Galbraith Award: Evaluation of Risk Factors Associated with Neurocognitive Changes after Carotid Endarterectomy

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INTRODUCTION

Although the incidence of perioperative stroke after carotid endarterectomy (CEA) is low,[8,14,20,33] nearly one in four CEA patients experiences a measurable decline in neurocognitive function on a series of neuropsychometric (NP) tests.[16,18] The pathophysiology of this decline remains unclear, and may implicate ischemic changes caused by hemispheric hypoperfusion during carotid artery cross-clamping,[4,6] dislodged microemboli,[10] or subclinical microinfarcts.[43]

Given that many of the roughly 100,000 CEAs performed annually[8,33] are performed with only borderline indications and small absolute benefit,[15,45] understanding what risk factors may predispose patients to subtle changes in neurocognitive function after CEA may aid in appropriate patient selection. In this study, we sought to identify those variables that predicted postoperative neurocognitive decline.

PATIENTS AND METHODS

Patient Population

We prospectively enrolled 186 consecutive patients undergoing elective CEA for symptomatic and asymptomatic carotid artery stenosis of at least 60% in the operative artery. All patients gave written informed consent to participate in this institutional review board-approved study, which entailed a battery of five NP tests before surgery, 1 day after surgery, and 30 days after surgery. To control for nonspecific effects of general anesthesia on neurocognitive performance,[21,40] we also enrolled 67 contemporaneous patients undergoing lumbar laminectomy (LL) with a similar anesthetic regimen, as described previously.[18] Because severe pain confounds NP test performance,[19] patients in either the CEA group or the LL control group who reported pain during testing greater than 5 on a 0 to 10 scale were excluded.

Anesthesia and Surgery

Patients in both the CEA and LL control groups received general anesthesia with routine hemodynamic and temperature monitoring, as described previously.[18] Patients in the CEA group were additionally monitored during the course of surgery using a radial artery catheter (for continuous surveillance of blood pressure) and an eight-channel encephalographic monitor (Neurotrac II; Moberg Medical, Inc., Ambler, PA). Preinduction sedation was achieved using fentanyl and midazolam. General anesthesia was induced with fentanyl, midazolam, and either rocuronium or vecuronium, and maintained with isoflurane. Intraoperatively, electroencephalographic changes indicative of ischemia necessitated shunt placement in five CEA patients. Members of the Columbia neurovascular or vascular service performed all CEAs, with surgical times averaging 153.6 ± 42 minutes. All patients were extubated in the operating room and brought to the neurological intensive care unit or postoperative care unit for recovery.

Neurocognitive Assessment

A battery of five NP tests was used to assess patients' neurocognitive performance before surgery, 1 day after surgery, and 30 days after surgery at a follow-up visit. The Boston Naming Test assessed patients' ability to verbally identify a series of objects pictured on cards. The Controlled Oral Word Association Test assessed verbal fluency and dominant ("left") hemisphere function by challenging patients to generate as many words as possible, in 60 seconds, that began with a certain letter. At each testing session, three separate trials were performed, using the letters C, F, and L. The Rey Complex Figure test (copy portion) assessed visuospatial organization and nondominant ("right") hemisphere function by challenging patients to copy the Rey Complex Figure; a standardized scoring system evaluated presence of design-specific features and the accuracy of their locations.[25] Halstead-Reitan Trails part A assessed visual conceptual and visuomotor tracking by measuring the time necessary for a patient to connect consecutively numbered circles with a

single line. Halstead-Reitan Trails part B further assessed patients' attention and cognitive flexibility by requiring patients to again connect circles with a single line, but to alternate between consecutive sequences of numbers and letters. All NP tests were administered by one of three research assistants trained and supervised by a neuropsychologist. Furthermore, all NP tests were performed at a time at least 3 hours after patients received any sedative or analgesic medication.

Statistical Analysis

Each patient in the CEA and LL control groups received a separate quantitative score for each NP test taken, so that changes in NP test performance from baseline (before surgery) to Day 1 and Day 30 after surgery could be measured. To normalize changes in CEA patients' NP test scores relative to those of the LL control group, each change was converted into a *Z*-score as follows:

Z-score = (score change − mean score change$_{LL}$) / (standard deviation of score change$_{LL}$)

To illustrate cognitive decline, negative *Z*-scores were then converted into a point system, as described previously[18]: *Z*-scores at least −0.5 equaled 0 points; between −0.5 and −1.0 equaled 1 point; between −1.0 and −1.5 equaled 2 points; between −1.5 and −2.0 equaled 3 points; between −2.0 and −2.5 equaled 4 points; between −2.5 and −3.0 equaled 5 points; and less than −3.0 equaled 6 points. A patient's *Z*-scores for each of the five NP tests were then summed to generate a total deficit (TD) score for Day 1 and Day 30. CEA patients with TD scores exceeding the mean total change score of the LL control group by two standard deviations were defined as "injured."

To assess the relationship between intraoperative variables and the risk of neurocognitive injury, univariate logistic regression was performed (separately for Day 1 and Day 30) for age, gender, obesity, history of smoking, diabetes mellitus, hypertension (defined as systolic blood pressure greater than 140 mmHg or use of antihypertensive medication), hypercholesterolemia (defined as blood cholesterol great than 200 mg/dl or use of anticholesterol medication), use of statin medication, previous myocardial infarction, previous contralateral CEA, operative side, duration of surgery, duration of carotid artery cross-clamp, and dose of midazolam. A subsequent multivariable analysis included those variables that had *P* values less than 0.10 in the univariate analysis. Patients were then separated into symptomatic and asymptomatic populations to explore the potential for subgroup analysis. Based on logistic regression, odds ratios (ORs) were calculated for each risk factor: for age, the OR per each decade increase in age; for fentanyl and midazolam, the OR per each additional µg/kg or 0.1 mg/kg, respectively, in weight-adjusted dose; and for all other factors, treated as categorical variables, the OR associated with presence of the

condition. Data is presented as mean ± standard deviation or (OR, 95% confidence interval, *P* value). *P* values less than 0.05 were deemed significant.

RESULTS

Patient Population

All 186 CEA patients completed NP testing before surgery and on postoperative Day 1 (59% symptomatic, 41% asymptomatic), whereas 153 patients completed NP testing on postoperative Day 30 (59% symptomatic, 41% asymptomatic). On Day 30, 33 patients were either lost to follow-up or refused to complete NP testing. Neurocognitive injury was present in 33 patients (18%) on Day 1 and 14 patients (9%) on Day 30. Mean TD scores for the CEA group were 3.80 ± 3.95 at Day 1 and 2.66 ± 1.99 at Day 30. Mean TD scores for the LL control group were 2.60 ± 2.27 at Day 1 and 2.66 ± 1.99 at Day 30. Demographic and intraoperative parameters of the CEA patient group are presented in *Table 34.1*.

Statistical Analysis

On Day 1, age (1.93, 1.15–3.25, 0.01; *Table 34.2*) was the only factor associated with an increased risk of neuro-

TABLE 34.1. Demographic and intraoperative parameters of carotid endarterectomy patients[a]

	CEA patients (%)
No. of patients	186 (100)
Age (yr)	69.8 ± 8.5
Men	129 (69)
Obesity[b]	39 (21)
History of smoking	102 (55)
Diabetes mellitus	47 (25)
Hypertension[c]	118 (63)
Hypercholesterolemia[d]	99 (53)
Statin medication	97 (52)
Previous MI	53 (28)
Symptomatic	77 (41)
Previous contralateral CEA	25 (13)
Right operative side	97 (52)
Duration of surgery (min)	153.6 ± 42.4
Cross-clamp time (min)	45.6 ± 18.8
Shunt placement	5 (3)
Fentanyl (µg/kg)	2.2 ± 1.2
Midazolam (mg/kg)	0.03 ± 0.01

[a]MI, myocardial infarction. Continuous data is presented as mean ± standard deviation.
[b]Obesity is defined as body mass index greater than or equal to 30.
[c]Hypertension is defined as systolic blood pressure greater than 140 mmHg or use of antihypertensive medication.
[d]Hypercholesterolemia is defined as blood cholesterol greater than 200 mg/dl or use of anticholesterol medication.

TABLE 34.2. Risk factors for neurocognitive decline on postoperative Day 1[a]

	Injured (%)	Uninjured (%)	OR (95% CI)	*P* value
No. of patients	33 (18)	153 (82)	—	—
Age (yr)	73.2 ± 7.7	69.1 ± 8.5	1.93 (1.15,3.25)	0.01
Men	22 (67)	107 (70)	—	—
Obesity[b]	6 (18)	33 (22)	—	—
History of smoking	19 (58)	83 (54)	—	—
Diabetes mellitus	11 (33)	36 (24)	—	—
Hypertension[c]	21 (64)	97 (63)	—	—
Hypercholesterolemia[d]	16 (48)	83 (54)	—	—
Statin medication	13 (39)	84 (55)	—	—
Previous MI	10 (30)	43 (28)	—	—
Symptomatic	16 (48)	61 (40)	—	—
Previous contralateral CEA	6 (18)	19 (12)	—	—
Right operative side	21 (64)	76 (50)	—	—
Duration of surgery (min)	153.3 ± 46.6	153.7 ± 18.2	—	—
Cross-clamp time (min)	47.5 ± 18.2	45.2 ± 19.0	—	—
Shunt placement	2 (6)	3 (2)	—	—
Fentanyl (μg/kg)	2.2 ± 1.3	2.2 ± 1.2	—	—
Midazolam (mg/kg)	0.03 ± 0.01	0.03 ± 0.01	—	—

[a]OR expressed in units of decades for age; CI, confidence interval; —,; MI, myocardial infarction. Continuous data is presented as mean ± standard deviation.
[b]Obesity is defined as body mass index greater than or equal to 30.
[c]Hypertension is defined as systolic blood pressure greater than 140 mmHg or use of antihypertensive medication.
[d]Hypercholesterolemia is defined as blood cholesterol greater than 200 mg/dl or use of anticholesterol medication.

cognitive injury. Age was the only variable that met criteria (*P* 0.10) for inclusion in multivariate analysis. Neurocognitive injury was present at Day 1 in 9.3% of CEA patients younger than 65 years old, 14.9% of CEA patients between 65 and 74 years old, and 28.6% of CEA patients older than 74 years old (analysis of variance [ANOVA], *P* = 0.03). Subgroup analysis revealed that age was the only significant predictor of neurocognitive injury among asymptomatic patients (2.84, 1.22–6.19, 0.01).

On Day 30, both age (2.57, 1.01–6.51, 0.049) and diabetes (4.26, 1.15–15.79, 0.03) were associated with an increased risk of neurocognitive injury. Neurocognitive injury was present at Day 30 in 5.3% of CEA patients without diabetes and 21.1% of CEA patients with diabetes (*P* = 0.007). Multivariate analysis, which also included obesity and dose of midazolam, revealed that higher weight-adjusted doses of midazolam reduced the risk of neurocognitive injury among symptomatic patients (0.53, 0.31–0.92, 0.02). All other factors failed to meet criteria for multivariate analysis. Subgroup analysis was underpowered to provide meaningful insights because of the limited number of symptomatic and asymptomatic patients at Day 30 with neurocognitive injury (five and nine, respectively).

DISCUSSION

Our results demonstrate that patient age predicts neurocognitive injury 1 day after surgery. Additionally, advanced patient age and diabetes mellitus are significant risk factors for neurocognitive injury 1 month after surgery. The pathophysiology of these subtle postoperative neurocognitive changes remains to be fully characterized. Current prevailing thought points to an ischemic mechanism, which may involve mobilization of microemboli during pre-clamp carotid artery dissection[10,46] or hypoperfusion of the brain during carotid artery cross-clamping.[4,6] Consistent with the presence of ischemic injury, neurocognitive decline is also associated with elevated serum levels of protein S100b, a marker of glial cell death.[5] However, although recent studies have identified new diffusion-weighted imaging (DWI)-positive lesions in as many as 20% of patients undergoing CEA, these lesions do not seem to be associated with post-CEA neurocognitive injury as described.[17]

Understanding how advanced age and diabetes mellitus may contribute to the mechanism of postoperative neurocognitive dysfunction requires further study. A recent study found that monocyte count independently predicted neurocognitive injury in asymptomatic patients undergoing CEA.[27]

This finding suggests a critical role for inflammatory mechanisms in post-CEA neurocognitive injury.[1,13] Diabetes mellitus, increasingly understood as a source of microvascular and macrovascular inflammation and oxidative stress,[28] may potentiate inflammatory pathophysiological mechanisms. Advanced age may affect the pathophysiology of the neurocognitive decline in a separate manner, such as through age-related changes in cerebral autoregulation and oxygenation.[3,14,26,35] The hypothesis that age and diabetes contribute to risk of neurocognitive injury through different mechanisms is supported by the fact that, in our study, age predicted injury at both Day 1 and Day 30, whereas diabetes predicted injury only at Day 30.

Our finding that age and diabetes are associated with post-CEA neurocognitive injury is consistent with patterns observed in stroke after CEA and neurocognitive dysfunction after coronary artery bypass surgery. Tu et al.[41] identified diabetes as an independent risk factor for stroke or death within 30 days of CEA (OR 1.28, $P = 0.04$) in a retrospective review of more than 6000 patients in the Ontario Carotid Endarterectomy Registry—an association confirmed by Kragsterman et al.[22] in a Swedish cohort (risk ratio 1.41, $P = 0.02$). Age, in turn, was associated with a 36% increase in risk of stroke or death after CEA in a meta-analysis of available literature.[36] Both age and diabetes have also been identified as independent predictors of neurocognitive injury after coronary artery bypass surgery,[31,32,37–39] a common phenomenon measurable via NP tests and similarly thought to be ischemic in origin.[3,42] The notion of a high-risk CEA population is controversial.[9,29,34] However, considered in light of these findings, our data raise the possibility that neurocognitive decline after CEA shares pathophysiology and risk factors with stroke after CEA and cognitive abnormalities after coronary artery bypass surgery.

Notable in our study was the apparently time-dependent course of neurocognitive injury. Half as many CEA patients exhibited neurocognitive decline at Day 30 (9%) as at Day 1 (18%), suggesting recovery of function with passage of time after surgery. Importantly, this improvement of NP test performance from Day 1 to Day 30, reflected in patients' TD scores at the two time points, was unique to CEA patients (3.80 ± 3.95 to 2.64 ± 2.93) and absent in the LL control group (2.60 ± 2.27 to 2.66 ± 1.99), which was composed of similarly aged patients with a comparable anesthetic regimen. This data supports the CEA-specific nature of the observed neurocognitive changes. The finding that age and diabetes predicted persistent neurocognitive injury 1 month after CEA is consistent with literature documenting increased risk of poor functional recovery after stroke in diabetic and older patients.[23,30,31,44]

Endeavoring to uncover possible differences between patients with symptomatic and asymptomatic carotid artery

TABLE 34.3. Risk factors for neurocognitive decline on postoperative Day 30[a]

	Injured (%)	Uninjured (%)	OR (95% CI)	*P* value
No. of patients	14 (9)	139 (91)	—	—
Age (yr)	73.2 ± 7.6	69.8 ± 8.2	2.57 (1.01, 6.51)	<0.05
Men	12 (86)	92 (66)	—	—
Obesity[b]	5 (36)	21 (15)	2.27 (0.61, 8.40)	NS
History of smoking	6 (43)	73 (53)	—	—
Diabetes mellitus	8 (57)	30 (22)	4.26 (1.15, 15.79)	0.03
Hypertension[c]	7 (50)	92 (66)	—	—
Hypercholesterolemia[d]	7 (50)	74 (53)	—	—
Statin medication	7 (50)	73 (53)	—	—
Previous MI	2 (14)	33 (24)	—	—
Symptomatic	5 (36)	58 (42)	—	—
Previous contralateral CEA	3 (21)	13 (9)	—	—
Right operative side	7 (50)	80 (58)	—	—
Duration of surgery (min)	159.6 ± 45.8	155.0 ± 43.9	—	—
Cross-clamp time (min)	44.1 ± 17.2	45.0 ± 19.1	—	—
Shunt placement	0 (0)	3 (2)	—	—
Fentanyl (µg/kg)	1.78 ± 0.73	2.32 ± 1.27	—	—
Midazolam (mg/kg)	0.03 ± 0.02	0.03 ± 0.01	0.73 (0.44, 1.24)	NS

[a]CI, confidence interval; —,; MI, myocardial infarction; NS, not significant. Continuous data is presented as mean ± standard deviation.
[b]Obesity is defined as body mass index greater than or equal to 30.
[c]Hypertension is defined as systolic blood pressure greater than 140 mmHg or use of antihypertensive medication.
[d]Hypercholesterolemia is defined as blood cholesterol greater than 200 mg/dl or use of anticholesterol medication.

stenosis, considered by some to be distinct pathological entities,[12,24] we attempted subgroup analyses at Day 1 and Day 30. Sufficiently powered analysis was not possible at Day 30 because of the paucity of injured patients (five symptomatic and nine asymptomatic). Analysis at Day 1, however, offered some preliminary insights: among asymptomatic patients, age was the only significant predictor of neurocognitive injury (2.84, 1.22–6.19, 0.01), whereas, among symptomatic patients, increasing weight-adjusted doses of midazolam predicted a lower risk of neurocognitive injury (0.53, 0.31–0.92, 0.2). Future exploration of a neuroprotective role for midazolam suggested by recent studies of animal stroke models[11,47] may shed light on the relevance of this second finding. Given continuing controversy regarding the role of CEA in treating asymptomatic carotid stenosis,[2,7] better-powered studies are necessary to evaluate the differential predictors of neurocognitive outcome in asymptomatic and symptomatic patients.

In conclusion, advanced age and diabetes mellitus increase the risk of neurocognitive injury 1 month after CEA: age by 157% for each additional decade and diabetes by more than fourfold. Advanced age also predicts neurocognitive dysfunction one day after surgery, conferring a 93% increase in the risk of decline per decade. Further work will be critical in determining how these neurocognitive changes may guide patient selection, outcome evaluation, and technical advancements.

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