidly with increasing delay." The guidelines note that recurrent stroke is most frequent within the first several weeks after symptoms and that delay beyond that period returns patients to a baseline level of risk. However, the issue remains controversial. Experiences, such as those reported by Rockman et al,[3] have noted an increased rate of perioperative complications for patients undergoing endarterectomy ≤4 weeks of symptoms compared with those treated in a more delayed fashion.

The current article emphasizes an important point: When stroke is treated in an organized stroke center with a protocol for evaluation by neurology and vascular surgery, good results can be obtained with rapid intervention. Such collaboration leads to proper patient selection and is critical to obtain results that further refine the benefit of carotid endarterectomy for stroke prevention.

REFERENCES

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