Early carotid endarterectomy in symptomatic patients is associated with poorer perioperative outcomes

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Objective: **The optimal timing of carotid endarterectomy (CEA) after ipsilateral hemispheric stroke is controversial. Although early studies suggested that an interval of about 6 weeks after a completed stroke was preferred, more recent data have suggested that delaying CEA for this period of time is not necessary. With these issues in mind, we reviewed our experience to examine perioperative outcome with respect to the timing of CEA in previously symptomatic patients.**

Methods: **A retrospective review of a prospectively maintained database of all CEAs performed at our institution from 1992 to 2003 showed that 2537 CEA were performed, of which 1158 (45.6%) were in symptomatic patients. Patients who were operated on emergently ≤48 hours of symptoms for crescendo transient ischemic attacks (TIAs) or stroke-in-evolution were excluded from analysis (n = 25). CEA was considered "early" if performed ≤4 weeks of symptoms, and "delayed" if performed after a minimum of a 4-week interval following the most recent symptom.**

Results: **Of nonurgent CEAs in symptomatic patients, in 87 instances the exact time interval from symptoms to surgery could not be precisely determined secondary to the remoteness of the symptoms (>18 months), and these were excluded from further analysis. Of the remaining 1046 cases, 62.7% had TIAs and 37.3% had completed strokes as their indication for surgery. Among the entire cohort, patients who underwent early CEA were significantly more likely to experience a perioperative stroke than patients who underwent delayed CEA (5.1% vs 1.6%, *P* = .002). Patients with TIAs alone were more likely to be operated on early rather than in a delayed fashion (64.3% vs 46.7%, *P* < .0001), likely reflecting institutional bias in selecting delayed CEA for stroke patients. However, even when examined as two separate groups, both TIA patients (n = 656) and CVA patients (n = 390) were significantly more likely to experience a perioperative stroke when operated upon early rather than in a delayed fashion (TIA patients, 3.3% vs 0.9%, *P* = .05; CVA patients, 9.4% vs 2.4%, *P* = .003). There were no significant differences in demographics or other meaningful variables between patients who underwent early CEA and those who underwent delayed CEA.**

Conclusions: **In a large institutional experience, patients who underwent CEA ≤4 weeks of ipsilateral TIA or stroke experienced a significantly increased rate of perioperative stroke compared with patients who underwent CEA in a more delayed fashion. This was true for both TIA and stroke patients, although the results were more impressive among stroke patients. On the basis of these results, we continue to recommend that waiting period of 4 weeks be considered in stroke patients who are candidates for CEA. (J Vasc Surg 2006;44:480-7.)**

The safety and efficacy of carotid endarterectomy (CEA) for patients with hemispheric neurologic symptoms, including transient ischemic attack (TIA) and ischemic stroke, has been demonstrated in randomized, prospective clinical trials.[1,2] The optimal timing of CEA after ipsilateral hemispheric stroke remains controversial. The initial CEA literature described the devastating conversion of pre-existing ischemic infarcts into fatal hemorrhagic strokes after early revascularization with CEA for acute infarcts.[3,4] Upon closer examination, however, several of these early studies reported surgical patients with pre-existing profound neurologic deficits or known internal carotid artery occlusion, patients at greatly increased risk for perioperative complications.[3,5] Nonetheless, these reports and the poor experience of others with these patients led to the recommendation of a waiting period of 4 to 8 weeks after acute stroke before revascularization.[3,4,6]

More recently, other individual investigators have suggested that earlier CEA after a completed, stable stroke is not only safe but may reduce the risk of recurrent infarction or the conversion of a severe stenosis to a complete carotid occlusion during an arbitrarily defined waiting period.[7-17] Analysis of data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[1] and the European Carotid Surgery Trial (ECST)[2] has suggested that early CEA may also be safe.[12,17,18]

Several investigators have stressed the importance of proper patient selection for early revascularization after stroke, mentioning the effects on postoperative outcome of such factors as the severity and stability of the neurologic deficit and the size of the infarction on preoperative computerized tomography (CT) scanning of the brain.[5,19,20] With these issues in mind, the objective of the current study was to review our institutional experience and to examine

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perioperative outcome with respect to the timing of CEA in previously symptomatic patients.

PATIENTS AND METHODS

A retrospective review was conducted of a prospectively compiled database encompassing all cerebrovascular surgery performed by the Division of Vascular Surgery at the New York University Medical Center from 1992 to 2003. CEA procedures combined with coronary artery bypass were excluded from this analysis. Patients who were operated on emergently ≤48 hours of symptoms for crescendo TIAs or stroke-in-evolution were excluded from analysis (n = 25). In our prospectively compiled database, the following categories of the timing of surgery after preoperative symptoms were collected and used: ≤48 hours of symptoms (ie, urgent), 2 days through 1 week, 1 week through 4 weeks, 1 month through 6 months, 6 months through 1 year, 1 year through 18 months, and remote symptoms unable to be precisely specified with regard to the timing of surgery. A total of 2537 CEA were performed, of which 1158 (45.6%) were in symptomatic patients. The precise time interval from symptom to surgery could not be exactly determined in 87 instances owing to the remoteness of the symptoms and difficulties with patient memory, and these were also excluded from further analysis. Preoperative symptoms were categorized as either hemispheric TIA (including amaurosis fugax) or completed stroke by clinical presentation and the results of brain imaging studies, when available.

The definitions or TIA and stroke were made according to the clinical judgment of the surgeon at the time of patient presentation. Patients whose clinical symptoms lasted <24 hours in whom a CT scan demonstrated an acute infarct consistent with the symptomatology were generally characterized as having had an acute stroke; however, not all patients with clinical TIAs underwent brain imaging. Patients who presented with nonspecific symptoms such as headache, dizziness, vertigo, or lightheadedness were not considered to be symptomatic for the purpose of this analysis.

CEA was considered "early" if performed ≤4 weeks of symptoms, and "delayed" if performed after a minimum of a 4-week interval following the most recent symptom. The choice of the 4-week interval to define patients having early surgery was made from the categorizations of the timing of surgery in our database, as described.

The choice of the timing of surgery was made by the individual surgeon from the patient's clinical characteristics and the results of one or more imaging studies, including carotid duplex ultrasonography, CT of the brain, magnetic resonance imaging (MRI) of the brain, or MR angiography of the carotid arteries and intracranial circulation. There is some pre-existing institutional bias towards performing CEA in a delayed fashion in patients who have experienced large preoperative cerebral infarcts as a result of the early reports described previously.

Other institutional practices for CEA include a preference for regional anesthetic with selective shunting determined by the neurologic status of the awake patient, mandatory shunting for patients operated on under general anesthetic, and routine patch angioplasty, nearly always with knitted polyester. No routine intraoperative imaging is used. Prophylactic shunts are often, but not always, used in patients with a recent stroke. A perioperative stroke was considered to have occurred if it manifested ≤30 days of the operative procedure.

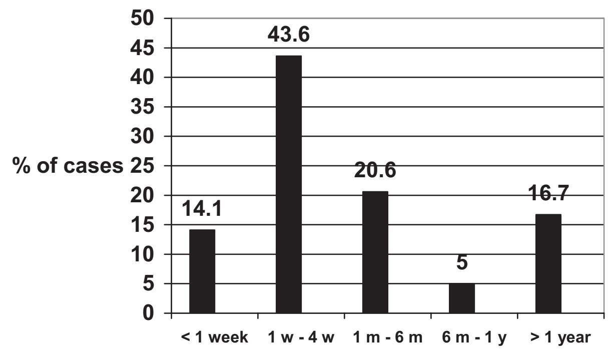

Fig 1. Distribution of the timing of surgery after neurologic symptoms in nonurgent carotid endarterectomy case (*w*, week; *m*, month; *y*, year).

Standard statistical analysis was performed with SPSS software (SPSS Inc, Chicago, Ill), using two-tailed Student's *t* test for analysis of continuous variables. Categoric variables were compared using χ^2 analysis or the Fisher's exact test, where appropriate. A result was considered to be statistically significant at $P < .05$.

RESULTS

Of a total of 2537 CEAs, 1158 (45.6%) were in symptomatic patients. After excluding urgent CEAs and cases in which the time interval could not be accurately determined owing to the remoteness of the prior symptoms, 1046 CEAs were performed in patients who had experienced a preoperative hemispheric TIA (n = 656, 62.7%) or completed stroke (n = 390, 37.3%). The overall distribution of the timing of surgery with regard to preoperative symptoms is depicted in Fig 1.

Demographic factors. Of the 1046 CEAs performed in symptomatic patients, 604 (57.7%) were performed "early" (≤4 weeks of the most recent symptom), and the remaining 442 (42.3%) were "delayed" anywhere from 1 to 15 months after the last symptom. Demographic factors were compared between the early and delayed cases. The results are summarized in Table I. No significant differences were noted in routine demographic factors between the two groups of patients.

Indications for surgery and the degree of carotid stenosis. Patients with TIAs were significantly more likely to have an operation in an early time period than CVA patients (Table II). Of TIA patients, 64.3% underwent early CEA compared with only 46.7% of CVA patients ($P < .001$). The proportion of patients with moderate carotid artery stenosis (50% to 79%) of the operated on

Table I. Comparison of demographic factors between "early" and "delayed" carotid endarterectomies in symptomatic patients

Factor	*Early (n = 604) (%)*	*Delayed (n = 442) (%)*
Gender (% male)	61.1	59.3
Hypertension	67.4	70.4
Diabetes mellitus	23.5	28.4
Cardiac disease	48.5	50.8
Smoking history	26.9	27.5

P = not significant for all data.

Table II. Comparison of preoperative neurologic symptoms and degree of ipsilateral and contralateral disease between "early" and "delayed" cases

	Early (n = 604) (%)	*Delayed (n = 442) (%)*	P
TIA	69.9	52.9	<.001
Stroke	30.1	47.1	<.001
Operated artery			
50%-79% stenotic	17.8	17.6	NS
80%-99% stenotic	82.2	82.4	NS
Contralateral			
Occlusion	11.2	14.7	NS
Severe stenosis (80%-99%)	11.6	10.1	NS

TIA, Transient ischemic attack.

Table III. Comparison of intraoperative factors between "early" and "delayed" carotid endarterectomies in symptomatic patients

	Early (n = 604) (%)	*Delayed (n = 442) (%)*
Regional anesthesia	76.2	75.8
Shunt used	40.8	39.2
Tolerated clamping*	86.8	89.4

P = not significant for all data.
*Denominator includes only cases performed with regional anesthesia.

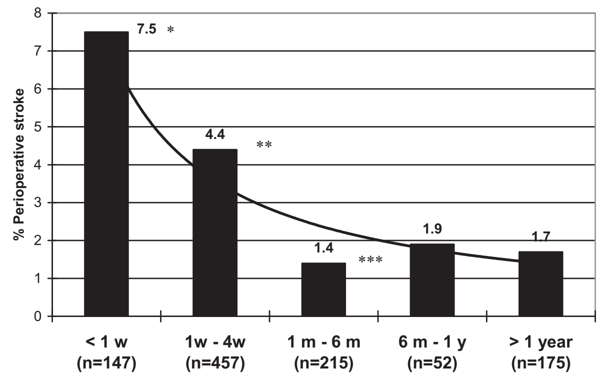

Fig 2. Outcome of perioperative stroke in relation to the timing of carotid endarterectomy after neurologic symptoms (*w*, week; *m*, month; *y*, year. * <1 week compared with 1 to 4 weeks (7.5% vs. 4.4%), *P* = NS. **1 to 4 weeks compared with 1 to 6 months (4.4% v. 1.4%), *P* = 0.047. ***<4 weeks compared with 1 to 6 months (5.1% vs 1.4%), *P* = .018.

Table IV. Comparison of perioperative outcome between "early" and "delayed" carotid endarterectomies in symptomatic patients

	Early (n = 604) (%)	*Delayed (n = 442) (%)*	P
Perioperative			
Stroke	5.1	1.6	.004
MI	0.5	0.5	NS
Death	0.7	0	NS

MI, Myocardial infarction; *NS,* not significant.

artery compared with severe disease (80% to 99%) of the operated on artery was equivalent between the early and delayed cases. The proportion of patients with contralateral carotid occlusion and contralateral severe stenosis (>80%) in both groups was also equivalent.

Surgical factors. Intraoperative factors were compared between early and delayed cases. No significant differences were noted in the method of anesthesia, the use of a shunt, or the degree of clamp tolerance between the two patient groups (Table III).

Comparison of perioperative outcome. The overall results of the perioperative stroke rates in relation to the more specific timing categories are depicted in Fig 2. Patients operated on in an early fashion (4 weeks) were significantly more likely to experience a perioperative stroke than those operated on in a delayed fashion (>4 weeks) (5.1% vs 1.6%, *P* = .004; Table IV). No significant differences in the rates of perioperative myocardial infarction or death were noted between the early and delayed patient groups.

When the timing interval categories were examined in more detail individually, it was found that patients operated on ≤1 week of symptoms did not have a significantly increased perioperative stroke rate compared with those operated on from 1 through 4 weeks after symptoms (7.5% vs 4.4%, *P* = NS). Patients operated on from 2 through 4 weeks after symptoms had a significantly higher perioperative stroke rate than those operated on from 1 to 6 months after surgery (4.4% vs 1.4%, *P* = .047). Patients operated on ≤4 weeks of symptoms had a significantly higher perioperative stroke rate than those operated on from 1 to 6 months after symptoms (5.1% vs 1.4%, *P* = .018). It therefore appears that the 4-week interval represents a point where the incidence of perioperative stroke decreased, and this decrease remained stable for patients operated on as long as 15 months after their neurologic symptom (Fig 2).

Analysis of TIA patients. Among the 656 TIA patients alone, 422 (64.3%) were operated upon in an early fashion, and 234 (35.7%) were operated upon in a delayed

Table V. Comparison of factors between "early" and "delayed" cases for transient ischemic attack

	Early (n = 422) (%)	*Delayed (n = 234) (%)*
Gender (% male)	61.6	60.3
Hypertension	67.1	69.1
Diabetes mellitus	23.3	26.6
Cardiac disease	47.9	53.2
Smoking history	26.9	28.6
Contralateral occlusion	11.1	11.4
Regional anesthesia	82.6	80.8
Shunt used	31.6	30.0
Clamp tolerant*	88.0	90.1
Perioperative		
MI	0.2	0.4
Death	0.0	0.0
Stroke	3.3	0.9

MI, Myocardial infarction.
P = not significant for all data except for perioperative stroke (P = .05).
*Denominator includes only cases performed with regional anesthesia.

Table VI. Comparison of factors between "early" and "delayed" cases for stroke patients alone

	Early (n = 182) (%)	*Delayed (n = 208)(%)*	P
Gender (% male)	60.0	58.2	NS
Hypertension	68.3	71.8	NS
Diabetes mellitus	24.0	30.4	NS
Cardiac disease	50.0	48.1	NS
Smoking history	27.0	26.3	NS
Contralateral occlusion	11.4	18.4	.06*
Regional anesthesia	61.5	70.2	.07*
Shunt used	62.1	49.5	<.02
Clamp tolerant†	82.9	88.4	NS
Perioperative			
MI	1.1	0.5	NS
Death	2.2	0	<.04
Stroke	9.4	2.4	.003

*These values of P are not significant *(NS)*.
†Denominator includes only cases performed with regional anesthesia.

fashion. No significant differences were noted in demographic factors between TIA patients operated on early and those who had a delayed operation. No significant differences were found in intraoperative factors or in the rates of perioperative myocardial infarction or death. However, TIA patients operated on early had a significantly higher rate of perioperative stroke than those operated on in a delayed fashion (3.3% vs 0.9%, P = .05; Table V).

Analysis of stroke patients. Among the 390 stroke patients alone, 182 (46.7%) were operated on early and 208 (53.3%) had delayed operations. No significant differences were noted in demographic factors between stroke patients operated on early and those who had a delayed operation. An intraoperative shunt was used significantly more frequently in stroke patients operated on early than in those who had a delayed procedure (62.1% vs 49.5%, $P < .02$), likely reflecting the surgeons' use of prophylactic shunts in patients with recent strokes. No other significant differences in intraoperative factors were found between the two groups; however, there was a trend towards increased clamp tolerance in the delayed group. No significant difference was found in the rates of perioperative myocardial infarction; however, stroke patients operated on early had a significantly higher rate of perioperative stroke (9.4% vs 2.4%, P = .003) and of perioperative death (2.2% vs 0%, $P < 0.04$) than those who had delayed operations. (Table VI).

Predictors of stroke among early cases. Univariate analysis was performed to determine the relationships between demographic and intraoperative factors and the outcome of perioperative stroke among operations performed in the early time period. No relationship was noted between patient demographic factors and the outcome of perioperative stroke among early CEAs. The indication for surgery did have a significant influence. Patients with a preoperative CVA who were operated on early were significantly more likely to have a perioperative CVA than TIA patients operated on early (9.4% vs 3.3%, P = .002). Patients operated on under regional anesthesia had a significantly lower perioperative stroke rate than those operated on under general anesthesia (3.9% vs 9.1%, $P < .02$). Patients in whom a shunt was used had a significantly higher perioperative stroke rate than those in whom no shunt was used (7.4% vs 3.7%, P = .05). However, general anesthesia and shunts were more frequently used in stroke patients compared with TIA patients.

Details and etiologies of the early perioperative strokes. Thirty-one perioperative strokes occurred (5.1%) in symptomatic patients with an early CEA, of which 17 (54.8%) occurred in patients with preoperative CVAs and 14 occurred in patients with preoperative TIAs alone (45.2%). Five (29.4%) of the 17 perioperative strokes that occurred in CVA patients were due to intracerebral hemorrhage, 2 were secondary to extension of the pre-existing strokes, presumably secondary to hyperperfusion (11.8%), 1 was secondary to hyperperfusion related seizures and edema (5.9%), and the remaining 9 were related to thromboembolic etiologies or other miscellaneous causes (52.9%) (Fig 3).

TIA patients operated on early had 14 strokes, of which one (7.1%) was related to the contralateral hemisphere, one (7.1%) was secondary to intraoperative embolization, and the remaining 12 (85.7%) were due to thromboembolic or other causes. No intracerebral hemorrhages occurred in TIA patients operated on early. Therefore, patients with preoperative CVA operated on early were significantly more likely to have postoperative intracerebral hemorrhage than TIA patients operated on early (29.4% vs 0%, $P < .05$).

Seven perioperative strokes occurred in patients operated on in a delayed fashion, of which five (71.4%) were in CVA patients and two (28.6%) were in TIA patients. No intracerebral hemorrhages or any clinically evident hyperperfusion occurred in any of these perioperative strokes in delayed CEA patients.

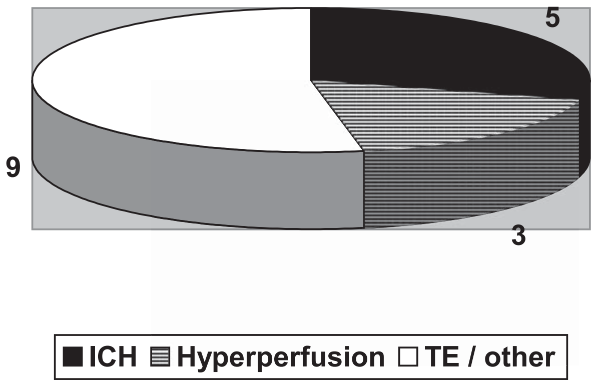

Fig 3. Causes of the perioperative strokes in patients with preoperative strokes operated on in an early time period. *ICH,* Intracerebral hemorrhage; *TE,* thromboembolic.

DISCUSSION

Although CEA has been shown to be efficacious in the prevention of future stroke in patients who have already experienced hemispheric TIA or stroke, the timing of the surgical intervention after the neurologic symptoms remains controversial, especially when a stroke has already occurred. During the early developmental era of CEA, the Joint Study of Extracranial Arterial Occlusion[4] and other investigators cautioned strongly against acute revascularization after a completed stroke.[3-5] They described the conversion of pre-existing bland ischemic infarcts into frank intracerebral hemorrhage. The presumed mechanism was related to cerebral reperfusion or hyperperfusion to an area of ischemic or infarcted brain that had lost its vascular autoregulatory control mechanisms.[21]

Upon re-examination of several of these early reports, however, it is notable that the patient selection for early surgery in some of these studies was not optimal. Several of the postoperative hemorrhages occurred in patients who underwent thrombectomy of an acutely occluded internal carotid artery in the face of severe or unstable neurologic symptoms or coma. Nonetheless, the recommendations of these early studies were echoed by at least one other more recent individual institutional report. Giordano et al[6] reported on 49 CEAs performed in patients with prior strokes. Surgery was performed ≤5 weeks of the acute infarct in 27 patients, and they had an 18.5% perioperative stroke rate compared with 0% in the delayed cases.[6] After these reports, many vascular surgeons became hesitant to perform CEA in the setting of acute stroke and preferred an arbitrarily defined waiting period of 4 to 6 weeks.

More recently, other authors have proposed that early CEA after stroke is safe when surgical patients are properly selected.[7-17] Presumably, the development of more sophisticated CT scanning and MRI of the brain should allow improved patient selection for early intervention. These authors additionally mention concern about the possibility of recurrent symptoms or reinfarction during an arbitrarily defined waiting period. In NASCET, 4.9% of the 103 medically treated patients with stroke and severe carotid stenosis had a recurrent ipsilateral stroke ≤30 days after entry into the trial.[1,12] Data from the two major randomized trials (NASCET[1] and ECST[1]) involving symptomatic patients undergoing CEA have demonstrated acceptable results with early CEA.[12,18] Pooled data from these two studies have led to recommendations that the greatest benefit from CEA is obtained when it is performed ≤2 weeks of an initial cerebrovascular event.[18]

A number of other trials and other individual investigators have echoed these recommendations and reported no differences in outcome based on the timing of CEA after stroke. Paty et al[15] found no difference when stroke patients underwent CEA 1, 2, 3, or 4 weeks after the acute event. They did not compare these results with patients operated on >4 weeks after the initial stroke. This study reports that the preoperative infarct size on CT was highly correlated with the probability of a perioperative stroke after CEA.[15]

A prospective study from Ballotta et al[8] reported no significant differences in outcome between 45 patients randomized to early and 41 to delayed (>30 days) surgery; no recurrent strokes occurred during the waiting period in the delayed group. Wolfe et al[19] reported no difference in outcome based on the timing of CEA in 66 stroke patients who underwent surgery from 1 to 28 days after the infarct. However, the initial stroke severity was found to be a significant predictor of postoperative worsening of the neurologic status of the patients. Unfortunately, a number of these studies, and others, encompassed a relatively small number of patients.

It is generally accepted that symptomatic patients with previous TIA or stroke have an increased risk of perioperative stroke compared with asymptomatic patients undergoing CEA. This is reflected in the American Heart Association Guidelines on Carotid Surgery Standards, which proposes an "acceptable" stroke/death rate of 6% for symptomatic patients, and <3% for asymptomatic patients.[21] The reasons for the poorer outcomes in these cases are not completely delineated, however.[22] It can be hypothesized that patients who have already had TIAs or strokes have an increased overall burden of cerebrovascular disease secondary to intracranial disease, prior atheroembolization, or cerebral infarction. Perhaps these factors predispose these patients towards perioperative neurologic complications, although the exact pathophysiologic mechanism remains unclear. Furthermore, patients who have had a completed stroke are speculated to have an unstable or ischemic area around the site of infarction that might be particularly susceptible to clamping, ischemia, and reperfusion injury, with subsequent extension of the prior infarct.[23]

However, because most postoperative strokes are related to technical error, it remains speculative why previously symptomatic patients should be more susceptible to these types of complications.[22,24] Perhaps owing to the reasons just discussed and decreased cerebrovascular reserve, these patients are simply more likely to clinically demonstrate further neurologic symptoms in the face of any new ischemic insult, even those related to technical error and thromboembolization, compared with previously asymptomatic patients.[22] Patients who have had previous TIA are believed to be at a somewhat increased risk for perioperative stroke compared with previously asymptomatic patients; however, most vascular surgeons consider hemispheric TIA in the setting of appropriate carotid stenosis a predictor of imminent future stroke and would not hesitate to perform CEA in a timely fashion.

Unlike many of the recent institutional reports described, our study did find an increased risk of perioperative stroke among previously symptomatic patients operated on within a 4-week period after symptoms. In patients with previous strokes, the improvement in surgical results for those undergoing delayed surgery was quite striking and highly statistically significant. Although no significant difference in the perioperative stroke rates was found between patients operated on ≤1 week and those operated on 1 to 4 weeks after their neurologic event, the rate of perioperative stroke appeared to be significantly reduced for patients in whom surgery was delayed at least 4 weeks. This reduction in the perioperative stroke rate persisted for patients operated on up to 15 months from the time of their original symptom (Fig 2). It is additionally concerning to us that a number of the stroke patients operated on early did experience intracerebral hemorrhage or clear extension of the previously existing infarct.

It is unclear why our results are different than several of the recent institutional experiences that have been reported; however, our results are echoed by at least one other study. Eckstein et al[25] reported a prospective multicenter trial in which 164 patients with nondisabling stroke underwent CEA ≤6 weeks. The combined stroke and mortality rate was 6.7%. In 10 patients, hemorrhagic transformation within the pre-existing ischemic infarct was detected on CT. Patients with a higher risk profile had a significantly higher perioperative risk when CEA was performed in the first 3 weeks after infarction (14.6% vs 4.8%).[25]

It is conceivable at our institution that despite the vascular surgeons' general bias towards delayed surgery in patients with large completed strokes, there was some additional factor about these particular stroke patients that compelled the surgeons towards earlier intervention, and additionally was responsible for their higher complication rate. If so, we have been unable to demonstrate this factor in our retrospective review. However, we remain concerned that a meaningful percentage of stroke patients undergoing early CEA did have postoperative intracerebral hemorrhage or extension of their prior infarct. A review of intracranial hemorrhage after CEA from our institution demonstrated that a preoperative head CT scan showing a recent infarction was not predictive of this entity.[23,26]

Among the early group of CEAs, we could find no meaningful predictors of perioperative stroke on univariate analysis other than a history of preoperative stroke compared with TIA alone. Although patients who had general anesthesia and those in whom a shunt was used had a significantly higher perioperative stroke rate when early CEA was performed, these findings seem to be clearly related to the use of prophylactic shunts in the patients with recent completed strokes. Rosenthal et al[27] reported that traditional methods of cerebral monitoring during carotid clamping are generally unreliable in patients with recent ischemic strokes. In concert with their recommendations, the surgeons at our institution are frequently using empiric shunts in some of these patients and thereby deferring direct neurologic monitoring under regional anesthesia in favor of general anesthesia in some cases.

Our demonstration of worse results in TIA patients operated on in an early time period was quite unexpected. As mentioned, most vascular surgeons would consider rapid intervention in a patient with hemispheric TIAs and appropriate carotid disease to prevent an impending infarction. We agree with this recommendation. Not all of our TIA patients had preoperative CT scanning, so it is possible that some of them had clinically unsuspected completed strokes. Our statistical comparison of outcome between early and delayed TIA cases resulted in a *P* value of just .05. We therefore believe that we must be explicit in stating that we are not recommending a change in practice for patients with TIA based on this report.

This report has several limitations. It is retrospective in nature, and the choice of the timing of the surgery was at the individual surgeons' discretion. We do not have precise information about the exact severity of the pre-existing neurologic deficit, the preoperative CT scan findings, or the possible occurrence of reinfarction or recurrent TIAs during the time interval between the primary neurologic event and the ultimate surgical treatment. The size of the infarct on the preoperative CT and the severity of the neurologic deficit have both been cited as critical determining factors of outcome in patients with previous strokes operated on within an early time period.[15,19] Conversely, several investigators have reported that the preoperative CT findings in stroke patients were not predictive of outcome after CEA.[12,28,29]

We also do not have information on plaque morphology or other anatomic considerations that may have prompted earlier intervention and also denoted a high-risk, unstable situation that would make perioperative complications more likely. Although our institutional preferences include continuing antiplatelet medication in the perioperative period, even if a patient is anticoagulated with heparin, it is possible that some patients inadvertently or deliberately had their antiplatelet medication stopped owing to bleeding concerns, again possibly increasing their risk of perioperative stroke.

There is clearly some pre-existing bias from the surgeons at our institution to choose delayed surgery for those patients who have had a particularly large stroke. However, we believe that this bias would likely mean that the patients operated on early would probably be those with smaller, stable neurologic deficits. Presumably then, this bias would function to actually improve the perioperative results of the early patient group. Furthermore, despite any surgeon bias present about when to choose early or delayed surgery, the current report represents an extensive real-world experience. With knowledge of the issue and the current literature, the surgeons are making their best judgments about the proper timing of intervention in individual patients, and the results have nonetheless shown that the stroke patients operated on early have worse outcomes. Ultimately, because of the above limitations, we believe we must be somewhat cautious in our recommendations to choose delayed surgery for all stroke patients. Stroke patients are a markedly heterogeneous group.[20] Further work should continue to focus on precisely which patients would benefit from early as opposed to delayed intervention.

CONCLUSIONS

In a large institutional experience, patients who underwent CEA ≤4 weeks of an ipsilateral TIA or stroke experienced a significantly increased rate of perioperative stroke compared with patients who underwent CEA in a more delayed fashion. This was true for both TIA and stroke patients, although the results were more impressive among stroke patients. The only factor found to be predictive of a perioperative stroke in patients undergoing early CEA after their symptoms was a preoperative completed stroke as opposed to TIA. Of 17 perioperative strokes that occurred in patients with completed strokes undergoing early CEA, seven (41.2%) involved an intracerebral hemorrhage or extension of the prior infarct secondary to reperfusion. On the basis of our results, we continue to recommend a consideration of a waiting period of 4 weeks in stroke patients who are candidates for carotid endarterectomy.

AUTHOR CONTRIBUTIONS

Conception and design: CR
Analysis and interpretation: CR, TM, GJ, NC, PG, TR
Data collection: CR, TM, GJ, NC, PG, TR
Writing the article: CR
Critical revision of the article: CR, TM, GJ, NC, PG, TR
Final approval of the article: CR, TM, GJ, NC, PG, TR
Statistical analysis: CR
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Overall responsibility: CR

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INVITED COMMENTARY

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Through retrospective analysis of a large prospectively gathered database of carotid endarterectomies (CEA) performed at New York University Medical Center between 1992 and 2003, Rockman and colleagues found that symptomatic patients undergoing CEA within 4 weeks of their neurologic event were at a higher risk for perioperative stroke than those undergoing delayed CEA. The difference was especially striking in patients presenting with stroke. In these patients, the perioperative stroke rate in the early and delayed CEA groups was 9.4% and 2.4%, respectively ($P = .0003$). In transient ischemic attack patients, the difference was more modest but still statistically significant (3.3% vs 0.9%; $P = .05$). These findings run counter to the findings of the North American Symptomatic Carotid Endarterectomy Trial, in which early CEA after minor stroke or transient ischemic attack was not associated with increased neurologic morbidity and in which recurrent stroke occurred within 30 days in 4.9% of the medically managed patients. Why do the findings in this study differ from those of North American Symptomatic Carotid Endarterectomy Trial? Can these results be generalized, and should they drive changes in prevailing practice?

The only truly valid means of determining the optimal timing of surgery for symptomatic carotid patients is a prospective randomized trial. Only through randomization of sufficient numbers of patients to achieve statistically robust conclusions can the innumerable potential confounding variables be neutralized. No database can be so well designed or so complete as to anticipate all potential questions to be asked of it in a retrospective review. Although Rockman and colleagues have observed a correlation between early CEA and increased perioperative stroke risk in symptomatic patients, it is not clear that the timing of surgery is the determinant of the increased risk, and it is not clear that those patients operated on early after their symptoms might not have done worse with deferred surgery.

In this study, patients were assigned to early or delayed surgery not randomly, but by individual surgeons' judgments, and these judgments were likely influenced by factors in the patients' presentations that prompted early intervention and were associated with a higher operative risk. The authors detected no differences between the early and deferred intervention groups in sex, comorbid conditions, degree of stenosis, incidence of contralateral occlusion or severe stenosis, or intraoperative technique, which might serve as an alternative explanation for the outcome difference. Still, it is likely that such factors exist. Data on plaque morphology were not available in the database, and data on brain imaging were incomplete. Stroke severity scale data were not given. Data on surgical timing preferences and outcomes for individual surgeons were not analyzed. Multivariate analysis of the effect on outcome of all likely determinants of risk was not carried out in this study.

The authors' findings cannot be disputed, but the underlying cause of the outcome difference remains unknown. It is certain that some patients are best managed with deferred surgery, but it is equally certain that others benefit from early surgery. For now, individual decisions regarding surgical timing must be based on our experiences and on all existing literature. Although this study should make us critically evaluate these decisions and perhaps prompt a prospective randomized trial, it is not sufficiently compelling to drive a change in prevailing practice.